CLINICAL STUDY PROTOCOL

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

Protocol Number: SY-1425-202

Amendment Number: 5

Compound: Tamibarotene (formerly SY-1425)

Brief Title: Tamibarotene/Venetoclax/Azacitidine in Previously Untreated Patients Selected for RARA-positive AML (SELECT-AML-1)

Study Phase: 2

Sponsor Name: Syros Pharmaceuticals, Inc.

Legal Registered Address: Syros Pharmaceuticals, Inc
35 CambridgePark Drive, 4th Floor
Cambridge, MA 02140
USA

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INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and all applicable regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (DD MMM YYYY): _____

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study:

PPD

Syros Pharmaceuticals, Inc.

Date
(DD MMM YYYY)

CONTACT INFORMATION

Sponsor: Syros Pharmaceuticals, Inc.
35 CambridgePark Drive, 4th Floor
Cambridge, MA 02140
USA

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1.1 Synopsis

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

Brief Title: Tamibarotene/Venetoclax/Azacitidine in Previously Untreated Patients Selected for RARA-positive AML (SELECT-AML-1)

Rationale:

Tamibarotene (formerly SY-1425) is a potent and selective agonist of retinoic acid receptor alpha (RARα) being developed in combination with azacitidine in a novel genomically defined subset of patients with non-acute promyelocytic leukemia (non-APL) acute myeloid leukemia (AML), characterized by overexpression of *RARA* (McKeown 2017). Approximately 30% of patients with newly diagnosed (ND) AML are expected to be positive for *RARA* overexpression (de Botton 2020).

Currently, ND AML patients who are ineligible for standard induction therapy are increasingly receiving venetoclax/azacitidine combination as initial treatment. In a randomized study of such AML patients, the combination of azacitidine with venetoclax has demonstrated a high composite complete remission (CR) rate and a survival benefit compared to treatment with azacitidine monotherapy (DiNardo 2020). However, approximately one-third of patients failed to respond to the venetoclax/azacitidine combination (DiNardo 2020), supporting the existing need to improve upon the outcomes in this subpopulation.

In RARA-positive ND AML patients who are ineligible for standard induction therapy, tamibarotene plus azacitidine is associated with high CR rates and a rapid onset of response (de Botton 2020). Further, recent data demonstrate that monocytic features associated with resistance to venetoclax are significantly present in those RARA-positive patients who achieve a complete response with tamibarotene plus azacitidine (Section 4.2, Fiore 2020, Pei 2020). Consequently, adding venetoclax to the tamibarotene plus azacitidine combination may address an unmet need in RARA-positive AML, allowing for the treatment of both primitive AML that may be sensitive to venetoclax and more mature monocytic subpopulations that may respond to treatment with tamibarotene plus azacitidine. Given that tamibarotene, venetoclax, and azacitidine have distinct adverse event (AE) profiles, it is anticipated that the 3 drugs can be administered safely in combination.

This open-label Phase 2 study in adult RARA-positive, previously untreated AML patients who are ineligible for standard induction therapy will consist of 3 parts. In Part 1, the safety and tolerability of the tamibarotene/venetoclax/azacitidine combination will be evaluated, pharmacokinetics (PK) of tamibarotene will be assessed when co-administered with venetoclax/azacitidine, and the dosing regimen of the combination for evaluation in Part 2 will be selected. In Part 2, patients who are ineligible for standard induction therapy will be randomized to tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine. In Part 3, patients

treated with venetoclax/azacitidine in Part 2 who experience progressive disease, relapse after initial CR or complete remission with incomplete blood count recovery (CRi) response, or treatment failure (defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator) may receive tamibarotene in addition to venetoclax/azacitidine.

Inclusion Criteria:

Note: all inclusion/exclusion criteria should be met prior to the first dose of venetoclax/azacitidine on Cycle 1 Day 1 with the exception of the RARA-biomarker test result referenced in inclusion criterion 2, which should be positive by Cycle 1 Day 8 to continue treatment on study.

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Patients must be at least 18 years old at the time of signing of an informed consent.

2. All patients must have obtained a blood sample for RARA biomarker investigational assay testing prior to starting treatment on Cycle 1 Day 1. The results of the investigational biomarker assay for all patients must be confirmed as RARA-positive by Cycle 1 Day 8 to enroll (Part 1) or to be randomized (Part 2) in the study.

3. Patients must have ND, previously untreated non-APL AML with a bone marrow or peripheral blood blast count ≥20% and must be unlikely to tolerate standard intensive chemotherapy at the time of Cycle 1 Day 1 Visit due to age, performance status, or comorbidities based on at least one of the following criteria (Ferrara 2013):

   a. age ≥75 years old

   OR

   b. age <75 years old, with at least one of the following:

      - Eastern Cooperative Oncology Group (ECOG) performance status of 3
      - cardiac history of congestive heart failure (CHF) or documented ejection fraction (EF) ≤50%
      - pulmonary disease with diffusing capacity of the lungs for carbon monoxide (DLCO) ≤65% or forced expiratory volume in one second (FEV_1) ≤65%
      - creatinine clearance ≥30 mL/min to <45 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation
      - hepatic impairment with total bilirubin >1.5 to ≤3.0 × upper limit of normal (ULN)

- any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy, and reviewed and approved by the sponsor

4. Patients must have ECOG of 0 to 3 (if <75 years old) or 0 to 2 (if ≥75 years old).

5. Patients must have a white blood cell (WBC) count <25,000/µL at the time of initiation of study drug (leukapheresis may be performed and/or hydroxyurea may be administered to decrease the WBC count to <25,000/µL).

6. Patients must have minimum baseline organ function, as defined by:

   a. total bilirubin ≤3.0 × ULN (if <75 years old) or ≤1.5 × ULN (if ≥75 years old)

   b. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN or ≤5 × ULN (if documented liver infiltration with leukemia cells)

   c. creatinine clearance ≥30 mL/min (if <75 years old) or ≥45 mL/min (if ≥75 years old) based on the Cockcroft-Gault glomerular filtration rate estimation

7. Patients must have a high-sensitivity urine or serum pregnancy test (for females of childbearing potential) that is negative at the Screening Visit and immediately prior to initiation of treatment (first dose of study drug).

8. Patients must be willing and able to comply with the scheduled study visits, treatment plans, laboratory tests, use of 2 methods of birth control (including a barrier method) for women of childbearing potential (WOCBP) and male patients (as described in Appendix 4), and other procedures.

9. Patients must be capable of giving signed and dated Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent.

Exclusion Criteria

Note: all inclusion/exclusion criteria should be met prior to the first dose of venetoclax/azacitidine on Cycle 1 Day 1 with the exception of the RARA-biomarker test result referenced in inclusion criterion 2, which should be positive by Cycle 1 Day 8 to continue treatment on study.

Patients are excluded from the study if any of the following criteria apply:

1. Patients have APL.

2. Patients have known active central nervous system involvement with AML.

3. Participants with a history of other cancers must not be receiving active treatment (with radiation or chemotherapy) and must be free of disease for 2 years prior to the Screening Visit with the exception of localized prostate cancer treated with hormone

therapy, breast cancer treated with hormone therapy, localized basal cell carcinoma, non-melanoma skin cancer, or cervical carcinoma in situ.

4. Patients have an active, life-threatening, or clinically-significant uncontrolled systemic infection requiring hospitalization.

5. Patients have a known malabsorption syndrome or other condition that may impair absorption of study medication (e.g., gastrectomy).

6. Immunocompromised patients with increased risk of opportunistic infections, including known human immunodeficiency virus (HIV)-positive patients with CD4 counts ≤350 cells/mm^3 or history of opportunistic infection in the last 12 months. Note: To ensure that effective anti-retroviral therapy (ART), when used in eligible HIV-positive patients, is tolerated and that toxicities are not confused with investigational drug toxicities, patients should be on an established ART for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to the Screening Visit.

7. Patients have a known active or chronic hepatitis B or active hepatitis C virus (HCV) infection. Patients with a history of HCV infection who have completed curative therapy for HCV at least 12 weeks before the Screening Visit and have a documented undetectable viral load at the Screening Visit are eligible for enrollment.

8. Patients have other severe acute or chronic medical conditions (and/or psychiatric conditions or laboratory abnormalities) that may increase the expected risk to the patient (i.e., the risk associated with the study participation or study drug administration) or that may interfere with the interpretation of study results or, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

9. Patients received prior treatment with all-trans retinoic acid (ATRA) or systemic retinoid for a hematologic malignancy.

10. Patients have not adequately recovered from a major surgery within 4 weeks of starting study drug administration.

11. Prior treatment (before Cycle 1 Day 1) for the diagnosis of AML, MDS, or antecedent hematologic malignancy with any hypomethylating agent, venetoclax, chemotherapy, or hematopoietic stem cell transplantation (HSCT), with the exception of prior treatment with hydroxyurea.

12. Patients with a diagnosis of hypervitaminosis A or patients taking vitamin A supplements >10,000 IU/day, unless treatment is discontinued at least 7 days prior to the first dose of the study drug.

13. Patients received any other investigational agents within 4 weeks of the Screening Visit or <5 half-lives since completion of previous investigational therapy have elapsed, whichever is shorter.

14. Patients require concurrent treatment with any investigational or approved oncology agent, except for hydroxyurea.
15. Patients with Grade ≥2 hypertriglyceridemia, defined as >300 mg/dL (Common Terminology Criteria for Adverse Events [CTCAE], version 5).
16. QTc >450 msec for male patients, QTc >470 msec for female patients, or QTc >480 msec in male or female patients with bundle branch block based on triplicate electrocardiogram (ECG) readings at the Screening Visit. NOTE: The QTc in this study should be the QT interval corrected for heart rate according to Fridericia formula (QTcF).
17. Pregnant females, breastfeeding females, and males not willing to comply with contraceptive requirements (as described in Appendix 4) or females of childbearing potential not willing to comply with contraceptive requirements (as described in Appendix 4).
18. Patients who have a hypersensitivity to tamibarotene, azacitidine, venetoclax or to any of their excipients.
19. Patients for whom treatment with tamibarotene, azacitidine, or venetoclax is contraindicated.
20. Protected persons (legally protected adults [under judicial protection, guardianship, or supervision] and persons deprived of their liberty).

Objectives and Endpoints:

OBJECTIVES	ENDPOINTS
Part 1	
Primary	
• Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine combination in RARA-positive, previously untreated AML patients to inform Part 2 dose and regimen of the tamibarotene/venetoclax/azacitidine therapy	• Incidence of AEs, changes in clinical laboratory values, ECGs, and vital sign measurements
Secondary	
• Characterize the ORR of tamibarotene/venetoclax/azacitidine combination	• Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of patients who achieve overall response
• Characterize PK of tamibarotene when administered as a part of tamibarotene/venetoclax/azacitidine therapy	• Tamibarotene PK parameters
Exploratory	
• Evaluate AML molecular features associated with response and with loss of response to treatment	• Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response

OBJECTIVES	ENDPOINTS
Part 2	
Primary	
• Characterize and compare the CR/CRi rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• CR/CRi assessment; CR/CRi rate is estimated by the proportion of patients who achieve CR/CRi (as determined by the investigator[a])
Secondary	
• Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine in RARA-positive, previously untreated AML patients	• Incidence of AEs, changes in clinical laboratory values, ECGs, and vital sign measurements
• Characterize and compare CR rate and CR/CRh rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• CR assessment; CR rate is estimated by the proportion of patients who achieve CR (as determined by the investigator[a]) • CR/CRh assessment; CR/CRh rate is estimated by the proportion of patients who achieve CR/CRh (as determined by the investigator[a])
• Characterize duration of CR, duration of CR/CRi, and duration of CR/CRh of tamibarotene/venetoclax/azacitidine combination versus venetoclax/azacitidine	• Duration of CR, defined as 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 • Duration of CR/CRi, defined as 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 • Duration of CR/CRh, defined as 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
• Characterize time to CR, time to CR/CRi, and time to CR/CRh of tamibarotene/venetoclax/azacitidine combination versus venetoclax/azacitidine	• Time to CR, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of the first documented evidence of CR as determined by the investigator[a] • Time to CR/CRi, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of the first documented evidence of CR/CRi as determined by the investigator[a] • Time to CR/CRh, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of the first documented evidence of CR/CRh as determined by the investigator[a]
• Characterize and compare the ORR of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of patients who achieve overall response

