STATISTICAL ANALYSIS PLAN

Syros Pharmaceuticals, Inc.

SY-1425-202

Protocol Title:	Tamibarotene in Combination with Venetoclax and Azacitidine in Previously Untreated Adult Patients Selected for RARA-positive AML Who Are Ineligible for Standard Induction Therapy
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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2 TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BMI	body mass index
BSA	body surface area
CMQ	Custom MedDRA Query
CO_2	bicarbonate
CR	complete remission
CRh	CR with partial hematologic recovery
CRi	CR with incomplete blood count recovery
CSR	clinical study report
DS	Differentiation syndrome
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFS	event-free survival
ELN	European LeukemiaNet
EMD	extramedullary disease
EoC	End of Cycle
EoT	End of Treatment
FAB	French-American-British
G-CSF	granulocyte colony stimulating growth factor
HLT	High Level Term
HSCT	hematopoietic stem cell transplantation
HSD	Hwang-Shi-DeCani
ICH	International Council for Harmonisation
INR	International normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MLFS	morphologically leukemia-free state
MPN	myeloproliferative neoplasm
MRD	minimal residual disease

Abbreviation	Definition
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PP	Per Protocol
PR	partial remission
PT	preferred term
Q1	25^{th} percentile
Q3	75^{th} percentile
qPCR	quantitative polymerase chain reaction
RARA	retinoic acid receptor alpha
RBC	red blood cell
RE	Response evaluable
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	Système International
SMQ	Standardized MedDRA Query
SOC	system organ class/standard of care
TEAE	treatment-emergent adverse event
TI	transfusion independence
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Syros Pharmaceuticals, Inc.'s Protocol SY-1425-202 (Tamibarotene in Combination with Venetoclax and Azacitidine in Previously Untreated Adult Patients Selected for RARA-positive AML Who Are Ineligible for Standard Induction Therapy). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and database lock to provide full details to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR. In this SAP, patients will hereafter be referred to as participants, with the exception of the study objectives. The interim CSR will use a subset of the analyses specified in this SAP.

5 STUDY OBJECTIVES

5.1 Primary Study Objectives

Part 1

The primary objective of Part 1 is to characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine combination in retinoic acid receptor alpha (RARA)-positive, previously untreated acute myeloid leukemia (AML) patients to inform Part 2 dose and regimen of the tamibarotene/venetoclax/azacitidine therapy.

Part 2

The primary objective of Part 2 is to characterize and compare the complete remission/complete remission with incomplete hematologic recovery (CR/CRi) rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine.

5.2 Secondary Study Objectives

Part 1

The secondary objectives of Part 1 are to

- characterize the overall response rate (ORR) of tamibarotene/venetoclax/azacitidine combination and
- characterize the pharmacokinetics (PK) of tamibarotene when administered as a part of tamibarotene/venetoclax/azacitidine therapy.

Part 2

The secondary objectives of Part 2 are to

- characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine in RARA-positive, previously untreated AML patients,
- characterize and compare CR rate and CR/CR with partial hematologic recovery (CRh) rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine,

- characterize duration of CR, duration of CR/CRi, and duration of CR/CRh of tamibarotene/venetoclax/azacitidine combination and venetoclax/azacitidine,

- characterize time to CR, time to CR/CRi, and time to CR/CRh of tamibarotene/venetoclax/azacitidine combination and venetoclax/azacitidine, and

- characterize and compare the ORR of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine.

5.3 Exploratory Study Objectives

Part 1

The exploratory objective of Part 1 is to evaluate AML molecular features associated with response and with loss of response to treatment.

Part 2

The exploratory objectives of Part 2 are to

- characterize and compare event-free survival (EFS) of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine,

- characterize and compare overall survival (OS) of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine,

- characterize and compare minimal residual disease (MRD)-negative response rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine,

- characterize time to MRD-negative response of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine,

- characterize and compare the transfusion independence (TI) rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine,

- characterize PK of tamibarotene when co-administered with venetoclax and azacitidine, and

- evaluate AML molecular features associated with response and with loss of response to treatment.

Part 3

The exploratory objectives of Part 3 are to

- characterize the ORR after treatment with tamibarotene/venetoclax/azacitidine for patients who have experienced progressive disease, relapse, or treatment failure[a] on venetoclax/azacitidine,

- characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine in patients who have experienced progressive disease, relapse, or treatment failure[a] on venetoclax/azacitidine,

- characterize the OS of tamibarotene/venetoclax/azacitidine in patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine, and

- evaluate AML molecular features associated with response and with loss of response to treatment.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a Phase 2, open-label, 3-part, multi-center study evaluating tamibarotene/venetoclax/azacitidine combination therapy in RARA-positive, previously untreated, non-acute promyelocytic leukemia (APL) AML participants who are unlikely to tolerate standard intensive chemotherapy at the time of study entry.

In Part 1, tamibarotene will be administered at 6 mg BID starting dose in combination with venetoclax/azacitidine, which will be administered at the approved dose and schedule (VIDAZA USPI/VIDAZA SmPC and VENCLEXTA USPI/VENCLYXTO SmPC). Tamibarotene dose modifications for AEs will follow guidelines outlined in the protocol (Section 6.5); venetoclax/azacitidine dose modifications will follow the standard dose modifications for AEs (VIDAZA USPI/VIDAZA SmPC and VENCLEXTA USPI/VENCLYXTO SmPC).

The safety, tolerability, and PK evaluation of tamibarotene/venetoclax/azacitidine combination will inform the appropriate tamibarotene dose to be combined with the standard of care (SOC) venetoclax/azacitidine (Döhner 2022) in Part 2 and Part 3. In Part 2, participants will be randomized 1:1 to receive either tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine to compare the clinical activity of the 2 combinations. In Part 3, tamibarotene will be added to the venetoclax/azacitidine regimen of a subset of Part 2 participants who experience progressive disease, relapse after initial CR or CRi response, or treatment failure. Enrollment is planned in the United States and France.

[a] Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.
[b] Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.

Start of Venetoclax/Azacitidine Therapy

Currently, ND AML participants who are ineligible for standard induction therapy are increasingly receiving venetoclax/azacitidine combination as the SOC therapy (DiNardo 2020; NCCN Guidelines). Since AML is an acute disease and prompt treatment may be required, in Part 1 and Part 2 of the study, the treating investigator may choose one of the two options below.

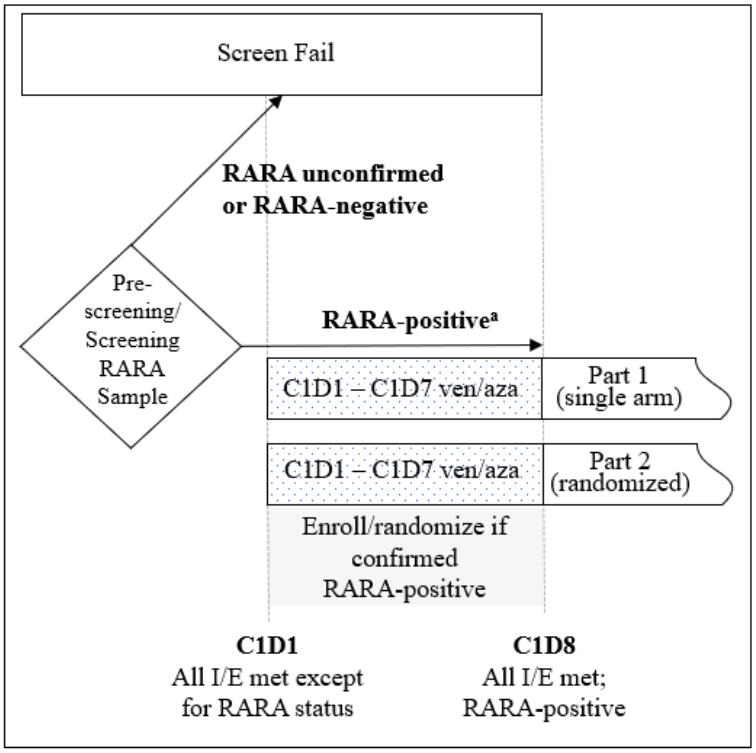
- Begin SOC venetoclax/azacitidine treatment on Cycle 1 Day 1 using protocol defined regimen and doses while awaiting pre-treatment screening RARA biomarker test result.

- Begin venetoclax/azacitidine treatment on Cycle 1 Day 1 after the participant is confirmed to be RARA-positive.

All eligibility requirements must be met prior to dosing on Cycle 1 Day 1, with the exception of RARA test results (inclusion criterion 2).

Pre-screening/Screening and Enrollment (Part 1)/Randomization (Part 2) Procedures

The sample for RARA biomarker testing must be collected and sent for assessment prior to starting venetoclax/azacitidine administration on Cycle 1 Day 1. Participants who meet all eligibility criteria (except for RARA-positive status confirmation; inclusion criterion 2) can begin venetoclax/azacitidine treatment on Cycle 1 Day 1 and are considered to be enrolled (Part 1)/randomized (Part 2) upon confirmation of RARA-positive status by Cycle 1 Day 8.



[a] If the participant discontinues treatment or study participation prior to confirmation of screening RARA results and RARA-positivity is confirmed by C1D8, the participant will be enrolled (Part 1)/randomized (Part 2), and the data from C1D1 until the time of study discontinuation will be captured (including AEs and the reason for discontinuation of treatment).

Part 1 Design

In total, up to approximately CCI participants may be enrolled in Part 1. Enrolled RARA-positive participants will receive the tamibarotene/venetoclax/azacitidine triplet combination as follows:

- Azacitidine (intravenously or subcutaneously) at 75 mg/m^2 each day on Days 1 through 7 of each 28-day therapy cycle (per VIDAZA USPI, VIDAZA SmPC). Alternative dosing of azacitidine (Days 1 through 5, 8, and 9) will be permitted throughout the study.

- Venetoclax (orally) at a dose described in the most current VENCLEXTA USPI/VENCLYXTO SmPC (including ramp-up and appropriate dosing for participants receiving concomitant CCI and P-glycoprotein (P-gp) inhibitors), daily on Days 1 through 28.

- Tamibarotene (orally) 6 mg BID on Days 8 through 28 of each 28-day therapy cycle. Tamibarotene will only be administered to participants who have been confirmed as RARA-positive.

If needed to manage toxicity, the study drugs will be modified as outlined in Section 6.5 of the protocol. After Cycle 1 data for at least 6 participants become available, the totality of data (including study drug administration record, dose modifications, and available PK data) will be evaluated to support advancing to Part 2 of the study. The ongoing enrollment of 6 to 9 additional participants to further characterize the dosing regimen or a modified regimen may occur in Part 1 of the study. A modified regimen may be evaluated if the starting dose of tamibarotene (6 mg BID) is not tolerated in combination with venetoclax/azacitidine or if the 6 mg BID dose of tamibarotene does not allow for participants to tolerate the approved regimen of venetoclax/azacitidine. A modified regimen would consist of a reduced dose of tamibarotene in combination with the approved regimen of venetoclax/azacitidine.

The dose and regimen of tamibarotene administered in combination with venetoclax/azacitidine in Part 2 and Part 3 will be informed by the totality of available data from all participants enrolled in Part 1, including the incidence of treatment-emergent AEs, the study drug administration record (including dose modifications and interruptions), safety laboratory data, physical examination and vital signs findings, and PK data.

Part 2 Design

In total, approximately CCI participants will be randomized in Part 2 of the study, RARA-positive participants will be randomized 1:1 to receive either tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine dosing as follows:

- Azacitidine (intravenously or subcutaneously) at 75 mg/m^2 each day on Days 1 through 7 of each 28-day therapy cycle (per VIDAZA USPI and VIDAZA SmPC). Alternative dosing of azacitidine (Days 1 through 5, 8, and 9) will be permitted throughout the study.