OBJECTIVES	ENDPOINTS
Exploratory	
• Characterize and compare EFS of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• EFS, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of progressive disease, relapse after CR or CRi, treatment failure[b], or death from any cause
• Characterize and compare OS of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Duration from the date of Cycle 1 Day 1 Visit to the date of death due to any cause
• Characterize and compare MRD-negative response rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Assessment of MRD; MRD-negative response rate estimated by the proportion of patients achieving an MRD-negative CR by multiparameter flow cytometry, qPCR, or next generation sequencing, as determined by the investigator[a]
• Characterize time to MRD-negative response of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Time to MRD-negative response, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of achieving an MRD-negative CR by multiparameter flow cytometry, qPCR, or next generation sequencing, as determined by the investigator[a]
• Characterize and compare the TI rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• TI rate, defined as the proportion of patients who achieve TI. TI is a period of at least 56 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
• Characterize PK of tamibarotene when co-administered with venetoclax and azacitidine	• Plasma tamibarotene PK parameters
• Evaluate AML molecular features associated with response and with loss of response to treatment	• Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response
Part 3	
Exploratory	
• Characterize the ORR after treatment with tamibarotene/venetoclax/azacitidine for patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine	• Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of patients who achieve overall response
• Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine in patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine	• Incidence of AEs, changes in clinical laboratory values, ECGs, and vital sign measurements
• Characterize the OS of tamibarotene/venetoclax/azacitidine in patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine	• Duration from the date of first dose in Part 3 to the date of death due to any cause

OBJECTIVES	ENDPOINTS
• Evaluate AML molecular features associated with response and with loss of response to treatment	• Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete blood count recovery; ECG = electrocardiogram; EFS = event-free survival; ELN = European LeukemiaNet; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; OS = overall survival; ORR = objective response rate; PK = pharmacokinetic(s); PR = partial remission; qPCR = quantitative polymerase chain reaction; RBC = red blood cell; TI = transfusion independence.

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

[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.

Overall 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-APL AML patients who are unlikely to tolerate standard intensive chemotherapy at the time of study entry.

In Part 1, tamibarotene will be administered at 6 mg twice per day (BID) starting dose in combination with venetoclax/azacitidine, which will be administered at the approved dose and schedule (VIDAZA United States Prescribing Information [USPI]/VIDAZA Summary of Product Characteristics [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, patients 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 patients who experience progressive disease, relapse after initial CR or CRi response, or treatment failure (see Part 3 Design section below). Enrollment is planned in the United States (US) and France.

Start of Venetoclax/Azacitidine Therapy

Currently, ND AML patients who are ineligible for standard induction therapy are increasingly receiving venetoclax/azacitidine combination as the SOC therapy. 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.

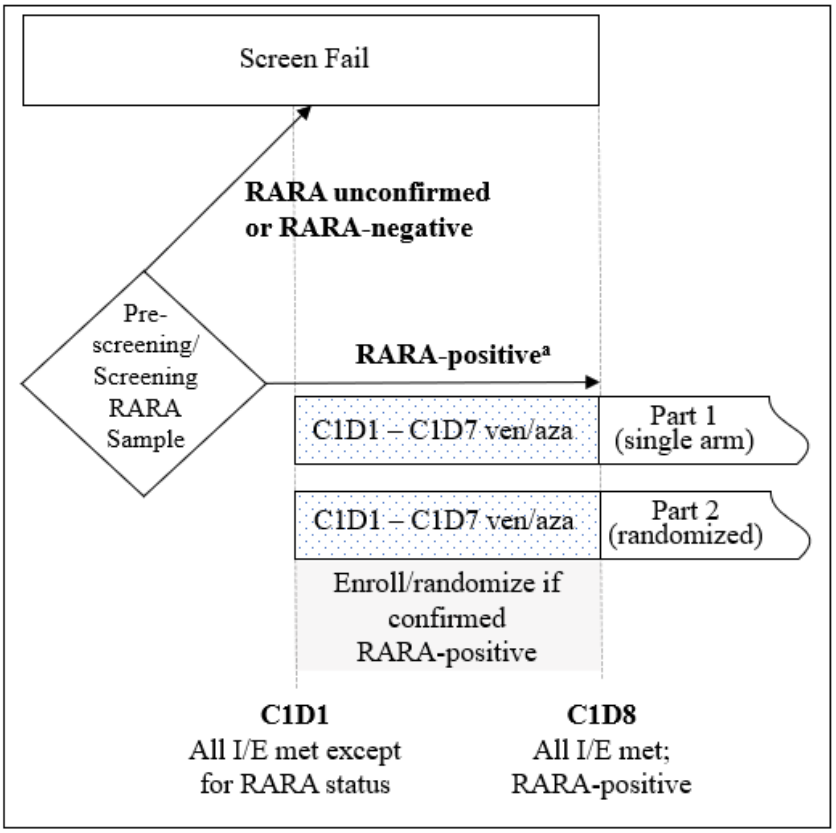
- Begin SOC venetoclax/azacitidine treatment on Cycle 1 Day 1 using protocol-defined regimen and doses while awaiting pre-treatment screening RARA biomarker test result.

- Begin venetoclax/azacitidine treatment on Cycle 1 Day 1 after the patient 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. Patients 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.



Abbreviations: AE = adverse event; I/E = inclusion/exclusion [criteria]; C1DX = Cycle 1 Day X; RARA = retinoic acid receptor alpha.

[a] If the patient discontinues treatment or study participation prior to confirmation of screening RARA results and RARA-positivity is confirmed by C1D8, the patient 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 [redacted] patients may be enrolled in Part 1. Enrolled RARA-positive patients 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 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 patients receiving concomitant CCI and P-gp inhibitors [Table 4]), 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 patients who have been confirmed as RARA-positive.

If needed to manage toxicity, the study drugs will be modified as outlined in Section 6.5. After Cycle 1 data for at least 6 patients 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 patients 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 patients to tolerate the approved regimen of venetoclax/azacitidine. A modified regimen would consist of a reduced dose of tamibarotene (Table 6) 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 patients 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 patients will be randomized in Part 2 of the study. RARA-positive patients 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 patients receiving concomitant CCI and P-gp inhibitors [Table 4]) 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 (Section 6.1.1). 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, patients will receive venetoclax daily beginning on Day 1 through Day 28 for each cycle, with dose modifications as needed for toxicity, as outlined in Table 5 (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 patients who have been confirmed as RARA-positive.

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

Part 3 Design

Part 2 patients 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

Patients will undergo safety and response evaluations throughout their study participation as detailed in the Schedules of Activities (Section 1.3). Response will be assessed by the investigator in alignment with European LeukemiaNet (ELN) AML criteria (Döhner 2017), with complete remission with partial hematologic recovery (CRh) assessed according to Bloomfield 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 patient achieves a 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 patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed. Subsequent bone marrow aspirates for all patients 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 patient achieves a CR/CRi within Cycle 1 response assessment(s), the Cycle 2 EoC bone marrow aspirate is not required.

The AE profiles of tamibarotene and venetoclax/azacitidine combination are well-documented and largely do not overlap (tamibarotene Investigator's Brochure [IB], VENCLEXTA USPI, VENCLYXTO SmPC). Consequently, in this study, it is recommended that hematologic toxicities and non-hematologic toxicities typically associated with the venetoclax/azacitidine

combination (VENCLEXTA USPI, VENCLYXTO SmPC) should be managed with adjustments to venetoclax/azacitidine administration. AEs that have been identified as tamibarotene adverse drug reactions (ADRs; tamibarotene IB) should be managed via modification to tamibarotene administration (Section 6.5). In patients receiving triplet combination therapy, if improvements in blood counts or relevant toxicities are not observed with recommended adjustments to venetoclax/azacitidine, an adjustment to the tamibarotene dose should be considered.

All patients who remain on study may continue to receive study drug until experiencing an unacceptable toxicity, disease progression, relapse, decision to pursue post-remission therapy (such as HSCT) or an alternative anticancer therapy, patient withdraws consent, or the investigator determines it is in the best interest of the patient to discontinue study drug. Note: Part 2 patients 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) patients, 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, patients 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. Patients 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 overall survival status for up to 3 years after discontinuation of study drug.

There will be no formal Independent Data Monitoring Committee (IDMC). The sponsor will provide oversight of safety and tolerability at regularly scheduled intervals (and ad hoc if needed) via Safety Review Team (SRT) meetings as detailed in the SRT Charter. In addition, regularly scheduled reviews of safety and tolerability will be performed by the sponsor in collaboration with the study investigators in Part 1 of the study. These reviews will inform the dose of tamibarotene to be combined with venetoclax/azacitidine in Part 2 of the study. Administrative interim analyses will be performed by the sponsor personnel or designee.

Number of Patients:

- Part 1: approximately CCI patients will be screened with up to approximately CCI patients enrolled to receive study drug
- Part 2: approximately CCI patients will be screened with approximately CCI patients randomized to receive study drug
- Part 3: approximately CCI patients treated with venetoclax/azacitidine in Part 2 will be enrolled

Intervention Groups and Duration:

- Part 1: tamibarotene/venetoclax/azacitidine
- Part 2: tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine
- Part 3: tamibarotene/venetoclax/azacitidine

Patients will receive treatment until they meet study drug discontinuation criteria, as described in the Overall Design. Patients will be followed for up to 3 years after discontinuation of study drug.

Statistical Methods:

Sample Size

Up to approximately CCI patients will be treated in Part 1. The actual number of tamibarotene dose levels explored in combination with venetoclax/azacitidine, and the number of patients treated at each dose regimen, will vary depending on the totality of evaluated data (including safety, dose modifications, and tamibarotene PK data) from patients treated with the tamibarotene/venetoclax/azacitidine combination. With CCI patients treated, there is approximately CCI% probability of observing at least 1 AE with an event rate of CCI%. With CCI patients treated, there is approximately CCI% probability of observing at least 1 AE with an event rate of CCI%.

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

Statistical Analysis

Part 1 Primary Endpoint Analysis

The number and percentage of patients with AEs, including AEs leading to dose modifications or discontinuations, and serious AEs (SAEs) will be summarized. Laboratory values and changes in values from baseline will be summarized descriptively by visit, and shift tables will be provided showing changes in National Cancer Institute (NCI) CTCAE (version 5) grade from baseline to worst grade postbaseline. Descriptive summaries will be provided for ECG and vital sign values, changes in values from baseline, and categorical summaries. The number and percentage of patients with dose modifications will be summarized.

Part 1 Secondary Endpoint Analysis

The estimated objective response rate (ORR) will be provided with corresponding 95% exact binomial confidence intervals (CIs).

Part 2 Primary Endpoint Analysis

CR/CRi rate and 95% exact binomial CIs will be calculated by treatment group. The Fisher's exact test will be applied to compare the CR/CRi rates between the 2 treatment groups.

Part 2 Secondary Endpoint Analyses

The number and percentage of patients with AEs, including AEs leading to dose modifications or discontinuations, and SAEs will be summarized. Laboratory values and changes in values from baseline will be summarized descriptively by visit, and shift tables will be provided showing changes in NCI CTCAE (version 5) grade from baseline to worst grade postbaseline. Descriptive summaries will be provided for ECG and vital sign values, changes in values from baseline, and categorical summaries. The number and percentage of patients with dose modifications will be summarized.

The difference in CR/CRi rate between the 2 treatment groups and corresponding 95% CIs will be calculated.

CR rate and 95% exact binomial CIs will be calculated by treatment group. The Fisher's exact test will be applied to compare the CR rates between the 2 treatment groups.

CR/CRh rate and 95% exact binomial CIs will be calculated by treatment group. The Fisher's exact test will be applied to compare the CR/CRh rates between the 2 treatment groups.

Kaplan-Meier estimation of median duration of CR, median duration of CR/CRi, and median duration of CR/CRh and respective 95% CIs will be presented by treatment group.

Time to CR, time to CR/CRi, and time to CR/CRh will be summarized descriptively for the 2 treatment groups.

ORR rate and 95% exact binomial CIs will be calculated by treatment group. The Fisher's exact test will be applied to compare the ORR rates between the 2 treatment groups.

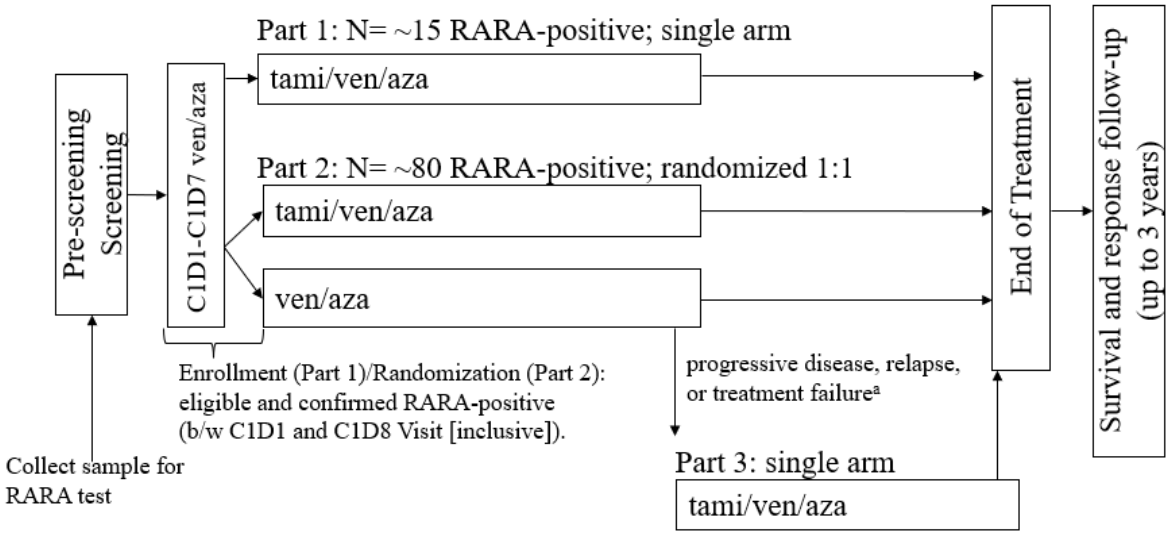
Part 2 Interim Analysis

An interim futility analysis of the CR/CRi rates is planned in Part 2 for the first 40 treated RARA-positive patients and will be performed after the 40th randomized patient has received approximately 3 months of study drug or has discontinued treatment due to disease progression, withdrawal of consent, or death. 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-Shih-DeCani (HSD) spending function with gamma = -2 (Hwang 1990).

Administrative interim analyses may be performed after approximately 25%, 50%, and 75% ([CCI redacted]) patients have had 3 cycles of treatment. No multiplicity adjustments are needed since the study will not be stopped for efficacy until the primary analysis.

Data Monitoring/Other Committee: There will be no formal IDMC. The sponsor will provide oversight of safety and tolerability at regularly scheduled intervals (and ad hoc if needed) via SRT meetings as detailed in the SRT Charter. In addition, regularly scheduled reviews of safety and tolerability will be performed by the sponsor in collaboration with the study investigators in Part 1 of the study. These reviews will inform the dose of tamibarotene to be combined with venetoclax/azacitidine in Part 2 of the study. Administrative interim analyses will be performed by the sponsor personnel or designee.

1.2 Schema



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.

1.3 Schedules of Activities

Table 1: Part 1 and Part 2 Schedule of Activities

Study Day (D/d)	Pre-screening (a) Day -30 to C1D1	Screening (a) Day -30 to C1D1	Cycle 1, 28 Days						Cycle 2, 3 28 Days				Cycles 4+ 28 Days (b)				EoT (c)	Safety Follow-up (d) 30d post EoT (±3d)	Disease Follow-up (e) q3mo post EoT (±30d)	Survival Follow-up (f) q3mo post EoT (±30d)
			D1 (g)	D2-7 ±2d	D8 ±1d	D15 ±1d	D22 ±1d	EoC (h) D28 ±3d	D1 (i)	D2-7 ±2d	D15 ±1d	EoC (h) D28 ±3d	D1 ±3d (i)	D2-7 ±2d	D15 ±2d (j)	EoC (h) D28 ±3d				
Prescreening Informed Consent	X																			
Main Informed Consent		X																		
Eligibility Review (k)		X	X (k)																	
Enrollment **(Part 1)** / Randomization **(Part 2)** (l)			X																	
Medical History (m)		X	X																	
Demographics		X																		
ECOG Status		X	X						X				X				X	X		
Height		X																		
Weight		X	X						X				X				X	X		
Vital Signs (n)		X	X	X (n)	X	X	X		X	X (n)	X		X	X (n)	X		X	X		
Physical Examination (o)		X (o)	X (o)		X	X	X		X		X		X				X (o)	X (o)	X	
Hematology (p), (q)		X	X		X	X	X	X (q)	X		X	X (q)	X			X (q)	X	X	X	
Serum Chemistries (p)		X	X		X	X	X		X		X		X				X	X		
Coagulation (p)		X	X						X				X				X	X		
Triglycerides, Total Cholesterol (p)		X	X						X				X				X	X		
Urinalysis (p)		X	X						X				X				X	X		
Pregnancy Test (r)		X	X						X				X				X	X		
Triplicate ECG (s)		X			X (s)		X (s)				X (s)				X (s)					
AE Monitoring (t)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior/Concomitant Medication Review (u)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
RBC and Platelet Transfusions Recorded (v)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dosing Compliance/Diary Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Day (D/d)	Pre-screening (a) Day -30 to C1D1	Screening (a) Day -30 to C1D1	Cycle 1, 28 Days						Cycle 2, 3 28 Days				Cycles 4+ 28 Days (b)				EoT (c)	Safety Follow-up (d) 30d post EoT (±3d)	Disease Follow-up (e) q3mo post EoT (±30d)	Survival Follow-up (f) q3mo post EoT (±30d)
			D1 (g)	D2-7 ±2d	D8 ±1d	D15 ±1d	D22 ±1d	EoC (h) D28 ±3d	D1 (i)	D2-7 ±2d	D15 ±1d	EoC (h) D28 ±3d	D1 ±3d (i)	D2-7 ±2d	D15 ±2d (j)	EoC (h) D28 ±3d				
Subsequent Anticancer Therapies (w)																		X		X
Response Assessment (q), (x)								X (q), (x)				X (q), (x)				X (q), (x)	X		X	
Part 1: Bone Marrow Aspirate		X (y)						X (i), (z)				X (i), (z)				X (i), (z)	X (z)		X (z)	
Part 2: Bone Marrow Aspirate		X (y)				X D14-D21 (aa)		X (i), (aa), (bb)				X (i), (aa)				X (i), (aa)	X (aa)		X (aa)	
Overall Survival																				X
Tamibarotene (i), (cc)					Dosing D8-D28 of each Cycle (i), (cc)															
Azacitidine (i), (dd), (ee)			X	X (ee)					X (i)	X (ee)			X (i)	X (ee)						
Venetoclax (i), (ff)			X	X	X (ff)	X (ff)	X (ff)	X	X (i)	X	X (ff)	X	X (i)	X	X	X				
Blood Sample for RARA Biomarker Test	X																X			
Blood Sample for Exploratory Research (gg)	X		X					X (gg)				X (gg)				X (gg)	X			
Blood Sample for CDx Development	X																			
Part 1 Blood for PK (hh)					X		X				X									
Part 2 Blood for PK (ii)						X	X				X									

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CDx = companion diagnostic; CR = complete remission; CRi = CR with incomplete blood count recovery; CXDX = Cycle X, Day X; D/d = day(s); ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EDC = electronic data capture [system]; ELN = European LeukemiaNet; EoC = End of Cycle; EoT = End of Treatment; HSCT = hematopoietic stem cell transplantation; MRD = minimal residual disease; PK = pharmacokinetic(s); q3mo = every 3 months; RBC = red blood cell; RARA = retinoic acid receptor alpha; SAE = serious adverse event; SOC = standard of care.

(a) Pre-screening (to evaluate RARA status) and screening assessments will be performed within 30 days of C1D1. Pre-screening and Screening Visits may be combined. If the Pre-screening and Screening Visits are not combined, Screening assessments may occur on C1D1 but must be completed and results reviewed prior to dosing on C1D1.

(b) Cycle 4 schedule should be followed for all subsequent cycles.

(c) An EoT Visit should occur within 3 days of the last dose of study drug (or within 3 days of decision to permanently stop study 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. If the EoT Visit occurs ≥30 days after the last dose of study drug, it may be combined with the Safety Follow-up Visit.
(d) A Safety Follow-up Visit should occur 30 days (±3 days) after the EoT Visit and before the start of any subsequent anticancer therapy. If the EoT Visit occurs ≥30 days after the last dose of study drug, it may be combined with the Safety Follow-up Visit.
(e) Patients who have not progressed/relapsed will enter the Disease Follow-up period. Visits should occur every 3 months for response assessment for up to 3 years after discontinuation of study drug or until disease progression/relapse, whichever occurs first. Disease Follow-up Visit window is ±30 days.
(f) Patients who progress/relapse will be followed to document the start of subsequent anticancer therapy, the date of disease progression/relapse, and overall survival status by telephone (or another appropriate method) for up to 3 years after discontinuation of study drug. Survival Follow-up Visit contact window is ±30 days.
(g) C1D1 assessments must be performed prior to study drug administration.
(h) EoC Visit should occur on Day 28 (±3 days) of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.).
(i) Response assessment results must be evaluated prior to start of Cycles 2, 3, and 4, followed by every third cycle (7, 10, 13, etc.). The timing of cycle start for these cycles will be determined as outlined in Section 6.1.1 and Table 5. **In Part 2 of the study only,** patients being treated with venetoclax/azacitidine who experience progressive disease, relapse after initial CR or CRi response, or treatment failure (failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator) will begin subsequent treatment cycle in Part 3, where tamibarotene will be added to their regimen (see Table 2).
(j) Cycle 4 only.
(k) All eligibility requirements (with exception of RARA test results [inclusion criterion 2]) must be met prior to venetoclax/azacitidine dosing on C1D1. Confirmation of all eligibility requirements (including confirmation of RARA-positive status) is required for enrollment (Part 1)/randomization (Part 2) and must occur by C1D8. Eligibility is based on meeting the inclusion/exclusion criteria on C1D1. While RARA results from screening may not become available until after C1D1, any patient confirmed to be RARA-positive by C1D8 will be enrolled (Part 1)/randomized (Part 2), even if the patient discontinues treatment and/or discontinues the study prior to receiving RARA results.
(l) Enrollment (Part 1)/randomization (Part 2) can occur between C1D1 Visit and C1D8 Visit (inclusive) as soon as all eligibility requirements are met, including confirmation of patient's RARA-positive status (inclusion criterion 2). **For Part 2 patients** who are confirmed RARA-positive prior to C1D1, randomization can occur within 72 hours prior to the first dose of venetoclax/azacitidine to accommodate operational needs.
(m) For all enrolled (**Part 1**)/randomized (**Part 2**) patients, any untoward medical occurrences that happen before the first dose of venetoclax/azacitidine on C1D1 should be captured as a part of medical history.
(n) If administration of the 6th and 7th doses of azacitidine of the cycle is delayed to Days 8 and 9 (see footnote (dd)), the vital sign evaluation will shift from Days 6 and 7 to Days 8 and 9 to parallel azacitidine administration. C1D8 vital sign evaluation is required for all patients.
(o) Full physical examination will be performed at the Screening Visit, C1D1, EoT, and the Safety Follow-up Visit; abbreviated physical examination will be performed at other visits indicated (see Section 8.2.3).
(p) Safety laboratory assessments will be performed locally.
(q) Additional unscheduled hematology evaluations may be performed prior to commencement of the next treatment cycle to reflect the best AML response achieved.
(r) A pregnancy test (high-sensitivity urine or serum) must be performed for women of childbearing potential.
(s) ECG should be performed after an approximately 10-minute rest period, 2 to 4 hours after tamibarotene and/or venetoclax administration.
(t) For all enrolled (**Part 1**)/randomized (**Part 2**) patients, AEs and SAEs will be captured from the time of the first dose of venetoclax/azacitidine on C1D1 through the Safety Follow-up Visit. This will require collecting safety data for all treated patients from C1D1 onward (until RARA status is confirmed) to enable timely reporting (SAEs) and capture in the eCRF (AEs) upon enrollment (Part 1)/randomization (Part 2).