- Venetoclax (orally) at a dose described in the most current VENCLEXTA USPI and VENCLYXTO SmPC (including ramp-up and appropriate dosing for participants receiving concomitant CCI and P-gp inhibitors) daily beginning on Day 1 for a minimum of 14 days and a maximum of 28 days for Cycle 1, with the duration of venetoclax determined by early response assessment conducted between Days 14 and 21 of the cycle. If bone marrow blasts are <5%, venetoclax administration will be stopped and held for up to 14 days prior to proceeding with Cycle 2. If bone marrow blasts are ≥5%, venetoclax administration will continue through Day 28 of Cycle 1. For Cycle 2 and beyond, participants will receive venetoclax daily beginning on Day 1 through Day 28 for each cycle, with dose modifications as needed for toxicity (Döhner 2022; Maiti 2022).

- Tamibarotene (orally) 6 mg BID on Days 8 through 28 of each 28-day therapy cycle. Tamibarotene will only be administered to participants who have been confirmed as RARA-positive.

PK evaluation of tamibarotene will be conducted using samples collected from participants receiving the triplet combination only.

Part 3 Design

Part 2 participants treated with venetoclax/azacitidine who experience progressive disease, relapse after initial CR or CRi response, or treatment failure may begin subsequent treatment in Part 3, where tamibarotene will be added to their regimen. Participation in Part 3 will begin as soon as possible, but within 30 days of the decision to stop participation in Part 2. Treatment failure is defined as a failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator. No PK evaluation will be performed in Part 3.

Parts 1 through 3 Assessments and Follow-up

Participants will undergo safety and response evaluations throughout their study participation as detailed in the Schedules of Activities. Response will be assessed by the investigator in alignment with European LeukemiaNet (ELN) AML criteria (Döhner 2017), with CRh assessed according to **Error! No bookmark name given.** 2018.

In Part 1, bone marrow aspirates will be collected to measure response at the End of Cycle (EoC) Visits of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.),

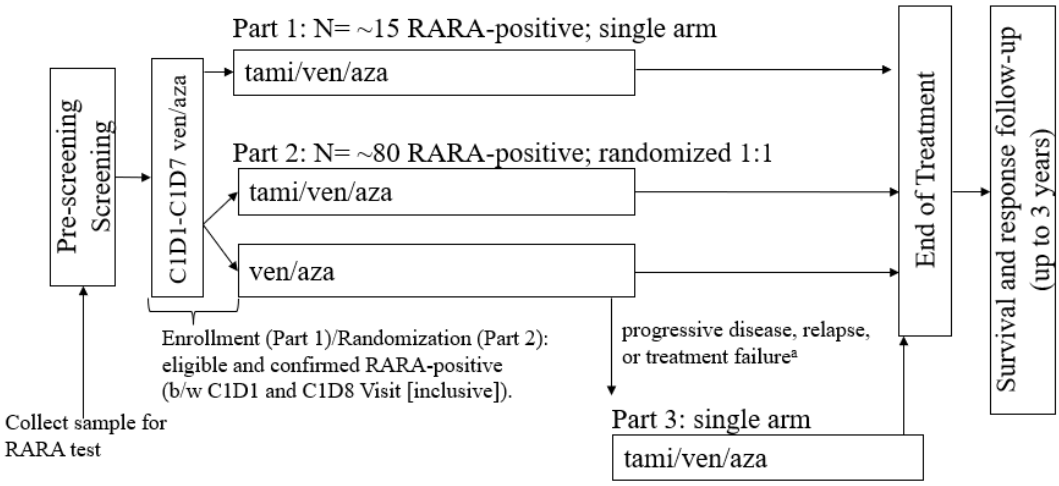
with bone marrow aspirates collected at other times as clinically determined based upon clinical findings or changes in peripheral blood counts. If a participant achieves CR/CRi at the Cycle 1 EoC Visit, the Cycle 2 EoC bone marrow aspirate is not required.

In Part 2 and Part 3, Cycle 1 response will initially be assessed between Days 14 and 21 of Cycle 1, as recommended by ELN guidelines (Döhner 2022), with venetoclax administration proceeding in alignment with these recommendations. For those with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required. For participants with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed. Subsequent bone marrow aspirates for all participants will be collected at the EoC Visit of Cycles 2 and 3, followed by every third cycle (6, 9, 12, etc.), with bone marrow aspirates collected at other times as clinically determined. If a participant achieves a CR/CRi within Cycle 1 response assessment(s), the Cycle 2 EoC bone marrow aspirate is not required.

All participants who remain on study may continue to receive study drug until experiencing an unacceptable toxicity, disease progression, relapse, decision to pursue post-remission dose anticancer therapy, participant withdraws consent, or the investigator determines it is in the best interest of the participant to discontinue study drug. Note: Part 2 participants assigned to venetoclax/azacitidine treatment may continue on study in Part 3 following progressive disease, relapse after initial CR or CRi response, or treatment failure as noted in section Part 3 Design above.

For all enrolled (Part 1)/randomized (Part 2) participants, an End of Treatment (EoT) Visit should occur within 3 days of the last dose of study drug (or within 3 days of decision to permanently stop drug treatment, if this decision directly follows a period when study drug has been on hold) and before the start of any subsequent anticancer therapy. A Safety Follow-up Visit should occur 30 days (±3 days) after the EoT Visit and before the start of any subsequent anticancer therapy. After the EoT Visit, participants who have not progressed/relapsed will enter the Disease Follow-up period, during which response assessments will be performed for up to 3 years after discontinuation of study drug, or until disease progression/relapse, whichever occurs first. Participants who progress/relapse will enter Survival Follow-up and will be followed to document the start of subsequent anticancer therapy, the date of disease progression/relapse, and OS status for up to 3 years after discontinuation of study drug.

Figure 1 Study Design



Abbreviations: aza = azacitidine; b/w = between; C1DX = Cycle 1 Day X; tami = tamibarotene; ven = venetoclax.
a Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.

6.2 Schedule of Assessments

Refer to the protocol (Section 1.3) for the complete Schedule of Assessments.

6.3 Treatments

6.3.1 Treatments Administered

The study drugs described in Table 2 will be administered. All participants enrolled will receive venetoclax/azacitidine from Cycle 1 Day 1 to Cycle 1 Day 7 in Part 1 and Part 2 of the study.

- Part 1 participants who meet all eligibility criteria and are enrolled by Cycle 1 Day 8 (once RARA-positive status has been confirmed) will receive tamibarotene/venetoclax/azacitidine combination therapy.
- Part 2 participants who meet all eligibility criteria and are randomized by Cycle 1 Day 8 (once RARA-positive status has been confirmed) will receive either tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine.
- In Part 3, tamibarotene will be added to venetoclax/azacitidine regimen of a subset of Part 2 participants.

Table 2 Study Treatments

Intervention Name	Tamibarotene	Venetoclax	Azacitidine
Type	Drug	Drug	Drug

Dose Formulation	Tablet	Tablet	Reconstituted as solution or suspension
Unit Dose Strength(s)	2-mg tablets	10-mg, 50-mg, 100-mg tablets	100-mg single-use vials
Dosage Level and Regimen	6 mg twice per day; Days 8 through 28 of each 28-day treatment cycle.	Daily, Days 1 through 28, as described in Table 3 (adapted from VENCLEXTA USPI/ VENCLYXTO SmPC).	75 mg/m^2 once per day; Days 1 through 7 of each 28-day treatment cycle (per VIDAZA USPI/VIDAZA SmPC). If dosing on Days 6 and 7 is not possible due to logistical limitations, these doses may be delayed to Days 8 and 9.
Route of Administration	Oral	Oral	Intravenous or subcutaneous
Use	Experimental	Background intervention	Background intervention

Table 3 Venetoclax Dosing

Day	Standard Ven Dosing	Drug Interaction Management		
		Ven + Posaconazole	Ven + Other CCI [redacted]	CCI [redacted] or P-gp Inhibitor
	Daily Ven Dose			
Day 1	100	10	10	Reduce standard venetoclax dose by at least 50%
Day 2	200	20	20	
Day 3	400	50	50	
Day 4 and beyond	400	70	100	

Source: adapted from VENCLEXTA USPI 2020
Note: Resume the venetoclax dosage that was used prior to concomitant use of a CCI [redacted] or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.
Abbreviations: P-gp = P-glycoprotein; ven = venetoclax

In each part of the study, the decision to begin Cycles 2, 3, 4, followed by every third cycle (7, 10, 13, etc.) will be made based on the response assessment. Participants will undergo a response assessment at the end of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.). The start of the next treatment cycle will be determined as follows:

- If a participant achieves CR at the EoC response assessment, the participant will begin the next treatment cycle.
- If a participant achieves CRi or has a morphologically leukemia-free state (MLFS) at the EoC response assessment, without absolute neutrophil count (ANC) recovery, the start of the next treatment cycle will be held to allow for ANC recovery until ANC is ≥500/μL or up to 14 days. Granulocyte colony stimulating growth factor (G-CSF) may be administered if clinically indicated for neutropenia. If ANC recovery does not occur within 14 days of the EoC response assessment, the next treatment cycle may begin in the absence of recovery of peripheral blood counts.
- If a participant is NOT in CR, CRi, or MLFS at the EoC response assessment, the start of the next treatment cycle should begin with supportive care, without modifications to the regimen, regardless of blood count recovery.

6.3.2 Method of Assigning Participants to Treatment Groups

This is an open-label study; no blinding will occur. Parts 1 and 3 of the study are not randomized. Randomization in Part 2 will be performed using an interactive response system. Randomization can occur between Cycle 1 Day 1 Visit and Cycle 1 Day 8 Visit (inclusive), as soon as all eligibility requirements are met, including confirmation of participant's RARA-positive status (inclusion criterion 2). For participants who are confirmed RARA-positive prior to Cycle 1 Day 1, randomization can occur within 72 hours prior to the first dose of venetoclax/azacitidine to accommodate operational needs.

6.4 Efficacy and Safety Endpoints

6.4.1 Efficacy Endpoints

6.4.1.1 Primary Efficacy Endpoint

Part 2

The primary efficacy endpoint of Part 2 is:

- CR/CRi assessment; CR/CRi rate is estimated by the proportion of participants who achieve CR/CRi (as determined by the investigator[a]).

Participants will be assessed for the primary endpoint of CR/CRi from the time of the index date until the initiation of non-study drug therapy or until time of disease progression/relapse. The index date is defined as the earlier of the (date of randomization and the date of Cycle 1 Day 1 Visit) for Part 2 and the date of Cycle 1 Day 1 Visit for Parts 1 and 3. The calculation of the primary efficacy endpoint is:

CR/CRi rate (%) = number of CR/CRi responders / number of participants in the modified Intent-to-Treat (mITT) Population × 100. The denominator is the mITT Population in each treatment group.

Non-responders are participants who do not achieve a CR/CRi response or meet any of the following criteria:

1. Do not have any post-baseline response assessments.
2. All response assessment results are missing or not done.
3. Discontinue prior to having a post-baseline assessment.
4. Withdraw consent before achieving a response.
5. Die before achieving a response.
6. Start a new systemic therapy before achieving a response.
7. Receive a transplant before achieving a response.
8. Experience prolonged treatment interruption requiring permanent withdrawal of study drug before achieving a response.

[a] Determination of response will be made by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

Table 4 Estimands

Objective	Treatment	Estimand Category			
		Variable	Population (Based on mITT Population)	Intercurrent Event Strategy	Population Level Summary Measure
Primary Objective: To demonstrate the superiority of tamibarotene/ venetoclax/ azacitidine compared to venetoclax/ azacitidine in CR/CRi in newly diagnosed RARA-positive AML participants	Tamibarotene/ venetoclax/ azacitidine versus venetoclax/ azacitidine	CR/CRi as determined by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.	Adult RARA-positive, previously untreated AML participants who are ineligible for standard induction therapy	• Treatment discontinuation: treatment policy • Composite strategy: Participants who die, withdraw consent, or start a new anticancer treatment before achieving a response	• CR/CRi rate by treatment arm • Difference in proportion of CR/CRi rate between the 2 treatment arms

Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRi = CR with incomplete blood count recovery; mITT = modified Intent-to-Treat; RARA = retinoic acid receptor alpha.