(u) For all enrolled (**Part 1**)/randomized (**Part 2**) patients, every medication within 30 days of C1D1 or at any time during the course of the study treatment, up to the Safety Follow-up Visit, must be documented.
(v) For all enrolled (**Part 1**)/randomized (**Part 2**) patients, all RBC and platelet transfusions received by the patient from 8 weeks prior to first dose of study drug on C1D1 through the Safety Follow-up period will be recorded.
(w) Subsequent anticancer therapies (including allogeneic HSCT) following EoT will be recorded.
(x) Response assessments will be performed at EoC Visit of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.), at the EoT Visit, and at each Disease Follow-up Visit, with additional assessments performed if clinically determined. If a patient achieves a CR/CRi at Cycle 1 EoC, the Cycle 2 EoC bone marrow aspirate is not required. Response assessments during Disease Follow-up visits where the bone marrow aspirates are not performed are based on hematology evaluation and physical examination findings.
(y) A screening bone marrow aspirate will be performed, with samples collected for local assessment of **blast count**, **cytogenetics**, **immunophenotype**, and **AML-associated gene mutations**. An additional aspirate sample should be collected if possible and sent to the **Central Laboratory** for **exploratory analyses**. Bone marrow samples collected within 30 days of C1D1 as a part of SOC are acceptable and in that setting a marrow would not need to be repeated for the sole purpose of gathering the exploratory sample; however, collection of the exploratory sample is encouraged. Anonymized reports will be uploaded to the EDC.
(z) **Part 1:** The bone marrow aspirate samples for local assessment of response (**blast count, cytogenetics, and assessment of MRD**) will be collected at the EoC Visit of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.), at the EoT Visit, and at every other visit during the Disease Follow-up period (every 6 months), with bone marrow aspirates collected at other times as clinically determined. If a patient achieves a CR/CRi at the Cycle 1 EoC Visit, the Cycle 2 EoC bone marrow aspirate is not required. Anonymized reports will be uploaded to the EDC. At each bone marrow aspirate draw, an additional aspirate sample will be collected and sent to the **Central Laboratory** for **exploratory analyses**.
(aa) **Part 2:** The bone marrow aspirate samples for local assessment of response (**blast count, cytogenetics, and assessment of MRD**) will be collected between Days 14 and 21 of Cycle 1, with venetoclax administration proceeding in alignment with ELN 2022 recommendations (Döhner 2022). For those with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required. For patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed. Subsequent bone marrow aspirates for all patients will be collected at the EoC Visit of Cycles 2 and 3, followed by every third cycle (6, 9, 12, etc.); at the EoT Visit; and at every other visit during the Disease Follow-up period (every 6 months), with bone marrow aspirates collected at other times as clinically determined. If a patient achieves a CR/CRi within Cycle 1 response assessment(s), the Cycle 2 EoC bone marrow aspirate is not required. Anonymized reports will be uploaded to the EDC. At each bone marrow aspirate draw, an additional aspirate sample will be collected and sent to the **Central Laboratory** for **exploratory analyses**.
(bb) For those with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required. For patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed.
(cc) Tamibarotene will only be administered to patients who have been confirmed as RARA-positive. For patients receiving tamibarotene/venetoclax/azacitidine, tamibarotene will be administered on Days 8 through 28 of each 28-day therapy cycle. On visit days when PK samples are collected, venetoclax and 1 dose of tamibarotene should be administered at the same time.
(dd) Patients may begin C1D1 using SOC treatment with venetoclax/azacitidine while awaiting RARA biomarker results to confirm eligibility (inclusion criterion 2). Azacitidine will be administered intravenously or subcutaneously as described in the most current VIDAZA USPI/VIDAZA SmPC.
(ee) Azacitidine will be administered each day on Days 1 through 7 of each 28-day therapy cycle. If dosing on Days 6 and 7 is not possible due to logistical limitations, these doses may be delayed to Days 8 and 9. Tamibarotene is permitted to overlap with azacitidine on Days 8 through 9 of this alternative schedule.
(ff) Patients may begin C1D1 using SOC treatment with venetoclax/azacitidine while awaiting RARA biomarker results to confirm eligibility (inclusion criterion 2). Venetoclax will be administered daily, as described in the most current VENCLEXTA USPI/VENCLYXTO SmPC with SOC modifications

consistent with ELN 2022 guidelines (Döhner 2022; Section 6.1.1; Table 5). On visit days when PK samples are collected, venetoclax and 1 dose of tamibarotene should be administered at the same time.

(gg) Blood samples will be collected for exploratory research at pre-screening, C1D1, at EoC Visit of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.), and at EoT. If a patient achieves a CR/CRi at the Cycle 1 EoC Visit, the Cycle 2 EoC blood sample is not required.

(hh) At C1D8 and C1D22 Visits, PK samples will be obtained: pre-dose, and at 0.5, 1, 2, 4, and 6 hours after tamibarotene dose. At C2D15 and C3D15, 1 sample will be collected and collection time/date recorded. The dose, time, and date of the 2 immediate prior doses (if applicable) of tamibarotene taken before the PK collection will be recorded. On visit days when PK samples are collected, venetoclax and the dose of tamibarotene should be administered at the same time. Additional details are provided in Section 8.4.

(ii) PK samples will be obtained only from patients receiving triplet combination therapy. At each applicable visit, 1 sample will be collected and collection time/date recorded. The dose, time, and date of the 2 immediate prior doses of tamibarotene taken before the PK collection will be recorded. On visit days when PK samples are collected, venetoclax and the dose of tamibarotene should be administered at the same time.

Table 2: Part 3 Schedule of Activities

	Cycle 1, 28 Days (a)						Cycle 2, 3 28 Days				Cycles 4+ 28 Days (b)				EoT (c)	Safety Follow-up (d)	Disease Follow-up (e)	Survival Follow-up (f)
Study Day (D/d)	**D1** (g)	**D2-7 ±2d**	**D8 ±1d**	**D15 ±1d**	**D22 ±1d**	**EoC** (h) **D28 ±3d**	**D1** (i)	**D2-7 ±2d**	**D15 ±2d**	**EoC** (h) **D28 ±3d**	**D1 ±3d** (i)	**D2-7 ±2d**	**D15 ±2d** (j)	**EoC** (h) **D28 ±3d**		**30d post EoT (±3d)**	**q3mo post EoT (±30d)**	**q3mo post EoT (±30d)**
ECOG Status	X						X				X				X	X		
Weight	X						X				X				X	X		
Vital Signs (k)	X	X (k)	X	X	X		X	X (k)	X		X	X (k)	X		X	X		
Physical Examination (l)	X (l)		X	X	X		X				X				X (l)	X (l)	X	
Hematology (m), (n)	X		X	X	X	X (n)	X			X (n)	X			X (n)	X	X	X	
Serum Chemistries (m)	X		X	X	X		X				X				X	X		
Coagulation (m)	X						X				X				X	X		
Triglycerides, Total Cholesterol (m)	X						X				X				X	X		
Urinalysis (m)	X						X				X				X	X		
Pregnancy Test (o)	X						X				X				X	X		
Triplicate ECG (p)			X		X				X				X					
AE Monitoring (q)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior/Concomitant Medication Review (r)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
RBC and Platelet Transfusions Recorded (s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dosing Compliance/Diary Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Subsequent Anticancer Therapies (t)																X		X
Response Assessment (n), (u)						X (n), (u)				X (n), (u)				X (n), (u)	X		X	
Bone Marrow Aspirate				X D14-D21 (v)		X (i), (v), (w)				X (i), (v)				X (i), (v)	X (v)		X (v)	
Overall Survival																		X
Tamibarotene (i), (x)			Dosing D8-D28 of each Cycle (i), (x)															
Azacitidine (i), (y)	X	X (y)					X (i)	X (y)			X	X (y)						
Venetoclax (i), (z)	X	X	X	X	X	X	X (i)	X	X	X	X	X	X	X				
Blood Sample for Exploratory Research (aa)	X					X (aa)				X (aa)				X (aa)	X			

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; CRi = CR with incomplete blood count recovery; CXDX = Cycle X, Day X; D/d = day(s); ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EDC = electronic data capture [system]; ELN = European LeukemiaNet; EoC = End of Cycle; EoT = End of Treatment; HSCT = hematopoietic stem cell transplantation; MRD = minimal residual disease; q3mo = every 3 months; RBC = red blood cell; RARA = retinoic acid receptor alpha; SAE = serious adverse event.

(a) Part 2 patients randomized to venetoclax/azacitidine treatment will begin their subsequent cycle in Part 3 as Part 3 Cycle 1, if they experience progressive disease, relapse after initial CR or CRi response, or treatment failure (failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator).
(b) Cycle 4 schedule should be followed for all subsequent cycles.
(c) An EoT Visit should occur within 3 days of the last dose of study drug (or within 3 days of decision to permanently stop study 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. If the EoT Visit occurs ≥30 days after the last dose of study drug, it may be combined with the Safety Follow-up Visit.
(d) A Safety Follow-up Visit should occur 30 days (±3 days) after the EoT Visit and before the start of any subsequent anticancer therapy. If the EoT Visit occurs ≥30 days after the last dose of study drug, it may be combined with the Safety Follow-up Visit.
(e) Patients who have not progressed/relapsed will enter the Disease Follow-up period. Visits should occur every 3 months for response assessment for up to 3 years after discontinuation of study drug or until disease progression/relapse, whichever occurs first. Disease Follow-up Visit window is ±30 days.
(f) Patients who progress/relapse will be followed to document the start of subsequent anticancer therapy, the date of disease progression/relapse, and overall survival status by telephone (or another appropriate method) for up to 3 years after discontinuation of study drug. Survival Follow-up Visit contact window is ±30 days.
(g) Participation in Part 3 will begin as soon as possible, but within 30 days of the decision to stop participation in Part 2. C1D1 assessments must be performed prior to study drug administration.
(h) EoC Visit should occur on Day 28 (±3 days) of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.)
(i) EoC response assessment results must be evaluated prior to start of Cycles 2, 3, and 4, followed by every third cycle (7, 10, 13, etc.). The timing of cycle start for these cycles will be determined as outlined in Section 6.1.1.
(j) Cycle 4 only.
(k) If administration of the 6th and 7th doses of azacitidine of the cycle is delayed to Days 8 and 9 (see footnote (y)), the vital sign evaluation will shift from Days 6 and 7 to Days 8 and 9 to parallel azacitidine administration. C1D8 vital sign evaluation is required for all patients.
(l) Full physical examination will be performed at C1D1, EoT, and the Safety Follow-up Visit; abbreviated physical examination will be performed at other visits indicated (see Section 8.2.3).
(m) Safety laboratory assessments will be performed locally.
(n) Additional unscheduled hematology evaluations may be performed prior to commencement of the next treatment cycle to reflect the best AML response achieved.
(o) A pregnancy test (high-sensitivity urine or serum) must be performed for women of childbearing potential.
(p) ECG should be performed after an approximately 10-minute rest period, 2 to 4 hours after tamibarotene and/or venetoclax administration.
(q) For all patients continuing on to Part 3, AEs and SAEs will be captured from Part 2 C1D1 through the Safety Follow-up Visit.
(r) For all patients continuing on to Part 3, every medication within 30 days of Part 2 C1D1 or at any time during the course of the study treatment, up to the Safety Follow-up Visit, must be documented.
(s) For all patients continuing on to Part 3, all RBC and platelet transfusions received by the patient from 8 weeks prior to Part 2 C1D1 through the Safety Follow-up period will be recorded.
(t) Subsequent anticancer therapies (including allogeneic HSCT) following EoT will be recorded.

(u) Response assessments will be performed at EoC Visit of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.), at the EoT Visit, and at each Disease Follow up Visit, with additional assessments performed if clinically determined. If a patient achieves a CR/CRi at the Cycle 1 EoC, the Cycle 2 EoC bone marrow aspirate is not required. Response assessments during Disease Follow-up visits where the bone marrow aspirates are not performed are based on hematology evaluation and physical examination findings.

(v) The bone marrow aspirate samples for local assessment of response (**blast count, cytogenetics, and assessment of MRD**) will be collected between Days 14 and 21 of Cycle 1, with venetoclax administration proceeding in alignment with ELN 2022 recommendations (Döhner 2022). For those with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required. For patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed. Subsequent bone marrow aspirates for all patients will be collected at the EoC Visit of Cycles 2 and 3, followed by every third cycle (6, 9, 12, etc.); at the EoT Visit; and at every other visit during the Disease Follow-up period (every 6 months), with bone marrow aspirates collected at other times as clinically determined. If a patient achieves a CR/CRi within Cycle 1 response assessment(s), the Cycle 2 EoC bone marrow aspirate is not required. Anonymized reports will be uploaded to the EDC. At each bone marrow aspirate draw, an additional aspirate sample will be collected and sent to the **Central Laboratory** for **exploratory analyses**.

(w) For those with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required. For patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed.

(x) Tamibarotene will be administered on Days 8 through 28 of each 28-day therapy cycle.

(y) Azacitidine will be administered intravenously or subcutaneously as described in the most current VIDAZA USPI/VIDAZA SmPC. Azacitidine will be administered each day on Days 1 through 7 of each 28-day therapy cycle. If dosing on Days 6 and 7 is not possible due to logistical limitations, these doses may be delayed to Days 8 and 9. Tamibarotene is permitted to overlap with azacitidine on Days 8 through 9 of this alternative schedule.

(z) Venetoclax will be administered daily, as described in the most current VENCLEXTA USPI/VENCLYXTO SmPC with SOC modifications consistent with ELN 2022 guidelines (Döhner 2022; Section 6.1.1; Table 5).

(aa) Blood samples will be collected for exploratory research at C1D1, at EoC Visit of Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.), and at EoT. If a patient achieves a CR/CRi at the Cycle 1 EoC, the Cycle 2 EoC blood sample is not required.

2 INTRODUCTION

2.1 Study Rationale

Tamibarotene is a potent and selective agonist of RARα being developed in combination with azacitidine in a novel genomically defined subset of patients with non-APL AML, characterized by overexpression of *RARA* (McKeown 2017). Approximately 30% of patients with ND AML are expected to be positive for *RARA* overexpression (de Botton 2020).

Currently, ND AML patients who are ineligible for standard induction therapy are increasingly receiving venetoclax/azacitidine combination as initial treatment. In a randomized study of such AML patients, the combination of azacitidine with venetoclax has demonstrated a high composite CR rate and a survival benefit compared to treatment with azacitidine monotherapy (DiNardo 2020). However, approximately one-third of patients failed to respond to the venetoclax/azacitidine combination (DiNardo 2020), supporting the existing need to improve upon the outcomes in this subpopulation.

In RARA-positive ND AML patients who are ineligible for standard induction therapy, tamibarotene plus azacitidine is associated with high CR rates and a rapid onset of response (de Botton 2020). Further, recent data demonstrate that monocytic features associated with resistance to venetoclax are significantly present in those RARA-positive patients who achieve a complete response with tamibarotene plus azacitidine (Section 4.2; Fiore 2020; Pei 2020). Consequently, adding venetoclax to the tamibarotene plus azacitidine combination may address an unmet need in RARA-positive AML, allowing for the treatment of both primitive AML that may be sensitive to venetoclax and more mature monocytic subpopulations that may respond to treatment with tamibarotene plus azacitidine. Given that tamibarotene, venetoclax, and azacitidine have distinct AE profiles, it is anticipated that the 3 drugs can be administered safely in combination.

This open-label Phase 2 study in adult RARA-positive, previously untreated AML patients who are ineligible for standard induction therapy will consist of 3 parts. In Part 1, the safety and tolerability of the tamibarotene/venetoclax/azacitidine combination will be evaluated, PK of tamibarotene will be assessed when co-administered with venetoclax/azacitidine, and the dosing regimen of the combination for evaluation in Part 2 will be selected. In Part 2, patients who are ineligible for standard induction therapy will be randomized to tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine. In Part 3, patients treated with venetoclax/azacitidine in Part 2 who experience progressive disease, relapse after initial CR or CRi response, or treatment failure (defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator) may receive tamibarotene in addition to venetoclax/azacitidine.

2.2 Background

2.2.1 Disease Under Study

AML is the most common leukemia in adults, with an estimated 20,000 individuals diagnosed with AML each year in the US. Current treatment paradigms in younger patients (<60 years) include induction regimens of standard cytotoxic chemotherapy (cytarabine and an anthracycline) and consolidation with additional chemotherapy and/or HSCT (Shallis 2019). However, the majority of ND AML patients are "unfit" for intensive induction chemotherapy, based on advanced age, comorbidities, and other factors (Ferrara 2013). For these patients, the combination of venetoclax and azacitidine has become the SOC (VENCLEXTA USPI, VENCLYXTO SmPC).

2.2.1.1 Venetoclax/Azacitidine Combination

Clinical efficacy of venetoclax/azacitidine was demonstrated in a randomized trial that compared the combination to placebo/azacitidine regimen. Venetoclax/azacitidine treatment was associated with a CR/CRi rate of 66.4% and an improvement in overall survival (OS) (14.7 months versus 9.6 months in placebo/azacitidine group) (DiNardo 2020). Despite this progress, there remains a high unmet need for new, effective, and well-tolerated therapies. From the tolerability perspective, myelosuppression is a known adverse reaction of venetoclax and venetoclax combination therapies (VENCLEXTA USPI, VENCLYXTO SmPC). Over 80% of patients treated have high grade (NCI CTCAE Grade 3 or 4) hematologic AEs, including various cytopenias and febrile neutropenia. From the efficacy perspective, one-third of patients treated with venetoclax/azacitidine do no respond (DiNardo 2020). The patients who are refractory to or relapse after venetoclax/hypomethylating agent (HMA) therapy have a shorter median OS (2.4 months) than the overall relapsed/refractory (R/R) AML patient population (Maiti 2020).

Markers of response and resistance to venetoclax treatment in the ND unfit setting have begun to emerge, with poor response associated with mutations in *TP53*, *NRAS*, and *DNMT3A* genes and with an AML monocytic phenotype (Pei 2020, Kuusanmäki 2020, Zhang 2018). Similarly, the loss of *BCL2* expression and concomitant overexpression of *MCL1* have been linked with primary and acquired resistance to venetoclax (Wang 2020, Knight 2019, Campos 2019). Further research is needed to fully characterize the drivers of resistance to venetoclax/azacitidine treatment.

2.2.1.2 Tamibarotene/Azacitidine Combination

RARA-positive AML is a novel patient subset with an actionable target for treatment with tamibarotene, an oral selective RARα agonist. RARA-positive AML is characterized by overexpression of the *RARA* gene in blasts. RARA-positive patients are identified with an investigational assay that assesses RARA expression in peripheral blood mononuclear cell blasts with quantitative polymerase chain reaction. Approximately 30% of AML patients are RARA-positive (de Botton 2020).

In a Phase 2 study evaluating tamibarotene plus azacitidine in ND unfit AML patients (Study SY-1425-201; N = 51), the combination was well tolerated. Additive myelosuppression was not observed when tamibarotene was combined with azacitidine, and the majority of non-

hematologic AEs were low grade and reversible. The combination of tamibarotene plus azacitidine was associated with a high CR/CRi rate (61%), CR rate (50%), and a rapid onset of response (median time to composite CR 1.2 months). Responses were observed irrespective of cytogenetic risk or the presence of AML-associated genetic mutations. A majority of patients achieved transfusion independence, and the median OS of those achieving CR/CRi was 18 months (de Botton 2020). Additional data from this study are provided in the IB.

2.2.1.3 Triplet (Tamibarotene/Venetoclax/Azacitidine) Combination

Currently, ND AML patients who are ineligible for standard induction therapy are increasingly receiving venetoclax plus azacitidine combination as initial treatment. In a randomized study of such AML patients, the combination of azacitidine with venetoclax has demonstrated a high composite CR rate and a survival benefit compared to treatment with azacitidine monotherapy (DiNardo 2020). However, approximately one-third of patients failed to respond to the venetoclax/azacitidine combination (DiNardo 2020), supporting the existing need to improve upon the outcomes in this subpopulation.

Several reports have shown that primary venetoclax resistance is associated with monocytic features in AML and that low-level monocytic clones present at diagnosis expand at relapse on venetoclax plus azacitidine treatment (Pei 2020, Kuusanmäki 2020, Zhang 2018). Syros recently reported that RARA positivity significantly enriched for ND unfit AML patients with monocytic gene expression features associated with venetoclax resistance (Fiore 2020), including low *BCL2* expression and high *MCL1* expression. A majority (80%) of RARA-positive ND unfit AML patients enrolled in Study SY-1425-201 had monocytic expression features in blasts collected at study entry, which included patients with CR/CRi responses to tamibarotene plus azacitidine. Collectively, these findings suggest that patient selection based on the RARA biomarker test identifies a distinct AML patient subset who may be likely to respond to tamibarotene plus azacitidine, but not to venetoclax plus azacitidine. Considering the non-overlapping toxicity profiles of tamibarotene, venetoclax, and azacitidine, the use of the triplet combination may be tolerable and improve outcomes in RARA-positive ND unfit AML patients by inducing deeper and more durable responses through inhibition of distinct blast cell populations:
1) RARA-positive mature monocytic blasts sensitive to tamibarotene plus azacitidine but resistant to venetoclax plus azacitidine; 2) subclonal RARA-negative primitive blasts sensitive to venetoclax plus azacitidine but not tamibarotene plus azacitidine.

2.2.2 Tamibarotene

Tamibarotene is an orally available, synthetic retinoid approved in Japan (AMNOLAKE® Tablets) since April 2005 for the treatment of relapsed or refractory APL, characterized by t(15;17), which results in the *PML-RARA* fusion. Tamibarotene was designed to be a more potent and selective RARα agonist with significantly improved in vivo pharmacologic properties compared to ATRA, a component of the current first-line treatment of APL. In vitro, tamibarotene is approximately 10-fold more potent than ATRA.

A detailed description of the chemistry, pharmacology, efficacy, and safety of tamibarotene is provided in the IB.

2.2.3 Venetoclax

Venetoclax is an orally bioavailable small molecule that is a potent and selective inhibitor of an anti-apoptotic protein BCL-2. BCL-2 over-expression prevents death of AML cells, with high levels associated with resistance to chemotherapy and poor survival (Konopleva 2006, Tsao 2012).

Venetoclax in combination with azacitidine is approved in the US and European Union (EU) for the treatment of newly diagnosed AML in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy.

Additional information is available in the venetoclax label (VENCLEXTA USPI, VENCLYXTO SmPC).

2.2.4 Azacitidine

Azacitidine is a pyrimidine analogue that exerts antineoplastic effects on abnormal hematopoietic bone marrow cells through multiple mechanisms including deoxyribonucleic acid (DNA) hypomethylation. Cytotoxicity may also result from incorporation into DNA and ribonucleic acid (RNA), with inhibition of DNA, RNA, and protein synthesis. Azacitidine is approved in the US and EU for treatment of MDS. Azacitidine is also approved for use in AML in the EU and is widely accepted as the SOC for treatment of AML in the US.

Additional information is available in the azacitidine label (VIDAZA USPI, VIDAZA SmPC).

2.3 Benefit/Risk Assessment

Despite an improvement in outcomes compared to historical treatment with HMA monotherapy in the recent studies of tamibarotene plus azacitidine and venetoclax plus azacitidine in ND AML patients (de Botton 2020, DiNardo 2020), approximately one-third of patients do not achieve a response after treatment with either combination.

In the SY-1425-201 study, Syros has explored the safety, PK, pharmacodynamic, and clinical activity of tamibarotene in combination with azacitidine in RARA-positive AML. Clinical activity data from that study (de Botton 2020) and from the study exploring clinical activity of the venetoclax plus azacitidine combination (DiNardo 2020) support the rationale for further development of the triplet combination of tamibarotene/venetoclax/azacitidine in a genomically defined subset of patients characterized by overexpression of *RARA* in blasts. The triplet combination of tamibarotene/venetoclax/azacitidine may improve response in RARA-positive AML patients by treating both primitive AML that may be sensitive to venetoclax and more mature monocytic subpopulations that may be resistant to venetoclax, but respond to treatment with tamibarotene plus azacitidine.