6.4.1.2 Secondary Efficacy Endpoints

Part 1

The secondary efficacy endpoint of Part 1 is:

- Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of participants who achieve overall response.

  ORR will be calculated as:

  ORR (%) = number of overall responders / number of participants in the Safety Population × 100.

  Non-responders are participants who do not achieve an overall response or meet any of the non-response criteria listed for the primary efficacy endpoint in Section 6.4.1.1.

Part 2

The secondary efficacy endpoints of Part 2 are:

[a] Determination of response will be made by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

- CR assessment; CR rate is estimated by the proportion of participants who achieve CR (as determined by the investigator[a]). CR rate will be calculated as:

  CR rate (%) = number of CR responders / number of participants in the mITT Population × 100. The denominator is the mITT Population in each treatment group.

  Non-responders are participants who do not achieve a CR response or meet any of the non-response criteria listed for the primary efficacy endpoint in Section 6.4.1.1.

- CR/CRh assessment; CR/CRh rate is estimated by the proportion of participants who achieve CR/CRh (as determined by the investigator[a]). CR/CRh rate will be calculated as:

  CR/CRh rate = number of CR/CRh responders / number of participants in the mITT Population × 100. The denominator is the mITT Population in each treatment group.

  Non-responders are participants who do not achieve a CR/CRh response or meet any of the non-response criteria listed for the primary efficacy endpoint in Section 6.4.1.1.

- Duration of CR, defined as the duration from the date of first documented evidence of CR to the date of relapse of disease, as determined by the investigator[a], or death due to any cause, whichever occurs first. Among CR responders, DOCR will be calculated in days as:

  Duration of CR (days) = first date of documented relapse of disease or death due to any cause - date of first documented evidence of CR + 1.

- Duration of CR/CRi, defined as the duration from the date of first documented evidence of CR/CRi to the date of relapse of disease as determined by the investigator[a], or death due to any cause, whichever occurs first. Among CR/CRi responders, duration will be calculated in days as:

  Duration of CR/CRi (days) = first date of documented relapse of disease or death due to any cause - date of first documented evidence of CR/CRi + 1.

- Duration of CR/CRh, defined as the duration from the date of first documented evidence of CR/CRh to the date of relapse of disease as determined by the investigator[a], or death due to any cause, whichever occurs first. Among CR/CRh responders, duration will be calculated in days as:

  Duration of CR/CRh (days) = first date of documented relapse of disease or death due to any cause - date of first documented evidence of CR/CRh + 1.

- Time to CR, defined as the duration from the index date to the date of the first documented evidence of CR as determined by the investigator[a]. The date of the bone

[a] Determination of response will be made by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

marrow aspirate will be used for determining the date of response. Among CR responders, this endpoint will be calculated as:

Time to CR (days) = date of the first documented evidence of CR – index date + 1.

- Time to CR/CRi, defined as the duration from the index date to the date of the first documented evidence of CR/CRi as determined by the investigator[a]. Among CR/CRi responders, this endpoint will be calculated as:

  Time to CR/CRi (days) = date of the first documented evidence of CR/CRi – index date + 1.

- Time to CR/CRh, defined as the duration from the index date to the date of the first documented evidence of CR/CRh as determined by the investigator[a]. Among CR/CRh responders, this endpoint will be calculated as:

  Time to CR/CRh (days) = date of the first documented evidence of CR/CRh – index date + 1.

- Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of participants who achieve overall response.

  ORR will be calculated as:

  ORR (%) = number of overall responders / number of participants in the mITT Population × 100. The denominator is the mITT Population in each treatment group.

  Non-responders are participants who do not achieve an overall response or meet any of the non-response criteria listed for the primary efficacy endpoint in Section 6.4.1.1.

6.4.1.3 Exploratory Efficacy Endpoints

Part 1

The exploratory endpoint of Part 1 is to assess for correlation between both molecular mutation profile and MES (monocytic expression score) and ORR/CR/CRi rate and evaluate changes to molecular mutation profile and MES score on treatment and/or at the time of loss of response.

Part 2

The exploratory efficacy endpoints of Part 2 are:

[a] Determination of response will be made by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

- EFS, defined as the duration from the index date to the date of progressive disease, relapse after CR/CRi, treatment failure[a], or death from any cause.

  EFS (months) = (date of progressive disease, relapse after CR/CRi, treatment failure, or death due to any cause – index date + 1) / 30.4375.

- OS, defined as the duration from the index date to the date of death due to any cause. OS will be calculated in months as:

  OS (months) = (date of death – index date + 1) / 30.4375.

- MRD-negative response rate, comprised of achieving an MRD-negative CR by multiparameter flow cytometry, quantitative polymerase chain reaction (qPCR), or next-generation sequencing, as determined by the investigator[b]; MRD-negative rate is estimated by the proportion of participants who achieve MRD-negative CR.

  MRD-negative response rate will be calculated as:

  MRD-negative response rate (%) = number of overall participants with MRD-negative CR / number of participants in the mITT Population × 100. The denominator is the mITT Population in each treatment group.

- Time to MRD-negative response, defined as the duration from the index date to the date of achieving an MRD-negative CR by multiparameter flow cytometry, quantitative polymerase chain reaction (qPCR), or next generation sequencing, as determined by the investigator[b]. Among participants with MRD-negative CR, this endpoint will be calculated as:

  Time to MRD-negative CR (days) = earliest date of MRD-negative CR – index date + 1.

- TI rate, defined as the proportion of participants who achieve TI. TI is a period of at least 56 consecutive days with no RBC or platelet transfusion since the date of Cycle 1 Day 1 Visit to the last dose of study drug + 30 days, the initiation of post-treatment therapy, or death, whichever occurs first. Among participants who achieved TI, this endpoint will be calculated as:

  TI rate (%) = number of participants who achieve TI / number of participants in the mITT Population × 100. The denominator is the mITT Population in each treatment group.

- Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response.

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[a] Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.
[b] Determination of response will be made by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

Part 3

The exploratory efficacy endpoints of Part 3 are:

- Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of participants who achieve overall response.

  ORR will be calculated as:

  ORR (%) = number of overall responders / number of participants in the Safety Population × 100.

  Non-responders are participants who do not achieve an overall response or meet any of the non-response criteria listed for the primary efficacy endpoint in Section 6.4.1.1.

- OS, defined as the duration from the index date to the date of death due to any cause. OS will be calculated in months as:

  OS (months) = (date of death – index date + 1) / 30.4375.

- Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response.

Response types (i.e., CR, CRi, CRh, etc.) included in the efficacy endpoints are defined in Table 5 below in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

Response definitions for participants with marrow blast clearance (<5%) may be adjusted to reflect the best hematologic response achieved prior to commencement of the next treatment cycle (Döhner 2022).

Table 5 Response Criteria for AML

Response Category	**Definition**			
	ANC (/µL)	*Platelets (/µL)*	*Bone Marrow Blasts(%)*	*Comment*
CR	≥1,000	≥100,000	<5	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease (EMD)
CRi	<1,000 -or	<100,000	<5	All CR criteria met except either neutrophils or platelets not recovered
CRh	>500	>50,000	<5	All CR criteria met except ANC and platelets with partial recovery of peripheral counts

MRD-negative CR	≥1,000	≥100,000	<5	All CR criteria met and absence of MRD as accessed by multiparameter flow cytometry, qPCR, or next generation sequencing
MLFS	NA	NA	<5	Absence of blasts with Auer rods and <5% blasts in marrow sample with a count of at least 200 nucleated cells or cellularity ≥10%. Absence of EMD. No hematologic criteria required.
PR	≥1,000	≥100,000		≥50% decrease from baseline, with decrease to 5-25
Stable disease (SD)	Absence of CR, MLFS, PR; and criteria for PD not met			
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to >500 and/or platelet count to >50,000 non-transfused); or • >50% increase in peripheral blasts (white blood cells (WBC) x % blasts) to >25,000 µL (in the absence of differentiation syndrome[a]); or • New extramedullary disease			
Treatment failure	Failure to achieve blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.			
Relapse	Bone marrow blasts ≥5%; or reappearance of blasts in blood; or development of EMD. If studied pre-treatment, reoccurrence of MRD.			

[a] Differentiation syndrome, i.e., a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts, may be observed with targeted therapies; in this setting, an increase in blasts may not necessarily indicate progressive disease.

6.4.2 Safety Endpoints

The safety endpoints for this study are incidence of AEs, changes in clinical laboratory values, electrocardiograms (ECGs), and vital sign measurements.

6.4.2.1 Adverse Events

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug whether or not related to the study drug. An AE can arise from any use of the study drug, and from any route of administration, formulation, or dose, including an overdose.

AEs will be captured from the time of the first dose of venetoclax/azacitidine on Cycle 1 Day 1 through the Safety Follow-up Visit.

6.4.2.2 Laboratory Parameters

All protocol-required local laboratory tests, as defined in Table 6, will be conducted in accordance with local laboratory practices.

Table 6 Protocol-Required Safety Laboratory Tests

Lab Tests	Parameters
Hematology	Platelet Count Hemoglobin WBC (leukocyte count including differential): Neutrophils (absolute neutrophil count, calculated from the leukocyte count and WBC differential count) Lymphocytes Monocytes Eosinophils Basophils % Blasts
Clinical Chemistry	Blood urea nitrogen/urea Creatinine Bicarbonate (CO_2) Uric acid Albumin Sodium Phosphorus Triglycerides Total cholesterol Magnesium Calcium Potassium Chloride Glucose Amylase Lipase Total protein Alkaline phosphatase Lactate dehydrogenase Total and direct bilirubin Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase Alanine aminotransferase/serum glutamic-pyruvic transaminase
Coagulation	International normalized ratio or prothrombin time Activated partial thromboplastin time/partial thromboplastin time
Routine Urinalysis	Specific gravity pH Protein Red blood cell White blood cell Leukocyte esterase Ketones Nitrite
Pregnancy testing	Highly sensitive serum or urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[a]

[a] Local urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or Institutional Review Board/Independent Ethics Committee.

6.4.2.3 Other Safety Endpoints

6.4.2.3.1 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

6.4.2.3.2 Electrocardiograms

Triplicate 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals (utilizing Fredericia's correction for QTc). Central and/or local overreads may be performed by a cardiologist in the event calculations made by the machine do not appear to be accurate.

6.4.3 Pharmacokinetic Endpoints

The PK endpoints will be provided in a separate report and is outside the scope of this SAP.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Syros Pharmaceuticals, Inc. biostatistics personnel or designee. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

There are 4 planned analyses for this study:

- An interim futility analysis of the CR/CRi rates is planned in Part 2 for the first [redacted] randomized RARA-positive participants and will be performed after approximately [redacted] randomized participants have been on treatment for approximately 3 months or discontinued treatment earlier than 3 months. If any additional analyses are performed at this time other than the futility, they will be based on the mITT, Response Evaluable (RE), and/or Per Protocol (PP) Populations, as deemed appropriate.

- Two administrative interim analyses may be performed after approximately 25% and 75% ([redacted]) of participants have had approximately 3 cycles of treatment. All interim analyses in Part 2 will be conducted on the mITT, RE, and/or PP Populations, as deemed necessary. No multiplicity adjustments are needed since the study will not be stopped for efficacy until the primary analysis.

- A final analysis when all participants are off study will be performed based on the mITT, RE, and/or PP Populations.

All relevant data from Parts 1, 2, and 3 of the study will be included as a part of the interim and final analyses.