The AE profile of the tamibarotene plus azacitidine combination was consistent with what has been previously reported for single agent tamibarotene or single agent azacitidine in treatment of AML/MDS patients (see IB, VIDAZA USPI, VIDAZA SmPC) and supports potential tolerability of the triplet regimen. Notably, the AE profile of tamibarotene plus azacitidine is distinct from the AE profile of the venetoclax plus azacitidine combination (DiNardo 2020) and

does not suggest overlapping toxicity. In particular, whereas hematologic toxicities are frequently observed with venetoclax effects (VENCLEXTA USPI, VENCLYXTO SmPC), the rates of myelosuppression with the tamibarotene plus azacitidine combination were comparable to single-agent azacitidine, without evidence for additive hematologic toxicity from the combination. To minimize the known myelosuppression from venetoclax (with a goal of improving patient safety and tolerability of treatment), the duration of venetoclax administration in Cycle 1 will be guided by blast clearance status at a response assessment performed between Days 14 and 21. For Cycle 2 and beyond, patients will receive venetoclax daily beginning on Day 1 through Day 28 for each cycle, with dose modifications based on time to recovery of blood counts, as recommended in ELN 2022 guidelines (Döhner 2022).

The majority of nonhematologic AEs observed with tamibarotene plus azacitidine therapy were low grade and reversible. The safety profile of tamibarotene plus azacitidine is further supported by the Japanese marketing experience with tamibarotene (AMNOLAKE®), in which more than 1000 patients have been treated for R/R APL.

Overall, the expected safety profile of the tamibarotene/venetoclax/azacitidine combination is predicted to be acceptable, with the potential for improved response rate in RARA-positive patients when treated with the triplet combination. All patients in the study will receive venetoclax and azacitidine, which is the current best practice for treating ND AML.

The risks of the underlying condition evaluated in this study are significant and represent areas of high unmet medical need. Patients undergoing treatment for AML undergo the procedural risk of repeated bone marrow aspirations, which are also required assessments in this study. There is a significant risk of complications due to leukemia and its treatment, including bleeding and life-threatening infections. The treatment-related mortality is historically high in clinical trials in AML (Estey 2018). The clinical activity of the individual venetoclax plus azacitidine combination, coupled with that of the tamibarotene plus azacitidine combination, suggest that the triplet combination has the potential to provide a valuable treatment option for RARA-positive patients with AML.

Detailed information about the known and expected benefits and risks and reasonably expected AEs for tamibarotene may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Part 1	
Primary	
• Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine combination in RARA-positive, previously untreated AML patients to inform Part 2 dose and regimen of the tamibarotene/venetoclax/azacitidine therapy	• Incidence of AEs, changes in clinical laboratory values, ECGs, and vital sign measurements

OBJECTIVES	ENDPOINTS
Secondary	
• Characterize the ORR of tamibarotene/venetoclax/azacitidine combination	• Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of patients who achieve overall response
• Characterize PK of tamibarotene when administered as a part of tamibarotene/venetoclax/azacitidine therapy	• Tamibarotene PK parameters
Exploratory	
• Evaluate AML molecular features associated with response and with loss of response to treatment	• Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response
Part 2	
Primary	
• Characterize and compare the CR/CRi rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• CR/CRi assessment; CR/CRi rate is estimated by the proportion of patients who achieve CR/CRi (as determined by the investigator[a])
Secondary	
• Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine in RARA-positive, previously untreated AML patients	• Incidence of AEs, changes in clinical laboratory values, ECGs, and vital sign measurements
• Characterize and compare CR rate and CR/CRh rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• CR assessment; CR rate is estimated by the proportion of patients who achieve CR (as determined by the investigator[a]) • CR/CRh assessment; CR/CRh rate is estimated by the proportion of patients who achieve CR/CRh (as determined by the investigator[a])
• Characterize duration of CR, duration of CR/CRi, and duration of CR/CRh of tamibarotene/venetoclax/azacitidine combination versus venetoclax/azacitidine	• Duration of CR, defined as 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 • Duration of CR/CRi, defined as 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 • Duration of CR/CRh, defined as 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

OBJECTIVES	ENDPOINTS
• Characterize time to CR, time to CR/CRi, and time to CR/CRh of tamibarotene/venetoclax/azacitidine combination versus venetoclax/azacitidine	• Time to CR, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of the first documented evidence of CR as determined by the investigator[a] • Time to CR/CRi, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of the first documented evidence of CR/CRi as determined by the investigator[a] • Time to CR/CRh, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of the first documented evidence of CR/CRh as determined by the investigator[a]
• Characterize and compare the ORR of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of patients who achieve overall response
Exploratory	
• Characterize and compare EFS of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• EFS, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of progressive disease, relapse after CR or CRi, treatment failure[b], or death from any cause
• Characterize and compare OS of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Duration from the date of Cycle 1 Day 1 Visit to the date of death due to any cause
• Characterize and compare MRD-negative response rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Assessment of MRD; MRD-negative response rate estimated by the proportion of patients achieving an MRD-negative CR by multiparameter flow cytometry, qPCR, or next generation sequencing, as determined by the investigator[a]
• Characterize time to MRD-negative response of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• Time to MRD-negative response, defined as the duration from the date of Cycle 1 Day 1 Visit to the date of achieving an MRD-negative CR by multiparameter flow cytometry, qPCR, or next generation sequencing, as determined by the investigator[a]
• Characterize and compare the TI rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine	• TI rate, defined as the proportion of patients who achieve TI. TI is a period of at least 56 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
• Characterize PK of tamibarotene when co-administered with venetoclax and azacitidine	• Plasma tamibarotene PK parameters
• Evaluate AML molecular features associated with response and with loss of response to treatment	• Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response

OBJECTIVES	ENDPOINTS
Part 3	
Exploratory	
• Characterize the ORR after treatment with tamibarotene/venetoclax/azacitidine for patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine	• Overall response assessment, comprised of CR, CRi, CRh, MLFS, or PR (as determined by the investigator[a]); ORR is estimated by the proportion of patients who achieve overall response
• Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine in patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine	• Incidence of AEs, changes in clinical laboratory values, ECGs, and vital sign measurements
• Characterize the OS of tamibarotene/venetoclax/azacitidine in patients who have experienced progressive disease, relapse, or treatment failure[b] on venetoclax/azacitidine	• Duration from the date of first dose in Part 3 to the date of death due to any cause
• Evaluate AML molecular features associated with response and with loss of response to treatment	• Clinical response and genetic mutations and/or gene expression markers at baseline, on treatment, and/or at time of loss of response

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete blood count recovery; ECG = electrocardiogram; EFS = event-free survival; ELN = European LeukemiaNet; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; OS = overall survival; ORR = objective response rate; PK = pharmacokinetic(s); PR = partial remission; qPCR = quantitative polymerase chain reaction; RBC = red blood cell; TI = transfusion independence.

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

[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.

4 STUDY DESIGN

4.1 Overall 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-APL AML patients 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 SOC venetoclax/azacitidine (Döhner 2022) in Part 2 and Part 3. In Part 2, patients 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 patients who experience progressive disease, relapse after initial CR or CRi response, or treatment failure (see Part 3 Design section below). Enrollment is planned in the United States (US) and France.

Start of Venetoclax/Azacitidine Therapy

Currently, ND AML patients who are ineligible for standard induction therapy are increasingly receiving venetoclax/azacitidine combination as the SOC therapy. 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.

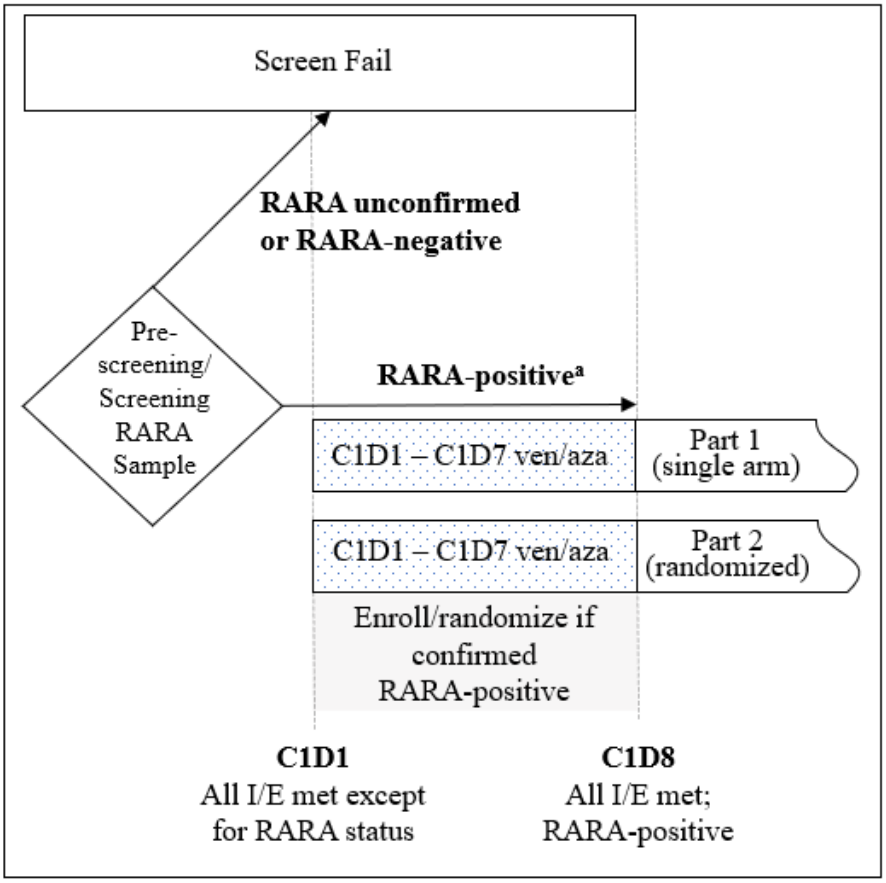
- Begin SOC venetoclax/azacitidine treatment on Cycle 1 Day 1 using protocol defined regimen and doses while awaiting pre-treatment screening RARA biomarker test result.

- Begin venetoclax/azacitidine treatment on Cycle 1 Day 1 after the patient 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. Patients 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.



Abbreviations: AE = adverse events; I/E = inclusion/exclusion [criteria]; C1DX = Cycle 1 Day X; RARA = retinoic acid receptor alpha.

[a] If the patient discontinues treatment or study participation prior to confirmation of screening RARA results and RARA-positivity is confirmed by C1D8, the patient 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 patients may be enrolled in Part 1. Enrolled RARA-positive patients 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 patients receiving concomitant CCI and P-gp inhibitors [Table 4]), 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 patients who have been confirmed as RARA-positive.

If needed to manage toxicity, the study drugs will be modified as outlined in Section 6.5. After Cycle 1 data for at least 6 patients 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 patients 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 patients to tolerate the approved regimen of venetoclax/azacitidine. A modified regimen would consist of a reduced dose of tamibarotene (Table 6) 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 patients 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 patients will be randomized in Part 2 of the study. RARA-positive patients 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 patients receiving concomitant CCI and P-gp inhibitors [Table 4]) 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 (Section 6.1.1). 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, patients will receive venetoclax daily beginning on Day 1 through Day 28 for each cycle, with dose modifications as needed for toxicity, as outlined in Table 5 (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 patients who have been confirmed as RARA-positive.

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

Part 3 Design

Part 2 patients 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

Patients will undergo safety and response evaluations throughout their study participation as detailed in the Schedules of Activities (Section 1.3). Response will be assessed by the investigator in alignment with ELN AML criteria (Döhner 2017), with CRh assessed according to Bloomfield 2018.

In Part 1, bone marrow aspirates will be collected to measure response at the 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 patient achieves a 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 patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed. Subsequent bone marrow aspirates for all patients 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 patient achieves a CR/CRi within Cycle 1 response assessment(s), the Cycle 2 EoC bone marrow aspirate is not required.

The AE profiles of tamibarotene and venetoclax/azacitidine combination are well-documented and largely do not overlap (tamibarotene IB, VENCLEXTA USPI, VENCLYXTO SmPC). Consequently, in this study, it is recommended that hematologic toxicities and non-hematologic toxicities typically associated with the venetoclax/azacitidine combination (VENCLEXTA USPI, VENCLYXTO SmPC) should be managed with adjustments to venetoclax/azacitidine administration. AEs that have been identified as tamibarotene ADRs (tamibarotene IB) should be managed via modification to tamibarotene administration (Section 6.5). In patients receiving triplet combination therapy, if improvements in blood counts or relevant toxicities are not observed with recommended adjustments to venetoclax/azacitidine, an adjustment to the tamibarotene dose should be considered.

All patients who remain on study may continue to receive study drug until experiencing an unacceptable toxicity, disease progression, relapse, decision to pursue post-remission therapy

(such as HSCT) or an alternative anticancer therapy, patient withdraws consent, or the investigator determines it is in the best interest of the patient to discontinue study drug. Note: Part 2 patients 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) patients, an 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, patients 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. Patients 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.

There will be no formal IDMC. The sponsor will provide oversight of safety and tolerability at regularly scheduled intervals (and ad hoc if needed) via SRT meetings as detailed in the SRT Charter. In addition, regularly scheduled reviews of safety and tolerability will be performed by the sponsor in collaboration with the study investigators in Part 1 of the study. These reviews will inform the dose of tamibarotene to be combined with venetoclax/azacitidine in Part 2 of the study. Administrative interim analyses will be performed by the sponsor personnel or designee.

4.2 Scientific Rationale for Study Design

This study is evaluating the addition of tamibarotene, a targeted therapy for RARA-positive AML patients who are not candidates for treatment with intensive chemotherapy, to the established venetoclax/azacitidine regimen.

The design of the study follows an accepted approach for initiating study of a novel combination, in that it will begin with a small cohort of patients in Part 1 (approximately [CCI]) to identify any safety issues and determine a tolerable regimen of tamibarotene in combination with venetoclax/azacitidine before proceeding to Part 2, where a larger number of patients (approximately [CCI]) will be treated. Part 2 has been structured to characterize and compare clinical activity of tamibarotene/venetoclax/azacitidine with that of venetoclax/azacitidine through 1:1 randomization of approximately [CCI] patients between the 2 treatment arms. Part 3 is designed to allow exploration of the activity of the tamibarotene addition to the venetoclax/azacitidine combination in patients who have failed to respond to venetoclax/azacitidine (Section 4.1) by adding tamibarotene to venetoclax/azacitidine in these patients and following them for response.

The inclusion criteria ensure enrollment of only RARA-positive patients and those who are not candidates for intensive treatment using standard criteria (Ferrara 2013). Treatment with prior cycles of HMA or other chemotherapy for AML is not permitted to ensure the enrollment of only ND patients.

The primary endpoint of Part 1 is safety to appropriately characterize the tolerability and safety of this novel combination. The primary endpoint of Part 2 is the CR/CRi rate. This outcome is accepted as a clinically meaningful outcome to investigators. CR is a surrogate for OS in AML. Achievement of CRi reflects the clearance of blasts from the bone marrow (and therefore anti-leukemic activity) in the context of an incomplete recovery of peripheral blood counts. Composite CR/CRi rates are well characterized for the venetoclax/azacitidine combination to which the tamibarotene/venetoclax/azacitidine combination will be compared.

In Part 3 of the study, the ORR for patients refractory to venetoclax/azacitidine will be explored following treatment with tamibarotene/venetoclax/azacitidine.

4.3 Rationale for Dose and Regimen

Tamibarotene

The selection of the 6 mg BID regimen of tamibarotene administered on Days 8 to 28 of a 28-day cycle is based on the totality of safety, efficacy, and PK data available for tamibarotene to date, including from the Phase 2 study of tamibarotene in adults with AML or MDS (Study SY-1425-201) and the Japanese clinical trial and marketing experience.

The dose and regimen used in Study SY-1425-201 (6 mg/m^2/day in 2 divided doses) were based on the dose and regimen approved in Japan for the treatment of APL. Population PK analysis from Study SY-1425-201 indicated that body size was not significantly associated with clearance; therefore, a body surface area-based adjustment to tamibarotene dosing is not necessary. Based on this analysis, the 6 mg BID flat dosing regimen is expected to provide similar PK exposures compared to the 6 mg/m^2/day (in 2 divided doses) regimen used in the SY-1425-201 study.

In Part 1, tamibarotene will be administered at 6 mg BID starting dose in combination with venetoclax/azacitidine. Tamibarotene dose modifications for AEs will follow guidelines outlined in the protocol (Section 6.5). Evaluation of tamibarotene/venetoclax/azacitidine combination in Part 1 will inform the appropriate tamibarotene dose to be combined with SOC venetoclax/azacitidine in Part 2.

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 patients to tolerate the SOC regimen of venetoclax/azacitidine. A modified regimen would consist of a reduced dose of tamibarotene (Table 6) in combination with the SOC 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 patients 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.

Venetoclax and Azacitidine

In Part 1 of the study, when administered as a part of the triplet combination, venetoclax and azacitidine will be given as described in VIDAZA USPI/VIDAZA SmPC and VENCLEXTA USPI/VENCLYXTO SmPC, respectively.

In Part 2 and Part 3 of the study, response assessment and SOC modifications will be consistent with ELN guidelines (Döhner 2022; Maiti 2022). Utilization of the ELN 2022 venetoclax dosing guidelines allows to minimize the known myelosuppression from venetoclax with a goal of improving patient safety and tolerability of treatment. Cycle 1 response will initially be assessed between Days 14 and 21, with Cycle 1 and subsequent venetoclax administration proceeding in alignment with ELN 2022 recommendations (Döhner 2022; Section 6.1.1; Table 5).

Venetoclax/azacitidine dose modifications will follow the standard dose modifications for AEs (VIDAZA USPI/VIDAZA SmPC and VENCLEXTA USPI/VENCLYXTO SmPC), with SOC modifications consistent with ELN 2022 guidelines in Part 2 and Part 3 (Döhner 2022; Maiti 2022).

4.4 End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the Schedules of Activities (SoAs) (Section 1.3) for the last patient in the study.

A patient is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Note: all inclusion/exclusion criteria should be met prior to the first dose of venetoclax/azacitidine on Cycle 1 Day 1 with the exception of the RARA-biomarker test result referenced in inclusion criterion 2, which should be positive by Cycle 1 Day 8 to continue treatment on study.

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Patients must be at least 18 years old at the time of signing of an informed consent.

2. All patients must have obtained a blood sample for RARA biomarker investigational assay testing prior to starting treatment on Cycle 1 Day 1. The results of the investigational biomarker assay for all patients must be confirmed as RARA-positive by Cycle 1 Day 8 to enroll (Part 1) or to be randomized (Part 2) in the study.

3. Patients must have ND, previously untreated non-APL AML with a bone marrow or peripheral blood blast count ≥20% and must be unlikely to tolerate standard intensive chemotherapy at the time of Cycle 1 Day 1 Visit due to age, performance status, or comorbidities based on at least one of the following criteria (Ferrara 2013):

   a. age ≥75 years old

   OR

   b. age <75 years old, with at least one of the following:

      - ECOG performance status of 3
      - cardiac history of CHF or documented EF ≤50%
      - pulmonary disease with DLCO ≤65% or FEV_1 ≤65%
      - creatinine clearance ≥30 mL/min to <45 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation
      - hepatic impairment with total bilirubin >1.5 to ≤3.0 × ULN
      - any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy, and reviewed and approved by the sponsor

4. Patients must have ECOG of 0 to 3 (if <75 years old) or 0 to 2 (if ≥75 years old).

5. Patients must have a WBC count <25,000/µL at the time of initiation of study drug (leukapheresis may be performed and/or hydroxyurea may be administered to decrease the WBC count to <25,000/µL).

6. Patients must have minimum baseline organ function, as defined by:

   a. total bilirubin ≤3.0 × ULN (if <75 years old) or ≤1.5 × ULN (if ≥75 years old)

   b. ALT and AST ≤3 × ULN or ≤5 × ULN (if documented liver infiltration with leukemia cells)

   c. creatinine clearance ≥30 mL/min (if <75 years old) or ≥45 mL/min (if ≥75 years old) based on the Cockcroft-Gault glomerular filtration rate estimation

7. Patients must have a high-sensitivity urine or serum pregnancy test (for females of childbearing potential) that is negative at the Screening Visit and immediately prior to initiation of treatment (first dose of study drug).

8. Patients must be willing and able to comply with the scheduled study visits, treatment plans, laboratory tests, use of 2 methods of birth control (including a barrier method) for WOCBP and male patients (as described in Appendix 4), and other procedures.

9. Patients must be capable of giving signed and dated IRB- or IEC-approved informed consent.

5.2 Exclusion Criteria

Note: all inclusion/exclusion criteria should be met prior to the first dose of venetoclax/azacitidine on Cycle 1 Day 1 with the exception of the RARA-biomarker test result referenced in inclusion criterion 2, which should be positive by Cycle 1 Day 8 to continue treatment on study.

Patients are excluded from the study if any of the following criteria apply:

1. Patients have APL.

2. Patients have known active central nervous system involvement with AML.

3. Participants with a history of other cancers must not be receiving active treatment (with radiation or chemotherapy) and must be free of disease for 2 years prior to the Screening Visit with the exception of localized prostate cancer treated with hormone therapy, breast cancer treated with hormone therapy, localized basal cell carcinoma, non-melanoma skin cancer, or cervical carcinoma in situ.

4. Patients have an active, life-threatening, or clinically-significant uncontrolled systemic infection requiring hospitalization.

5. Patients have a known malabsorption syndrome or other condition that may impair absorption of study medication (e.g., gastrectomy).

6. Immunocompromised patients with increased risk of opportunistic infections, including known HIV-positive patients with CD4 counts $\leq$350 cells/mm^3 or history of opportunistic infection in the last 12 months. Note: To ensure that effective ART, when used in eligible HIV-positive patients, is tolerated and that toxicities are not confused with investigational drug toxicities, patients should be on an established ART for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to the Screening Visit.

7. Patients have a known active or chronic hepatitis B or active HCV infection. Patients with a history of HCV infection who have completed curative therapy for HCV at least

12 weeks before the Screening Visit and have a documented undetectable viral load at the Screening Visit are eligible for enrollment.

8. Patients have other severe acute or chronic medical conditions (and/or psychiatric conditions or laboratory abnormalities) that may increase the expected risk to the patient (i.e., the risk associated with the study participation or study drug administration) or that may interfere with the interpretation of study results or, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

9. Patients received prior treatment with ATRA or systemic retinoid for a hematologic malignancy.

10. Patients have not adequately recovered from a major surgery within 4 weeks of starting study drug administration.

11. Prior treatment (before Cycle 1 Day 1) for the diagnosis of AML, MDS, or antecedent hematologic malignancy with any hypomethylating agent, venetoclax, chemotherapy, or HSCT, with the exception of prior treatment with hydroxyurea.

12. Patients with a diagnosis of hypervitaminosis A or patients taking vitamin A supplements >10,000 IU/day, unless treatment is discontinued at least 7 days prior to the first dose of the study drug.

13. Patients received any other investigational agents within 4 weeks of the Screening Visit or <5 half-lives since completion of previous investigational therapy have elapsed, whichever is shorter.

14. Patients require concurrent treatment with any investigational or approved oncology agent, except for hydroxyurea.

15. Patients with Grade ≥2 hypertriglyceridemia, defined as >300 mg/dL (CTCAE, version 5).

16. QTc >450 msec for male patients, QTc >470 msec for female patients, or QTc >480 msec in male or female patients with bundle branch block based on triplicate ECG readings at the Screening Visit. NOTE: The QTc in this study should be the QT interval corrected for heart rate according to QTcF formula.

17. Pregnant females, breastfeeding females, and males not willing to comply with contraceptive requirements (as described in Appendix 4) or females of childbearing potential not willing to comply with contraceptive requirements (as described in Appendix 4).

18. Patients who have a hypersensitivity to tamibarotene, azacitidine, venetoclax or to any of their excipients.

19. Patients for whom treatment with tamibarotene, azacitidine, venetoclax is contraindicated.

20. Protected persons (legally protected adults [under judicial protection, guardianship, or supervision] and persons deprived of their liberty).