7.1.1 Reporting Conventions

Tables and figures will be summarized separately by study part (Parts 1, 2, and 3) and treatment group (tamibarotene/venetoclax/azacitidine and venetoclax/azacitidine). Non-efficacy tables in Part 2 will also include a column for all participants combined. In general, all data collected and any derived data will be presented in participant data listings, for all enrolled participants. Listings will be ordered by study part, treatment group, site, participant number, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the number of participants with available data (n), mean, SD, median, minimum, and maximum values. Categorical variables, unless otherwise specified, will be summarized by the number of participants with available data (n), and number and percentage of participants in each category. If there is a subcategory under a categorical variable, this subcategory will be summarized by the number and percentage of participants based on the number of participants under this categorical variable. A category for "Missing" will be added and populated to make the total percentage of each category equal to 100%. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of participants in each category, as appropriate.

Non-zero percentages will be rounded to 2 decimal places. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to 1 more decimal place than the precision of the variable of summarization and up to 3 decimal places.
- Measures of variability (e.g., SD, SE) will be rounded to 2 more decimal places than the precision of the variable of summarization and up to 4 decimal places.
- Minimum and maximum values will be presented using the same precision as the variable of summarization and up to 2 decimal places.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

The level of significance for the analysis of the Part 2 primary endpoint is 1-sided at 5%. Secondary efficacy endpoints for Part 1 and Part 2 may be tested using a 2-sided, 5% significance level. Two (2)-sided 95% CIs will be reported for all endpoints/analyses, when appropriate, unless otherwise specified. P-values will be rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF. For safety analysis, in the case of multiple observations at a specific visit, the observation which is the latest will be used. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

Data collected at unscheduled visits will not be included in by-visit summaries but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in participant listings.

7.1.3 Data Handling Rules

7.1.3.1 Threshold Values

Unless otherwise noted, values that include a threshold sign (i.e., "<" or ">") will be imputed for summary tables in the following manner:

- A value that is 1 unit less than the limit of quantitation will be used for the calculation of descriptive statistics if the datum is reported in the form of "<x" (where x is considered the limit of quantitation). For example, if the values are reported as <50 and <5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported <1. For the values reported as <1 or <0.1, a value of 0.9 or 0.09 will be used for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for the calculation of descriptive statistics if the datum is reported in the form of ">x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.
- The limit of quantitation will be used for the calculation of descriptive statistics if the datum is reported in the form of "≤x" or "≥x" (where x is considered the limit of quantitation).

The original data including the threshold signs will be displayed in the listings.

7.1.3.2 Baseline Definition

For all endpoints, unless otherwise specified, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Cycle 1 Day 1 assessments are assumed to be taken prior to first dose and used as baseline. When scheduled assessments and unscheduled assessments occur on the same day as the first dose and the time of assessment or the time of the first dose is not available, the following convention to determine baseline will be used:

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

- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, the unscheduled assessment will be used as baseline.

For participants who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value. Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing. For purposes of defining "pre-dose", reference should be made to the first dose of tamibarotene, azacitidine, or venetoclax, whichever comes first.

For ECG analyses, if the latest, non-missing pre-dose value is from triplicate, the participant level baseline is defined as the mean of the triplicate baseline assessments.

For all analyses in Part 3, the visit corresponding to Part 3 Cycle 1 Day 1 will be used as baseline.

7.1.3.3 Imputation of Partial or Missing AE Dates for Analysis

Rules for imputing partial or missing AE dates for analysis are provided in Table 7.

Table 7 Date Imputation Rules for AEs

Adverse Events	**Partial/missing AE dates recorded in the CRF will be imputed using the following conventions:**
Missing start day	First of the month will be used unless it is before the start date of study treatment; in this case, the study treatment start date will be used and hence the event is considered treatment emergent.
Missing start day and month	No imputation.
Missing end day	Last day of the month will be used.
Missing end day and month	No imputation.
Completely missing start/end day	No imputation.

7.1.3.4 Imputation of Partial or Missing Medical History/Concomitant Medication Dates for Analysis

Rules for imputing partial or missing medical history or concomitant dates for analysis are provided in Table 8.

Table 8 Date Imputation Rules for Medical History/Prior and Concomitant Medications/Prior Cancer Therapy

Medical History/Prior and Concomitant Medications/Prior Cancer Therapy	**Partial/Missing Medical History/Prior and Concomitant Medication/Prior Cancer Therapy Dates Recorded in the CRF Will Be Imputed Using the Following Conventions:**
Missing start day	"01" will be used for the day.
Missing start day and month	"01" will be used for the day and "Jan" will be used for the month.
Missing end day	"28/29/30/31" will be used for the day (dependent on the month and year) and the earlier of last day of the month and the end of study date will be used as the imputed value except in the following 2 cases: 1) For prior cancer therapy 2) If it is not ongoing and the start date is prior to the study treatment start date For these 2 cases, the end date will be imputed as (study treatment start date - 1).
Missing end day and month	"31" will be used for the day and "Dec" will be used for the month, and the earlier of 31 Dec of the given year and the end of study date will be used as the imputed value except in the following 2 cases: 1) For prior cancer therapy 2) If it is not ongoing and the start date is prior to the study treatment start date For these 2 cases, the end date will be imputed as (study treatment start date - 1).
Completely missing start/end day	No imputation.

7.1.3.5 Imputation of Partial or Missing New Anticancer Dates for Efficacy Evaluation

Start dates for follow-up anticancer therapy will be temporarily imputed in order to define event and censoring rules for event-free survival, response rate, time to event, duration of response or time to response (e.g., start date for new anticancer therapy). The imputed dates will be stored in the systemic therapy derived dataset.

- If missing start day, month, and year, then no imputation.
- If missing start day and month, then no imputation.
- If missing start day only, then do the following:

  - If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment + 1, last day of month).
  - If partial date falls in the same month as the participant's last assessment and the participant's last assessment is progressive disease, relapse after CR/CRi, or treatment failure[a], then assign to earlier of (date of progressive disease, relapse after CR/CRi, or treatment failure + 1, last day of month).
  - If both rules above apply, then assign to latest of the 2 dates.
  - Otherwise, impute missing day to the first of the month.
- If missing end date, then no imputation should be done.

7.1.3.6 Imputation of Partial or Missing Date of Birth and the Calculation of Age

Age in years will be calculated as (date of main informed consent – date of birth + 1) / 365.25 and will be stored in the adsl dataset.

- If missing day, month, and year of birth, then no imputation.
- If missing day and month of birth, then impute date of birth to June 30.
- If missing day only, then impute date of birth to 15th of the month.

7.1.3.7 Imputation of Partial or Missing Date of Death

Date of death will be temporarily imputed in order to define event and censoring rules for time to event endpoints. The imputed dates will be stored in the adsl dataset.

- If missing day, month, and year, then no imputation.
- If missing day and month, then impute to later of January 1st or (last known alive date + 1).
- If missing day only, then impute to later of first date of the month or (last known alive date + 1).

7.1.3.8 Calculation of ECG Data

Three reads are taken during ECG at each visit. The average of the available reads will be used as the ECG data at the corresponding visit. If none of the three reads are available, then the observation will be considered as missing, and no imputation will be performed.

7.1.3.9 Post-baseline Missing Values

- If post-baseline Common Terminology Criteria for Adverse Events (CTCAE) grade for laboratory parameters is missing, there will be no imputation for missing values, and in the shift from baseline to worst post-baseline CTCAE

[a] Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.

grade by parameter tables, a missing category will be added in order to have the total number of post-baseline participants equal to the total number at baseline.
- Missing category for post-baseline values will be added to ECG shift table, similar to the bullet above. The same rules will be applied for vital sign shift tables and ECOG shift tables.
- If AE grade is missing, the previous worst grade under the same preferred term (PT) will be assigned if it is available, otherwise a grade of 4 will be assigned for classification purpose in the tables, figures, and listings.
- If the transfusion eCRF page is missing or if the blood product received information is missing, then there will be no imputation, and the participants will be classified as having missing transfusion dependence status. If the date of the transfusion is missing, then the transfusion dependence status at baseline and post-baseline will both be missing.

7.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on participant data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and

- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated as the later date – the earlier date + 1.

- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (30.4375).

- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.

- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value.

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

7.2 Analysis Populations

The analysis populations are defined as follows:

- Part 1 Safety Population: Includes all enrolled participants who have received any amount of study drug (tamibarotene, venetoclax, or azacitidine).

- Part 1 RE Population: Includes all RARA-positive participants enrolled in Part 1 who have received any amount of study drug (tamibarotene, venetoclax, or azacitidine) and have either completed at least 1 response assessment or have discontinued treatment due to clinical progression/progressive disease prior to any response assessments.

- Part 2 ITT Population: Includes all participants who are randomized in Part 2. Treatment groups for this population will be determined according to the treatment assignment at the time of randomization.

- Part 2 mITT Population: Includes all RARA-positive participants who are randomized in Part 2 and start dosing from Cycle 1 Day 1. Treatment groups for this population will be determined according to the treatment assignment at the time of randomization.

- Part 2 RE Population: Includes all mITT participants who have either completed at least 1 response assessment or have discontinued treatment due to clinical progression/progressive disease prior to any response assessments. Treatment groups for this population will be determined according to the treatment assignment at the time of randomization.

- Part 2 PP Population: Includes all mITT participants who are considered to be sufficiently compliant with the protocol as determined by the sponsor before database lock. Treatment groups for this population will be determined according to the treatment assignment at the time of randomization.

- Part 2 Safety Population: Includes all randomized participants who have received any amount of study drug (tamibarotene, venetoclax, or azacitidine). Treatment groups for this population will be determined according to the actual treatment the participants received. Participants who have only received venetoclax and/or azacitidine will be assigned to the doublet treatment group.

- Part 3 Safety Population: Includes all enrolled participants who have received any amount of study drug (tamibarotene, venetoclax, or azacitidine).

- Part 3 RE Population: Includes all RARA-positive participants enrolled in Part 3 who have received any amount of study drug (tamibarotene, venetoclax, or azacitidine) and have either completed at least 1 response assessment or have discontinued treatment due to clinical progression/progressive disease prior to any response assessments.

- PK Evaluable Population: Includes all participants who have received at least 1 dose of tamibarotene and have at least 1 quantifiable PK concentration.

Treatment groups for this population will be determined according to the actual treatment the participants received.

Data summaries to be presented for multiple populations will only be produced for each separate population if there is a difference between the population group counts.

All data collected from participants who received venetoclax and azacitidine in Part 2 but were not randomized will be listed separately.

All efficacy analyses in Part 2 of the interim CSR will be based on the RE Population, and all efficacy analyses in the final CSR will be based on the mITT and/or RE Populations.

7.3 Study Participants

7.3.1 Disposition of Participants

7.3.1.1 Part 1

Participant disposition in Part 1 will be summarized for all enrolled participants. The summary will include

- the number and percentage of participants in the Safety Population
- the number and percentage of participants completing and discontinuing each study treatment
- the number and percentage of participants by primary reason for discontinuation of each study treatment
- the number and percentage of participants by primary reason for study termination.

7.3.1.2 Part 2

Participant disposition in Part 2 will be summarized for all randomized participants by treatment group (venetoclax/azacitidine or tamibarotene/venetoclax/azacitidine) and for all participants combined (total). Summaries will include

- the number and percentage of participants in ITT Population
- the number and percentage of participants by primary reason for exclusion from the PP Population
- the number and percentage of participants completing and discontinuing each study treatment
- the number and percentage of participants by primary reason for discontinuation of each study treatment
- the number and percentage of participants by primary reason for study termination
- the number and percentage of participants enrolling in Part 3
- the number and percentage of participants by reason for enrolling in Part 3.

The primary reasons for exclusion from the PP Population will be identified by the Sponsor prior to database lock.

7.3.1.3 Part 3

Participant disposition in Part 3 will be summarized for all participants enrolled in Part 3. The summary will include

- the number and percentage of participants in the Safety Population
- the number and percentage of participants completing and discontinuing each study treatment
- the number and percentage of participants by primary reason for discontinuation of each study treatment
- the number and percentage of participants by primary reason for study termination.

Listings of participant disposition by study part and treatment group will be provided. Participants from Part 2 who continue to Part 3 will be flagged.

Additionally, listings of randomization schemes and codes (Part 2 only), discontinuation from study treatments, and study eligibility will be provided. Screen failures will be included in the study eligibility listing but will not be included in any summary tables for analysis.

7.3.2 Protocol Deviations

Major protocol deviations will be summarized separately by study part for all enrolled participants in Parts 1 and 3 and by treatment group and over all participants combined for the ITT Population in Part 2. Major protocol deviations are protocol deviations, including non-compliance with the protocol, captured on study that are be deemed by the Sponsor to potentially impact the efficacy or safety conclusions of the study.

Protocol deviation review will be conducted and agreed upon by the sponsor and CRO stakeholders regularly throughout the study. All protocol deviations including major protocol deviations will be determined and appropriately categorized (as specified in the study Protocol Deviation Assessment Plan) prior to database lock. The number and percentage of participants with protocol deviations that impact the efficacy or safety conclusions, as well as the number and percentage of participants with deviations within all categories will be presented.

The reasons for protocol deviations will be summarized for the PP Population.

By-participant listings of all protocol deviations, including those related to Covid-19, will be provided for each study part.

7.3.3 Demographic and Baseline Characteristics

Demographic variables and baseline characteristics will be summarized separately by study part, for all participants in the Safety Populations for Parts 1 and 3, and by treatment group and total in the ITT Population for Part 2. Additional tables for the Part 2 mITT Populations will be presented if the population counts are different from the ITT Population.

Continuous variables will be summarized using descriptive statistics (mean, standard deviation, and median, as well as the minimum and maximum values).

Categorical variables will be summarized with the number and percentage of participants in each category by treatment group and overall. The number of participants with missing information will also be summarized.

The demographic variables include:

- Age (years)
- Age categories (≥18 to <65, ≥65 to <75, ≥75)
- Sex (male, female)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI)
- Body Surface Area (BSA)
- ECOG Performance Status (0, 1, 2, 3)

BMI will be calculated as: weight (kg) / [height (cm) / 100]^2. BSA will be calculated as (height (cm) × weight (kg)) / 3600)$^{1/2}$. The demographic and baseline data listed above as well as female child-bearing potential will be presented in listings for each study part. Participants from Part 2 who continue to Part 3 will be flagged.

7.3.4 AML Disease History

AML disease history characteristics include:

- Time since initial diagnosis of AML
- AML type (de novo, AML associated with treatment from prior malignancy, myelodysplastic syndrome and/or MPN if AML evolved from antecedent hematologic malignancy
- ELN risk status (Favorable, Intermediate, Adverse)
- FAB classification (M0-M7)
- RARA status (positive, negative)
- Bone marrow blast category (≤30%, >30 - ≤50%, >50%)
- Molecular mutation status (e.g., FLT3, CEBPA, TP53, etc.)
- WBC count (low (<4 10^9/L), normal (4-11 10^9/L), high (>11 10^9/L))
- Low hemoglobin (<10 g/dL)
- Low platelets (<100 10^9/L)

- Low ANC (<1.0 10^9/L)

The above AML disease characteristics will be summarized separately by study part (excluding Part 3), treatment group and total (Part 2 only) for the Part 1 Safety Population and Part 2 ITT Population.

Time since initial diagnosis in months will be calculated as: (Index Date - Date of Initial Diagnosis of AML + 1) / 30.4375. Index date is defined as date of Cycle 1 Day 1 visit for Parts 1 and 3, and the earlier of the date of randomization and the date of Cycle 1 Day 1 Visit for Part 2. Time since initial diagnosis will be summarized using descriptive statistics and the remaining characteristics will be summarized with the number and percentage of participants in each category. The number of participants with missing information will also be summarized.

A listing of AML disease history will be provided for Parts 1 and 2. Participants from Part 2 who continue to Part 3 will be flagged.

7.3.5 Medical History

Medical History is collected prior to dosing and will be summarized by study part (excluding Part 3), treatment group, and total (Part 2 only) for the Part 1 Safety Population and Part 2 ITT Population. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1 or higher.

Summaries will be ordered by descending incidence of system organ class and descending incidence of preferred term within each system organ class for all participants. A listing of medical history will be provided for Parts 1 and 2. Participants from Part 2 who continue to Part 3 will be flagged.

7.3.6 Prior and Post-treatment Cancer Therapies

All prior cancer therapy data, including regimen number, indication, drug/agent name, and start/end dates, will be collected prior to dosing. Any systemic therapy that is started after the end of study treatment will also be recorded. Medications will be coded using the World Health Organization (WHO) Drug Dictionary Global B3 01 September 2020 version or a more recent version and will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name. Prior and post-treatment cancer therapies will be summarized separately by study part (excluding Part 3 for prior cancer therapies), treatment group, and total (Part 2 only) for the Part 1 Safety Population, Part 2 ITT Population, and Part 3 Safety Population. Summaries will be ordered by descending incidence of ATC class and descending incidence of drug name within ATC class for all participants.

Separate by-participant listings of prior and post-treatment cancer therapies will be provided for each study part (excluding Part 3 for prior cancer therapies, for which participants from Part 2 who continue to Part 3 will be flagged).

7.3.7 Prior and Concomitant Medications

Medications will be coded using the WHO Drug Dictionary Global B3 01 September 2020 version or a more recent version. Medications entered on the eCRF will be mapped to ATC drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately, and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication that was used by the participant within 30 days of Cycle 1 Day 1. A concomitant medication is defined as any medication that (1) started before the first dose of study drug and was continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug through 30 days after the participant's last dose of study drug.

For both prior and concomitant medication summaries, the number and percentage of participants receiving any medication will be summarized by study part (excluding Part 3 for prior medications), treatment group and total (Part 2 only) as will the number and percentage receiving any medication by ATC drug class and generic drug name. Participants reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence for all participants, as will generic drug names within each ATC class. Whether the medication is prior or concomitant will be presented on the listings of prior and concomitant medications (excluding Part 3 for prior medications, for which participants from Part 2 who continue to Part 3 will be flagged). Prior and concomitant medications will be summarized separately by study part (excluding Part 3 for prior medications), treatment group, and total (Part 2 only) for the Part 1 Safety Population, Part 2 ITT Population (mITT for concomitant medications), and Part 3 Safety Population.

7.3.8 Prior and Concomitant Blood Transfusions

For all enrolled (Part 1)/randomized (Part 2) participants, any transfusions from 8 weeks (or 56 days) prior to first dose of study drug on Cycle 1 Day 1 through the Safety Follow-up period will be recorded. Transfusions will be classified as prior or concomitant based on the start date. A prior transfusion is defined as any transfusion that started up to 8 weeks prior to the date of the Cycle 1 Day 1 Visit. A concomitant transfusion is defined as any transfusion that started on or after the date of the Cycle 1 Day 1 Visit through the Safety Follow-up period. Prior and concomitant blood transfusions will be summarized separately by study part (excluding Part 3 for prior transfusions), treatment group, and total (Part 2 only) for the Part 1 Safety Population, Part 2 ITT Population (mITT for concomitant transfusions), and Part 3 Safety Population.

Separate by-participant listings of prior and concomitant blood transfusions will be provided for each study part (excluding Part 3 for prior blood transfusions, for which participants from Part 2 who continue to Part 3 will be flagged).

7.3.9 Other Therapies, Treatments, and Procedures

Any other therapies, treatments or procedures that occur during the study will be provided in a by-participant listing for each study part.

7.3.10 Extent of Study Drug Exposure

The total number of cycles will be summarized using descriptive statistics for the Part 1, 2, and 3 Safety Populations for each study drug (tamibarotene, venetoclax, and azacitidine) and treatment group (for Part 2 only). Additionally, the number and percentage of participants will be summarized for each study treatment group (for Part 2 only), separately for each study drug, by the total number of cycles in which they were treated, according to the following categories: <1, 1-2, 3-4, >4 cycles.

Actual and planned total dose, duration of exposure, and actual, planned, and relative dose intensity will be summarized using descriptive statistics for the Part 1, 2 and 3 Safety Populations for each study drug.

The duration of exposure in months will be calculated as:

duration of exposure (months) = (date of last dose of study drug – date of first dose of study drug + 1) / 30.4375.

Actual dose intensity in dose units (mg for tamibarotene and venetoclax and mg/m^2 for azacitidine) per month will be calculated as:

actual dose intensity (units/month) = total dose received (units) / duration of exposure (months).

The planned total dose of tamibarotene will be calculated as 12 mg × 21 days for each cycle. The planned total dose of azacitidine will be calculated as 75 mg/m^2 × 7 days for each cycle.

For the planned total dose of venetoclax for each cycle, refer to Table 4 in the protocol. For example, the planned total dose for standard venetoclax dosing during Cycle 1 will be calculated as 100 mg (Day 1) + 200 mg (Day 2) + 400 mg × (the remaining days on treatment (between 12 and 26)). For standard venetoclax dosing during Cycles 2 and above, the planned total dose will be calculated as 100 mg (Day 1) + 200 mg (Day 2) + 400 mg × (26 days) for Cycles 2 and above. The planned total dose calculation for venetoclax in combination with other drugs will be modified using the dose amounts indicated in Table 4 of the protocol.

For each study drug, the planned total dose will be calculated as two steps:

1) Sum of the doses in each cycle (Cycle 1 (unit) = X1 dose, Cycle 2 (unit)= X2 dose, ... Cycle n (unit)= Xn dose)

2) Sum of non-zero dosing in all cycles (Cycle 1 (unit) + Cycle 2 (unit) + … + Cycle n (unit))

Planned dose intensity in dose units (mg for tamibarotene and venetoclax and mg/m^2 for azacitidine) per month will be calculated as:

planned dose intensity (units/month) = planned total dose (units) / duration of exposure (months).

Relative dose intensity will be calculated as:

relative dose intensity = actual dose intensity (units/month) / planned dose intensity (units/month).

Summary of duration of exposure to study treatment will include categorical summaries. Duration of exposure will be categorized into time intervals (i.e., <1 month, ≥1 - <2 months, ≥2 - <3 months, ≥3 - <4 months, and ≥4 months); frequency counts and percentages will be presented for the number and percentage of participants in each interval.

Additionally, the total number of delayed, interrupted/held, missed/incorrect, discontinued, increased, decreased, and Part 2 discontinued doses will be summarized separately using descriptive statistics for the Part 1, 2 and 3 Safety Populations by study drug.

All study treatment administration data will be listed for each study drug.

7.4 Efficacy Evaluation

7.4.1 Datasets Analyzed

All efficacy summaries will be based on the mITT and/or RE Population for Part 2 and the Safety Population for Parts 1 and 3. An additional summary of the primary endpoint will be based on the PP and RE Populations for Part 2 and on the RE Population for Parts 1 and 3. Time to response and duration of response in Part 2 will be analyzed using the RE Population. Listings and descriptive summaries of AML disease response assessments, bone marrow sample results, detection of MRD and EMD, cytogenetics and molecular abnormalities and post-treatment survival follow-up will be provided to support the efficacy analyses.

All efficacy analyses in Part 2 of the interim CSR will be based on the RE Population and all efficacy analyses in the final CSR will be based on the mITT and/or RE Populations.

7.4.2 Primary Efficacy Endpoint Analysis Methods

7.4.2.1 Part 2

Participants will be assessed for the primary endpoint of CR/CRi from the time of the index date until the initiation of non-study drug therapy or until time of disease progression/relapse in Part 2 of the study. Further details of the calculation of the primary endpoint are provided in Section 6.4.1.1. The analysis of the CR/CRi rate is planned for the time when all participants have completed the Cycle 3 EoC response assessment or discontinued treatment earlier.

The primary estimand is the CR/CRi rate, which is estimated by the proportion of participants who achieve CR/CRi (as determined by the investigator[a]).

The null hypothesis (H_0) to be tested is:

In RARA-positive participants with previously untreated AML who are ineligible for standard induction therapy, the CR/CRi rate after treatment with tamibarotene/venetoclax/azacitidine is the same as the CR/CRi rate after treatment with venetoclax/azacitidine.

The alternate hypothesis (H_A) to be tested is:

In RARA-positive participants with previously untreated AML who are ineligible for standard induction therapy, the CR/CRi rate after treatment with tamibarotene/venetoclax/azacitidine is higher than the CR/CRi rate after treatment with venetoclax/azacitidine.

The number (%) of participants and 95% exact binomial CIs of the percentage of responders and non-responders (along with criteria for non-response) will be summarized by treatment group for the mITT Population, based on the Clopper-Pearson method. A p-value from a Fisher's exact test comparing the CR/CRi rates (%) between the two treatment groups with a 1-sided 5% level of significance will also be presented. The primary analysis will be repeated for the PP Population as a sensitivity analysis.

A by-participant listing of the derived efficacy data used for the CR/CRi rate will be provided. Sensitivity analyses based on the RE Population may also be performed.

7.4.3 Secondary Efficacy Endpoint Analysis Methods

7.4.3.1 Part 1

7.4.3.1.1 Overall Response Rate

[a] Determination of response will be made by the investigator in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

The number (%) of participants and 95% exact binomial CIs of the percentage of overall responders and non-overall responders (along with criteria for non-response), based on the Clopper-Pearson method, will be summarized for the Part 1 Safety Population. The number (%) of participants and 95% exact binomial CIs for the individual and combined rates of CR, CRi, CRh, MLFS, and PR will also be summarized based on the Clopper-Pearson method. A by-participant listing of the derived efficacy data used for determining the ORR will be provided. A sensitivity analysis based on the RE Population may also be conducted.

7.4.3.2 Part 2

7.4.3.2.1 CR and CR/CRh Rates

The CR and CR/CRh rates will be analyzed separately using the same statistical methodologies applied to the primary efficacy endpoint for the mITT Population, as described in Section 7.4.2. A by-participant listing of the derived efficacy data used for determining the CR and CR/CRh rates will be provided.

7.4.3.2.2 Duration of CR, CR/CRi, CR/CRh

The duration of CR, CR/CRi, and CR/CRh will be estimated using Kaplan-Meier product-limit estimates and will be presented in separate summaries by treatment group for the mITT Population and only for participants who are responders as defined in Section 6.4.1 for the respective categories.

The median estimate of duration of CR, CR/CRi, and CR/CRh and corresponding 95% CIs based on the Brookmeyer and Crowley method will be provided for each treatment group. The analysis will only be for participants who are CR, CR/CRi, and CR/CRh responders, respectively, or who are censored after achieving response. Event and censoring rules for duration of CR, CR/CRi, and CR/CRh are provided in Table 9. A sensitivity analysis of the duration of CR, CR/CRi, and CR/CRh will also be performed using the alternative censoring rule identified in situation number 5. A sensitivity analysis based on the RE Population may also be conducted for duration of CR/CRi.

Table 9 Assignments for Event and Censoring Dates for Duration of CR Analysis

Situation #	Situation (Occurring on or After First Date of CR Response)	Date of Event or Censoring	Outcome
1	No post-baseline response assessments after the first CR/CRi/CRh and the participant has not died or developed disease progression/ relapse (if the participant has died or developed disease	First date of CR, CR/CRi, CR/CRh response	Censored

Situation #	Situation (Occurring on or After First Date of CR Response)	Date of Event or Censoring	Outcome
	progression/relapse follow the rules for death indicated in situations #6-7)		
2	Disease progression / relapse documented at scheduled visits within extended loss-to-follow-up time [1]	Date of assessment of disease progression / relapse	Event
3	Disease progression / relapse documented between scheduled (unscheduled) visits within extended loss-to-follow-up time [1]	Date of assessment of disease progression/ relapse	Event
4	No disease progression / relapse (or death)	Date of last adequate response assessment [2]	Censored
5	HSCT and/or systemic therapy started prior to documented disease progression / relapse or death	Date of last adequate response assessment occurring prior to documented disease progression/relapse or death, irrespective of HSCT/systemic therapy date[2]	Censored
		Date of assessment of disease progression/ relapse or death [SA]	*Event*
6	Death within extended loss-to-follow-up time [1]	Date of death	Event
7	Death or disease progression / relapse after an extended loss-to-follow-up time [1]	Date of last adequate response assessment [2] prior to the ≥2 missed consecutive assessments	Censored

[SA] Alternative rule for handling of events for duration of CR.
[1] Extended loss-to-follow-up time is defined as the last non-missing adequate response assessment and event (death or disease relapse). Extended loss-to-follow-up time is 240 days. This cutoff is calculated based on the protocol scheduled procedure: the 28-day treatment cycle has ± 3 days window, response assessment is expected to be conducted every 3 months (with ± 30 days window). Thus, 2 consecutive scheduled assessments window is 2 × [30 × 3 + 30] = 240 days. Within extended loss-to-follow up time is defined as ≤240 days; after an extended loss-to-follow-up time is defined as: >240 days.
[2] An adequate response assessment is defined as an assessment where the investigator performed all the procedures required for assessment and documented the outcome.

7.4.3.2.3 Time to CR, CR/CRi, CR/CRh

Time to CR, CR/CRi, and CR/CRh will be summarized separately using descriptive statistics by treatment group and only for participants who are responders for the mITT Population. A sensitivity analysis based on the RE Population may also be conducted for time to CR/CRi.

7.4.3.2.4 Overall Response Rate

The ORR will be analyzed using the same statistical methodologies applied to the primary efficacy endpoint, described in Section 7.4.2, for the mITT Population. A by-

participant listing of the derived efficacy data used for determining the ORR will be provided. Sensitivity analyses of ORR based on the RE Population may also be conducted.

7.4.4 Exploratory Efficacy Endpoint Analysis Methods

7.4.4.1 Part 1

Analysis of clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response will be detailed in a separate document and is outside the scope of this SAP.

7.4.4.2 Part 2

7.4.4.2.1 Event-Free Survival

EFS is defined as the duration from the index date to the date of progressive disease, relapse after CR/CRi, treatment failure[a], or death from any cause. EFS will be estimated using Kaplan-Meier product-limit estimates for the mITT Population and will be presented for each treatment group. The number and percentage of participants with an event or who were censored will be summarized by treatment group. The 25th percentile, median and 75th percentile (along with corresponding 95% CIs based on the Brookmeyer and Crowley method), will also be presented. Landmark analyses (EFS rates, 95% CI, and number of participants at risk) will occur at 6, 12, and 18 months from the index date. An unstratified log rank test will be used to analyze the difference in EFS between treatment groups and a 2-sided p-value with 5% level significance will be presented. A sensitivity analysis of EFS will also be performed using the alternative censoring rules identified in situation numbers 4, 6, 8, and 10 in Table 10.

Additionally, a separate summary of reasons for censoring, plots of the Kaplan-Meier estimates a by-participant listing of the derived efficacy data used for the EFS analysis, and a listing of reasons for censoring will be provided.

Table 10 Assignments for Primary and Alternative Event and Censoring Dates for EFS Analysis

Situation #	Situation	Date of Event or Censoring	Outcome
1	No (or inadequate) baseline disease assessments [1] and the participant has not died (if the participant has died follow the rules for death indicated in situations #7-9).	Index Date	Censored
2	No post-baseline response assessments and the participant has not died (if the	Index Date	Censored

[a] Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator.

Situation #	Situation	Date of Event or Censoring	Outcome
	participant has died follow the rules for death indicated in situations #7-9)		
3	Progressive disease, relapse after CR/CRi, or treatment failure documented at scheduled visits without extended loss-to-follow-up time [2]	Date of assessment of Progressive disease, relapse after CR/CRi, or treatment failure	Event
4	Progressive disease, relapse after CR/CRi, or treatment failure documented between scheduled visits without extended loss-to-follow-up time [2]	Date of assessment of Progressive disease, relapse after CR/CRi, or treatment failure	Event
		Date of next scheduled response assessment [SA]	*Event [SA]*
5	No progressive disease, relapse after CR/CRi, or treatment failure (or death).	Date of last adequate response assessment [3]	Censored
6	New systemic therapy and/or HSCT started (prior to documented progressive disease, relapse after CR/CRi, treatment failure, or death).	Date of last adequate response assessment irrespective of new systemic therapy and/or HSCT date [3]	Censored
		Date of assessment of progressive disease, relapse after CR/CRi, treatment failure, or death [SA]	*Event [SA]*
7	Death without extended loss-to-follow-up time [2]	Date of death	Event
8	Death, progressive disease, relapse after CR/CRi, or treatment failure after an extended loss-to-follow-up time [2]	Date of last adequate response assessment [3] prior to event (prior to missed assessments)	Censored
		Date of death or event [SA]	*Event [SA]*
9	Death, progressive disease, relapse after CR/CRi, or treatment failure after an extended loss-to-follow-up time [2] from index date	Index Date	Censored
10	*Treatment discontinuation due to progressive disease, relapse after CR/CRi, or treatment failure before progressive disease, relapse after CR/CRi, treatment failure or death [SA]*	*Date of treatment discontinuation [SA]*	*Event [SA]*

[SA] Alternative rule for handling of events for supplementary estimand of EFS.
[1] Adequate baseline assessments are defined as at least one non-missing bone marrow sample or peripheral blood (ANC, platelets, and blasts) result at baseline.
[2] Extended loss-to-follow-up time is defined as the last non-missing adequate response assessment and event (death or disease relapse). Extended loss-to-follow-up time is 240 days. This cutoff is calculated based on the protocol scheduled procedure: the 28-day treatment cycle has ± 3 days window, response assessment is expected to be conducted every 3 months (with ± 30 days window). Thus, 2 consecutive scheduled assessments window is 2 × [30 × 3 + 30] = 240 days. Within extended loss-to-follow up time is defined as ≤240 days; after an extended loss-to-follow-up time is defined as: >240 days.
[3] An adequate response assessment is defined as an assessment where the investigator performed all the procedures required for assessment and documented the outcome.

7.4.4.2.2 Overall Survival

Overall Survival is defined as the time from the index date to the date of death due to any cause. Participants who do not die by the end of the study and participants lost to follow-up before data cutoff will be censored at the date that the participant was last known to be alive. OS will be estimated using Kaplan-Meier product-limit estimates for the mITT Population. The number and percentage of participants with an event or who were censored will be presented along with the range of values (including and excluding censored participants). The 25th percentile, median and 75th percentile along with corresponding 95% CIs based on the Brookmeyer and Crowley method will also be presented. Landmark analyses (OS rates, 95% CI, and number of participants at risk) will occur at 6, 12, 18, and 24 months from the index date. Additionally, plots of the Kaplan-Meier estimates will be provided. A by-participant listing of the derived efficacy data used for determining OS will be provided.

7.4.4.2.3 MRD-negative Response Rates

The MRD-negative response rate will be analyzed using the same statistical methodologies as applied to the primary efficacy endpoint, as described in Section 7.4.2, for the mITT Population. A by-participant listing of the derived efficacy data used for determining the MRD-negative CR rate will be provided.

7.4.4.2.4 Time to MRD-negative Response

Time to MRD-negative response will be summarized using descriptive statistics by treatment group and only for participants who are responders for the mITT Population.

7.4.4.2.5 TI Rate

The TI rate will be analyzed using the same statistical methodologies as applied to the primary efficacy endpoint for the mITT Population, described in Section 7.4.2. A by-participant listing of the derived efficacy data used for determining the TI rate will be provided.

7.4.4.2.6 Clinical Response and Genetic Mutations and/or Gene Expression Markers

Analysis of clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response will be detailed in a separate document and is outside the scope of this SAP.

7.4.4.3 Part 3

7.4.4.3.1 Overall Response Rate

The number (%) of participants and 95% exact binomial CIs of the percentage of overall responders and non-overall responders (along with criteria for non-response) will be summarized for the Part 3 Safety Population. The number (%) of participants and 95%

exact binomial CIs for overall response, comprised of the combined rates of CR, CRi, CRh, MLFS, and PR will be summarized. A by-participant listing of the ORR will be provided. A sensitivity analysis based on the RE Population may also be conducted.

7.4.4.3.2 Overall Survival

Overall Survival is defined as the time from the index date to death due to any cause. Participants who do not die by the end of the study will be censored at the date that the participant was last known to be alive. OS will be estimated using Kaplan-Meier product-limit estimates for the Part 3 Safety Population. Participants who do not die by the end of the study will be censored at the last date the participant is known to be alive.

The number and percentage of participants with an event or who were censored will be summarized. The 25th percentile, median and 75th percentile (along with corresponding 95% CIs), will also be presented. Landmark analyses (OS rates, 95% CI, and number of participants at risk) will occur at 6, 12, 18, and 24 months post-first dose. Additionally, a plot of the Kaplan-Meier estimates will be provided. A by-participant listing of the derived efficacy data used for determining OS will be provided.

7.4.4.3.3 Clinical Response and Genetic Mutations and/or Gene Expression Markers

Analysis of clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response will be detailed in a separate document and is outside the scope of this SAP.

7.4.5 Statistical/Analytical Issues

7.4.5.1 Interim Analysis

An interim futility analysis of the CR/CRi rates is planned in Part 2 for the first CCI randomized RARA-positive participants and will be performed after approximately CCI randomized participants have been on treatment for approximately 3 months or discontinued treatment earlier than 3 months. The study may be terminated at this interim analysis for futility if the 1-sided p-value from the Fisher's exact test comparing the CR/CRi rates (tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine) is CCI. The non-binding futility bound is derived using a Hwang-Shi-DeCani (HSD) spending function with gamma = -2 (Hwang 1990). Refer to Section 7.4.2 for a description of the analysis of the CR/CRi rate.

Administrative interim analyses may be performed after approximately 25% and 75% (CCI) of participants have had approximately 3 cycles of treatment. All interim analyses in Part 2 will be conducted on mITT, RE, and/or PP Populations, as deemed necessary. No multiplicity adjustments are needed since the study will not be stopped for efficacy until the primary analysis.

7.4.5.2 Multiplicity Adjustments

Multiplicity adjustment is not applicable. The formal hypothesis testing is only performed on the primary efficacy endpoint CR/CRi rate on the mITT Population. CR/CRi rate will be formally tested at the 5% level (one-sided). No formal hypotheses testing will be performed for the secondary endpoints.

7.4.5.3 Examination of Subgroups

To determine whether the treatment effect is consistent across various subgroups, subgroup analyses of the CR/CRi rate in Part 2 will be performed based on the participant subgroup categories listed below.

- Age Group:
  - ≥18 to <65
  - ≥65 to <75
  - ≥75
- Gender:
  - Female
  - Male
- Race:
  - Asian
  - Black or African American
  - White
  - Other/Multiple
- Geographical Region:
  - North America
  - France
- ECOG Performance Status:
  - 0 or 1
  - 2
  - 3
- TP53:
  - Mutated
  - Wild type
- IDH1/IDH2:
  - IDH1 mutated/IDH2 wild type
  - IDH1 wild type/IDH2 mutated
  - IDH1 wild type/IDH2 wild type
    IDH1 mutated/IDH2 mutated

- FLT3, ITD, or TKD:
  - Any or all mutated
  - Other

- NPM1:
  - Mutated
  - Wild type

A forest plot of the estimated treatment effect along with 95% CIs of CR/CRi rate will be provided by the subgroup factors listed above. A subgroup analysis may not be performed if the number of participants in the subgroup in each treatment group is not sufficiently large (e.g., <10%). Additional subgroup analyses may be performed post-hoc, as appropriate.

7.5 Pharmacokinetic Evaluation

The PK analyses will be provided in a separate report and is outside the scope of this SAP.

7.6 Safety Evaluation

Safety analyses will be carried out for the Part 1, 2, and 3 Safety Populations. All safety data from participants in Part 2 who received venetoclax/azacitidine but were not randomized will be listed separately. For safety analyses presented by study visit, the baseline value will be defined as the last non-missing value reported prior to first study drug administration.

7.6.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study up until the last dose of study drug + 30 days. TEAEs will be summarized by study part, treatment group and total (Part 2 only).

Summaries of the number and fraction of participants with the Selected AEs in Table 11 will be presented for Part 2. The searching strategy for Selected AE groups and their associated SMQ, HLT, or CMQ is listed in Table 11.

Table 11 Search Strategy for Selected TEAE Groups

Selected TEAE Group	Search Strategy
Rash	HLT *Rashes, eruptions, and exanthems NEC*
	Hypersensitivity (SMQ) broad search
Pain	HLT *Pain and discomfort NEC*
	HLT *Bone Related Signs and Symptoms*
	HLT *Musculoskeletal and Connective Tissue Pain & Discomfort*
Hypertriglyceridemia	HLT *Elevated triglycerides*

	PT *Blood triglycerides increased*
	PT *Blood triglycerides abnormal*
Infections (all)	SOC *Infections and infestations*
Pneumonia/Respiratory infections	*Infective pneumonia (SMQ)* narrow search
Sepsis	*Sepsis (SMQ)* narrow search
Febrile neutropenia	PT *Febrile neutropenia*
Differentiation syndrome	PT *Differentiation syndrome*
Anemia/Red blood cell count decreased	*Hematopoietic erythropenia (SMQ)* narrow search
Thrombocytopenia/Platelet count decreased	*Hematopoietic thrombocytopenia (SMQ)* narrow search
Leukopenia/White blood cell count decreased	*Hematopoietic leukopenia (SMQ)* narrow search
Neutropenia/Neutrophil count decreased	*Hematopoietic leukopenia (SMQ)* narrow search filtered for any PT with "neutro"
Intracranial hypertension	HLT *Increased intracranial pressure disorders (in the SOC Nervous System Disorders)*
Elevated transaminases	PT *Transaminases elevated (in the investigations SOC)*
Arterial embolic and thrombotic events	*Embolic and thrombotic events (SMQ) Narrow search*
Venous embolic and thrombotic events	*Embolic and thrombotic events (SMQ) Narrow search*

Abbreviations: HLT = high-level term; MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified; PT = preferred term; SMQ = Standardized MedDRA Query; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: This list is based on MedDRA version 23.1 and will be updated based on the dictionary or relevant SMQ/HLT updates at the time of the analysis.

AEs with missing start and/or stop dates will be considered TEAEs. Imputation rules for partial and missing dates are described in Table 7.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 23.1 or higher. AEs are graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5. If an AE grade is missing, the previous worst grade under the same PT will be assigned if it is available, otherwise a grade of 4 will be assigned for classification purposes in the TLFs.

The CTCAE Grade will be summarized by grouping Grade 1 and Grade 2 together, then Grade 3 and Grade 4 together, as well as any grade for all relevant TEAE tables.

- Overall summary of the number of TEAEs, TEAEs by relationship to study drug, TEAEs by CTCAE grade, serious AEs (SAEs), SAEs related to study drug, selected TEAEs, TEAEs requiring concomitant medications, TEAEs leading to dose interruption, TEAEs leading to dose reduction of study drug, TEAEs leading to discontinuation of study drug, TEAEs leading to death
- TEAEs by SOC and PT

- TEAEs by PT
- TEAEs occurring in ≥10% of participants in any treatment group by PT
- TEAEs related to study drug by SOC and PT
- TEAEs related to study drug by PT
- TEAEs by CTCAE grade, SOC and PT
- TEAEs by CTCAE grade and PT
- SAEs by SOC and PT
- SAEs by PT
- SAEs occurring in ≥5% of participants in any treatment group by PT
- SAEs related to study drug by SOC and PT
- SAEs related to study drug by PT
- Selected TEAEs by PT
- Selected TEAEs related to study drug by PT
- Selected TEAEs with CTCAE Grade 3 or 4 by PT
- Selected TEAEs related to study drug with CTCAE Grade 3 or 4 by PT
- TEAEs requiring concomitant medications by SOC and PT
- TEAEs requiring concomitant medications by PT
- TEAEs related to study drug requiring concomitant medications by SOC and PT
- TEAEs related to study drug requiring concomitant medications by PT
- TEAEs leading to dose interruption of study drug by SOC and PT
- TEAEs leading to dose interruption of study drug by PT
- TEAEs leading to dose reduction of study drug by SOC and PT
- TEAEs leading to dose reduction of study drug by PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to discontinuation of study drug by PT
- TEAEs leading to death by SOC and PT
- TEAEs leading to death by PT

Summaries by SOC and PT will be ordered by descending incidence of SOC and descending incidence of PT within each SOC. At each level of summarization (e.g., any AE, SOC, and PT), participants experiencing more than one TEAE will be counted only once. In the summary of TEAEs by CTCAE grade, participants will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, participants will be counted once at the closest relationship to study drug. A TEAE will be considered related to study drug if it is related to at least one of the study drugs or relationship to all study drugs is missing.

Additionally, a summary of all deaths will be provided, including the number and percentage of deaths, deaths occurring within 30 days of last dose, deaths occurring later than 30 days of last dose, treatment-related deaths, and primary reason for death.

Adverse event data will be presented in data listings. SAEs, selected AEs, AEs requiring concomitant medications, AEs leading to dose interruption/dose reductions/discontinuation of study drug, AEs leading to death, and deaths will be presented in separate data listings.

For the Selected AE of (suspected) differentiation syndrome (DS), an additional table and/or listing for all cases of DS or suspected DS using the following algorithmic approach based on the Montesinos et al scoring system (Montesinos 2009) will be provided:

a. This will include i) all participants with investigator-reported PT = Differentiation Syndrome and ii) additional participants with ≥2 different AE or Vital Sign (VS) abnormalities from the table below, if:

- ≥2 of the AE or VS abnormalities started within 7 days of each other;
- the events occurred in ≤90 days of study drug start.

Criteria (Montesinos Sign/Symptom)	**Variable**	**Variable**
≥1 of these (pulmonary infiltrates or pleuropericardial effusion)	PT	Acute pulmonary oedema Acute respiratory distress syndrome Non-cardiogenic pulmonary edema Pulmonary congestion Pulmonary oedema Pleural effusion Pericardial effusion Acute interstitial pneumonitis Acute lung injury Atypical pneumonia Lower respiratory tract infection Lower respiratory tract inflammation Lung infection Lung infiltration Pneumonia Pneumonitis Pulmonary toxicity
≥1 of these (fever)	PT	Pyrexia Febrile neutropenia
	VS result	Temperature (any value ≥38.3)
≥1 of these (weight gain >5 kg)	PT	Capillary leak syndrome Fluid overload Fluid retention Generalized oedema Hydraemia Hypervolaemia Oedema Oedema peripheral
	VS result	Weight (any value >5 kg from baseline)
≥1 of these (hypotension)	PT	Hypotension
	VS result	Systolic blood pressure (any value <90 mmHg)

≥1 of these (dyspnea)	PT	Acute respiratory failure Cardiopulmonary failure Cardio-respiratory distress Cough Dyspnoea Respiratory arrest Respiratory distress Respiratory failure
≥1 of these (acute renal failure)	PT	Acute kidney injury Anuria Cardiorenal syndrome Hepatorenal failure Prerenal failure Renal failure Renal failure acute Renal impairment Renal injury
	Laboratory result	Creatinine (any value >26.52 µmol/L or 1.5 × above baseline)
("catch-all")	PT	Multi-organ failure

Abbreviations: PT = preferred term; VS = vital sign.

b. The DS listing will include for all cases found by the search strategy (a) above:

Demographics, details of the AE including PTs, severity, start and end dates, onset and duration of AE, study drug held or decreased, and dates.

The listing will also include whether an AE occurred with PT of Leukocytosis, Hyperleukocytosis, or White blood cell count increased, or laboratory results showing leukocyte count >10 Gi/L <7 days before or >7 days after AE of DS. For those participants, the maximum value of leukocyte count during <7 days before or >7 days after AE of DS (or grade if no laboratory value), and repeat cases of DS for participants who met the criteria more than once, separated by >14 days between recovery of earlier AE of DS and onset of new AE of DS, will be presented.

7.6.2 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the local laboratory and presented in Système International (SI) units. All clinical laboratory data (hematology, serum chemistry, coagulation, urinalysis, and pregnancy test) will be listed. Laboratory measurements identified as abnormal (i.e., outside the normal range) will be flagged in the listings.

Clinical laboratory measurements, including hematology, serum chemistry, and coagulation will be summarized by study part, treatment group and total (Part 2 only). Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Urinalysis parameters will be summarized using the following categories: “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”. A 3-by-3 contingency table will be presented to summarize the shift from the baseline category to the worst post-baseline category. Summary results will include the count and percentage of participants within each shift category and treatment group.

Where applicable, hematology and chemistry results for select parameters will be assigned a toxicity grade based on the NCI CTCAE, version 5.0. If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (e.g., separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

Six-by-six contingency tables will be presented for lab tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0; i.e., measurements did not meet any CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or missing grade. Summary results will include the count and percentage of participants within each shift category.

In addition, non-CTCAE-graded hematology, chemistry, and coagulation parameters will be summarized using the following categories: low, normal, high, and missing. A 4-by-4 contingency table will be presented to summarize the shift from the baseline category to the worst post-baseline category. Summary results will include the count and percentage of participants within each shift category and treatment group.

Prothrombin time will not be summarized and will only be available in a listing. International normalized ratio (INR) will be summarized.

7.6.2.1 Liver Safety Assessment

The following potentially clinically significant (PCS) criteria in liver function tests for alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin (TB), aspartate transaminase (AST), International Normalized Ratio (INR), and their combination are defined as follows. The participant’s worst post-baseline value (highest for all parameters and lowest for ALP, for combination values where ALP <2 × upper limit of normal [ULN]) will be used.

- ALT or AST >3 × ULN
- ALT or AST >5 × ULN
- ALT or AST >8 × ULN
- ALT or AST >10 × ULN
- ALT or AST >20 × ULN
- TB >2 × ULN

- ALP >1.5 × ULN
- INR >1.5
- ALT or AST >3 × ULN and TB >2 × ULN (*)
- ALT or AST >3 × ULN and INR >1.5 (*)
- ALT or AST >3 × ULN and ALP <2 × ULN and TB >2 × ULN (*)

(*) Combination of values measured within same day or within 1 day apart

The number and percentage of participants with potentially clinically significant values in liver enzymes and total bilirubin will be presented by study part, treatment group, and total (Part 2 only). A listing of participants who met above PCS criteria will be provided.

7.6.3 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.6.3.1 Vital Signs

Vital sign measurements will be summarized by study part, treatment group and total (Part 2 only). Descriptive statistics will be presented for results and change from baseline at each time point where vital signs were scheduled to be collected.

A shift from baseline to the worst post-baseline blood pressure category (normal to stage 2 hypertension) summary will be presented by treatment group and total (Part 2 only) according to each of the American College of Cardiology (ACC) and American Heart Association (AHA) 2017 guidelines as outlined in the table below.

Table 12 Vital Signs ACC/AHA Blood Pressure Categories

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 mmHg	and	<80 mmHg
Elevated	120 - 129 mmHg	and	<80 mmHg
Stage 1 Hypertension	130 - 139 mmHg	or	80 - 89 mmHg
Stage 2 Hypertension	≥140 mmHg	or	≥90 mmHg

Additionally, temperature will be summarized by treatment group and total (Part 2) for each visit according to CTCAE grading criteria guidelines as outlined in the table below.

Table 13 CTCAE Grading Criteria for Temperature

CTCAE Grade	Criteria
Grade 0	<38.0 degrees C (<100.4 degrees F)
Grade 1	38.0 – 39.0 degrees C (100.4 - 102.2 degrees F)
Grade 2	>39.0 – 40.0 degrees C (102.3 - 104.0 degrees F)
Grade 3	>40.0 degrees C (>104.0 degrees F) for ≤24 hrs
Grade 4	>40.0 degrees C (>104.0 degrees F) for >24 hrs

All vital signs data including scheduled and unscheduled time points will be presented in the participant data listings.

7.6.3.2 12-Lead Electrocardiogram

Twelve-Lead ECG continuous parameters (heart rate, PR Interval, QT Interval, QRS Duration, QTcF Interval) as calculated automatically by machine will be summarized by study part, treatment group and total (Part 2 only). Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

ECG recordings will be classified by the investigator as "normal," "abnormal, not clinically significant," or "abnormal, clinically significant." A 3-by-3 contingency table 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 participants within each shift category and treatment group.

Prolonged QTcF intervals will be summarized as QTcF measurements (msec) that are >450 msec, >480 msec, and >500 msec at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change >30 msec or >60 msec relative to the baseline value. Summary results will include the percentage of participants within each category and treatment group.

All ECG data including scheduled and unscheduled time points will be listed. Abnormalities occurring at any point in the study post-baseline will also be included in the ECG listing.

7.6.3.3 Physical Examination

Any abnormal clinically significant finding identified during the physical examination will be recorded as medical history or AE depending on when it started or worsened. Otherwise, no other physical examination data will be listed or summarized.

7.6.3.4 ECOG Performance Status

ECOG performance scores will be summarized by study part, treatment group, and total (Part 2 only). The number and percentage of participants will be presented by ECOG performance score (ranging from 0 to 5) at each time point where ECOG performance scoring was scheduled to be collected. The change from baseline by visit will be summarized. Additionally, 4-by-6 contingency table will be presented to summarize the shift from the baseline category to the worst post-baseline score. Summary results will include the count and percentage of participants within each shift category and treatment group. By-participant ECOG performance status results will be provided in a listing.

7.7 Determination of Sample Size

Up to approximately CCI participants will be treated in Part 1. The actual number of tamibarotene dose levels explored in combination with venetoclax/azacitidine, and the number of participants treated at each dose regimen, will vary depending on the totality of evaluated data (including safety, dose modifications, and tamibarotene PK data) from

participants treated with the tamibarotene/venetoclax/azacitidine combination. With CCI participants treated, there is approximately CCI% probability of observing at least 1 AE with an event rate of CCI%. With CCI participants treated, there is approximately CCI% probability of observing at least 1 AE with an event rate of CCI%.

Approximately CCI participants will be randomized in Part 2, which provides approximately CCI% power to detect a difference in CR/CRi rates between tamibarotene/venetoclax/azacitidine and venetoclax/azacitidine, with assumed CR/CRi rates of CCI% versus CCI% in the 2 groups, respectively, a 1:1 randomization, and a 1-sided alpha of CCI.

Part 3 of the study is exploratory in nature and the number of participants who will receive tamibarotene in addition to venetoclax/azacitidine will vary depending on the number of participants who experienced disease progression, relapse after initial CR or CRi response, or treatment failure when randomized and treated with venetoclax/azacitidine in Part 2.

7.8 Changes in the Conduct of the Study or Planned Analyses

The planned analyses outlined in this SAP include deviations from the protocol as outlined below:

- The Estimands table in the protocol (Table 7) has been modified (see Table 4 in the SAP).

8 AMENDMENT HISTORY

Version 2.0

The number of participants in Part 2 and the dosing regimen have been clarified. The timeline for response assessments, as well as the criteria have been detailed. The estimand framework for the primary objective in Part 2 has been added. The participant population used for the different analyses have been detailed. Clarification added that PK analyses are not in scope for this SAP.

Version 3.0

A Response Evaluable Population has been defined. Efficacy analyses for Part 2 may be conducted for the mITT, PP, and/or RE Populations, as appropriate. The definition of index date has been added, which is the date of randomization for Part 2 and the date of Cycle 1 Day 1 visit for Parts 1 and 3. TTE endpoints, such as EFS and OS, will be calculated from the index date, instead of the Cycle 1 Day 1 visit date. Additional details have been added to the subgroup analysis section.

The definition of protocol deviations has been updated. The definition of concomitant medications has been updated, and a definition of transfusion burden has been added. Additional details have been added about liver assessments and on how to address

missing AE grades. A search strategy for selected AE groups and their associated SMQ/HLT or CMQ has been added as an appendix.

Version 4.0

In Section 6.4.1, the following updates were made:

- The index date for Part 2 was changed to earlier of (date of randomization, Cycle 1 Day 1) to accommodate for all scenarios.
- Definitions of all response rates were clarified to represent the respective analysis population in the denominator.
- All time to response and duration endpoints were changed from months to days.
- It was specified that the date of the bone marrow aspirate will be used for determining the date of response.
- MRD-negative rate has been added to align with the protocol.
- Response definitions for participants with marrow blast clearance (<5%) were added based on Döhner 2022.

In Section 7.1, the following updates were made:

- Descriptions of the planned analyses for this study were added.
- Deleted Q1 and Q3 from the standard summary of continuous variables.
- Details of handling subcategories under a categorical variable were added.
- Formatting of decimal places has been modified to align with pivotal Study SY-1425-301.
- Testing and p-values for exploratory endpoints have been deleted.
- In Section 7.1.3.4, Table 8 has been updated to ensure that proper imputation methods are used for both events that should end prior to the treatment start date (e.g., prior cancer therapy) and events that should end after the treatment start date (e.g., concomitant medications).
- Section 7.1.3.6 was added to detail the imputation rules for missing date of birth and the calculation of age. Sections 7.1.3.7, 7.1.3.8, and 7.1.3.9 were added to detail the imputation rules for missing date of death, calculation of ECG data, and post-baseline missing values, respectively. For all analyses in Part 3, the baseline visit definition has been added.
- Rules in threshold values and text regarding scheduled/unscheduled visits was also added.

In Section 7.2, the following updates were made:

- Part 2 ITT Population was changed to include all randomized participants not just RARA-positive participants.
- Added PP Population to be aligned with the protocol.
- Clarified that participants who received only venetoclax and/or azacitidine will be assigned to the doublet treatment group in the Safety Population.

- To account for participants who received venetoclax and azacitidine in Part 2 but were not randomized, listings were added.
- It was specified that all efficacy analyses in Part 2 of the interim CSR will be based on the RE Population and in the final CSR will be based on the mITT and RE Populations.

In Section 7.3, the following updates were made:

- The populations to be used for various analyses of baseline data were updated and/or clarified.
- Baseline ECOG status of 4 was deleted to be in alignment with the protocol eligibility criteria.
- The bone marrow blast categories were updated for AML disease history.
- Clarification was added that a separate listing of prior and concomitant blood transfusions will be provided for each study part.
- Clarification was added to flag participants continuing in Part 3 in the Part 2 listings, where applicable.

In Section 7.4.1, time to response and duration of response based on the RE Population were added to be consistent with the response rate calculation.

In Section 7.4.5.3, the following updates were made:

- New subgroup analyses of CR/CRi rate based on additional mutation status have been added to find possible predictors.
- Subgroup analyses of OS were removed.

In Section 7.6, the following updates were made:

- Additional TEAE groups based on FDA feedback were added to Table 11.
- Detailed analysis of DS was added based on FDA feedback.
- A listing of all safety data from participants in Part 2 who received venetoclax/azacitidine but were not randomized was added.
- Details of the analyses that will be performed for urinalysis and prothrombin time were added.
- Box and whisker plots of change from baseline for specific labs were removed.

In addition to the changes noted above, updates were made throughout the document to note that MedDRA and WHO dictionaries will be using version 23.1 or higher to align with more current studies in the New Drug Application.

9 REFERENCE LIST

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