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

A screen failure occurs when a patient who has consented to participate in the clinical study is not subsequently enrolled (Part 1)/randomized (Part 2) in the study. In particular, patients determined to be RARA-negative or who do not have a RARA biomarker result by Cycle 1 Day 8 will be classified as screen failures.

A minimal set of information will be collected and is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE that occurs after the first dose of venetoclax/azacitidine on Cycle 1 Day 1 and prior to screen failure.

Individuals who do not meet the criteria for participation in this study may be rescreened.

5.5 Criteria for Temporarily Delaying Randomization

Not applicable.

6 STUDY DRUGS AND CONCOMITANT THERAPY

Study drug is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a patient according to the study protocol beginning on Cycle 1 Day 1.

6.1 Study Drugs Administered

Study drugs described in Table 3 will be administered. All patients 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 patients 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 patients 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 patients.

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 as described in Section 6.1.1.

Table 3: Study Drugs

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. See Section 6.2.1 for details of dose administration.	Daily, Days 1 through 28, as described in Table 4 (adapted from VENCLEXTA USPI/ VENCLYXTO SmPC). See Section 6.2.2 for details of dose administration.	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. See Section 6.2.3 for details of dose administration.
Route of Administration	Oral	Oral	Intravenous or subcutaneous
Use	Experimental	Background intervention	Background intervention
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	As regionally applicable	Sourced by the site
Packaging and Labeling	Study drug will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study drug is commercially available and will be provided in the commercial packaging. Each container will be labeled as required per country requirement.	Study drug is commercially available and will be provided in the commercial packaging. Each container will be labeled as required per country requirement.

Table 4: 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

6.1.1 Study Procedures at the time of Response Assessment

Part 1

Patients 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 patient achieves CR at the EoC response assessment, the patient will begin the next treatment cycle.
- If a patient 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 patient 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 peripheral blood count recovery.

Part 2 and Part 3

Patients will undergo a response assessment between Days 14 and 21 of Cycle 1 and at the EoC of Cycles 1 (only for patients with ≥5% blasts when assessed between Days 14 and 21), 2, and 3, followed by every third cycle (6, 9, 12, etc.). The start of the next treatment cycle will be determined as follows:

Cycle 1 Assessments:

- If a patient has <5% bone marrow blasts at the response assessment conducted between Days 14 and 21 of Cycle 1, stop venetoclax **for up to 14 days** prior to proceeding to Cycle 2 to allow for count recovery to ≥CRh (ANC ≥500/µL and platelets ≥50,000/µL;

Döhner 2022). For these patients with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required.

- If a patient has ≥5% bone marrow blasts at the response assessment conducted between Days 14 and 21 of Cycle 1, venetoclax administration will continue for the remainder of the cycle, and another bone marrow aspirate will be performed at Cycle 1 EoC. If blast clearance (<5% blasts) is documented, Cycle 2 will be held to allow for peripheral blood count recovery to ≥CRh.

- If a patient has ≥5% blasts at the EoC response assessment, the start of the next treatment cycle should begin on schedule with supportive care, without modifications to the regimen, regardless of peripheral blood count recovery.

Cycle 2 and Beyond:

- If a patient has bone marrow blasts <5% at the EoC response assessment, without count recovery, the start of the next treatment cycle will be held to allow for count recovery to ≥CRh. G-CSF may be administered as clinically indicated for neutropenia. See Table 5 to guide venetoclax schedule adjustment for cytopenia management (Döhner 2022).

Cytopenias and dose adjustments should be managed per the guidance in the most current VENCLEXTA USPI/ VENCLYXTO SmPC (e.g., Table 5) in conjunction with Döhner 2022.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Tamibarotene

A total of 6 tablets (12 mg total) will be taken each day, 3 tablets (6 mg) in the morning and 3 tablets (6 mg) in the evening. Patients will be instructed to take the dose with a glass of water after their morning meal and after their evening meal. Tablets should not be crushed, broken, or split. Dosing should not be repeated if a patient vomits. A dose missed by greater than 4 hours should be skipped.

Until dispensed to the patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only. Tablets should be stored at room temperature (15°C [59°F] to 30°C [86°F]) and should not be removed from bottles until immediately before administration.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all tamibarotene received, and any discrepancies are reported and resolved before its use.

Only patients enrolled in the study may receive tamibarotene and only authorized site staff may supply or administer it. All tamibarotene must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for tamibarotene accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused tamibarotene are provided in the Pharmacy Manual.

6.2.2 Venetoclax

Venetoclax is commercially available as 10-mg, 50-mg, and 100-mg tablets.

Tablets must be stored at room temperature (15°C [59°F] to 25°C [77°F]). Refer to the venetoclax package insert for complete details, as applicable (VENCLEXTA USPI, VENCLYXTO SmPC).

6.2.3 Azacitidine

Azacitidine is commercially available as a lyophilized powder. The product is reconstituted as a suspension for subcutaneous injection or as a solution with further dilution for intravenous infusion.

Unreconstituted vials must be stored at room temperature (15°C [59°F] to 25°C [77°F]). Refer to the azacitidine package insert for complete details, as applicable (VIDAZA USPI, VIDAZA SmPC).

6.3 Measures to Minimize Bias: Randomization and Blinding

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. Approximately CCI patients will be randomized 1:1 to receive tamibarotene/venetoclax/azacitidine or venetoclax/azacitidine. 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 patient's RARA-positive status (inclusion criterion 2). For patients 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 Study Drug Compliance

Tamibarotene and venetoclax may be administered at the site or self-administered at home.

Azacitidine (subcutaneous or intravenous) will be administered under the supervision of the study site staff or trained designee (as needed).

When the study drug is administered at the site, patients will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

Compliance with tamibarotene will be assessed at each applicable study visit (Section 1.3). Patients will maintain diaries to include the date and time each dose of study drug is taken, including hour and minute. Patients are required to return the bottle(s) and unused study drug at each study visit. If a tablet is damaged (broken, crushed, split, etc.), the patient should record the information in the diary and bring the damaged tablet to the next study visit. The diaries, unused study drug, and study drug bottle will be used to assess study drug compliance and accountability.

A record of the quantity of study drug dispensed to and administered by each patient must be maintained and reconciled with study drug accountability records. Study drug start and stop dates, including dates for study drug delays and/or dose reductions, will also be recorded.

6.5 Dose Modification and Management of Toxicities

The instructions provided in Table 5 and Table 6 must be followed to adjust tamibarotene, azacitidine, or venetoclax dosing for management of toxicities.

It is not anticipated that tamibarotene dose modifications would be needed for hematologic events (i.e., cytopenias, complications associated with cytopenias [including infection], or bleeding). Consideration for relatedness should be given to the timing of the AE, the temporal association between the onset of the AE and the administration of azacitidine (Days 1 through 7) and tamibarotene (Days 8 through 28), and the known adverse reactions for tamibarotene (see IB) and venetoclax/azacitidine (see most current VIDAZA USPI/VIDAZA SmPC, VENCLEXTA USPI, VENCLYXTO SmPC).

Table 5: Dose Modifications

Adverse Events (AEs)	Dosage Modification
Grade 4 hematologic toxicity *Part 1*	**Occurrence of Grade 4 neutropenia (with or without fever or infection) or Grade 4 thrombocytopenia prior to achieving remission:** In most instances, do not interrupt venetoclax in combination with azacitidine due to cytopenias prior to achieving remission. **First occurrence of Grade 4 neutropenia (with or without fever or infection) or Grade 4 thrombocytopenia after achieving remission and lasting at least 7 days:** Delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine.[a] **Subsequent occurrences of Grade 4 neutropenia (with or without fever or infection) or Grade 4 thrombocytopenia in cycles after achieving remission and lasting 7 days or longer:** Delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine and reduce venetoclax

Adverse Events (AEs)	Dosage Modification
	duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.[a] If Grade 4 hematologic toxicity does not resolve after venetoclax/azacitidine dose modifications have been attempted, the dose of tamibarotene may be reduced by 1 Dose Reduction Level (Table 6).
Part 2 and Part 3	**Occurrence of Grade 4 neutropenia (with or without fever or infection) or Grade 4 thrombocytopenia prior to achieving remission:** In most instances, do not interrupt venetoclax in combination with azacitidine due to cytopenias prior to achieving remission. **Subsequent Grade 4 neutropenia/thrombocytopenia after achieving remission (<5% blasts) and lasting 7 days or longer** Döhner **2022):** Delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine but reduce the venetoclax duration by 7 days during subsequent cycle (first occurrence reduce from 28 to 21 days, second occurrence reduce from 21 to 14 days, third occurrence reduce from 14 to 7 days). For severe marrow hypoplasia, azacitidine dosing may be modified as outlined in the most current VIDAZA USPI/VIDAZA SmPC. If Grade 4 hematologic toxicity does not resolve after venetoclax adjustments above, the dose of tamibarotene may be reduced by 1 Dose Reduction Level (Table 6).
Retinoic acid syndrome (RAS)[b]	Hold tamibarotene until RAS is considered controlled and Grade ≤2. See Section 6.8.8 for additional information on monitoring and treatment of RAS.
Grade 4 hypertriglyceridemia	Hold tamibarotene until AE resolves to Grade ≤1 or baseline. Tamibarotene treatment may resume at the previous dose level once the AE has resolved to Grade ≤1 or baseline. Should the same AE recur, the dose of tamibarotene will be reduced by 1 Dose Reduction Level (Table 6). Dosing may be increased to a prior dose level if the AE remains Grade ≤1 or at baseline for 14 days.
Serum electrolyte and renal toxicity	The dose of azacitidine should be modified as described in the most current VIDAZA USPI/VIDAZA SmPC or applicable locally approved labeling. If serum electrolyte and renal toxicity does not resolve after azacitidine dose modifications have been attempted, the dose of tamibarotene may be reduced by 1 Dose Reduction Level (Table 6).

Adverse Events (AEs)	Dosage Modification
Grade ≥3 non-hematologic toxicity (excluding hypertriglyceridemia and renal toxicity)	Hold venetoclax, if deemed related to venetoclax and not resolved with supportive care. Upon resolution of AE to Grade ≤1 or baseline, resume venetoclax at the same dose. Hold tamibarotene, if deemed related to tamibarotene and not resolved with supportive care, until AE resolves to Grade ≤1 or baseline. Tamibarotene treatment may resume at the previous dose level once the event has resolved to Grade ≤1 or baseline. Should the same AE recur, the dose of tamibarotene will be reduced by 1 Dose Reduction Level (Table 6). Dosing may be increased to a prior dose level if the AE remains Grade ≤1 or at baseline for 14 days. If attribution is unclear, follow tamibarotene dose modification first. If AE does not resolve, next attempt venetoclax modifications.

Note: Tamibarotene administration should not be resumed in the case of ≥28-day dose delay due to treatment-related AEs.

[a] Venetoclax will be discontinued for patients with ≥21-day delay in starting the next cycle; treatment with azacitidine and tamibarotene may continue.

[b] Also referred to as differentiation syndrome.

Table 6: Dose Reductions of Tamibarotene

Dose Level	Tamibarotene Dose
Initial Dose: Level 0	6 mg twice per day (BID)
CCI [redacted]	[redacted]
[redacted]	[redacted]

6.5.1 Dose Delay or Toxicity-related Discontinuation of One or More Study Drugs

If criteria for hold of 1 study drug in the combination regimen are met (Table 5), the administration of the other drug(s) in the regimen may continue, unless hold criteria for the other drug(s) are met. If azacitidine is held, then Day 1 of the next treatment cycle is delayed until azacitidine dosing may resume.

If implementation of the dose modification guidelines described in Table 5 (including dose holds and reductions) was not sufficient to adequately manage toxicity, the relevant study drug(s) should be discontinued. Discontinuation of 1 or 2 of the 3 drugs, while continuing administration of the other study drug(s), may occur. If only azacitidine is permanently discontinued, Day 1 of the next treatment cycle may resume within 3 days of the decision to discontinue azacitidine.

If implementation of dose modifications described in Table 5 is insufficient to adequately manage toxicity and discontinuation of all study drugs in the patient's regimen is required, the patient should have an EoT Visit.

6.5.2 Hypertriglyceridemia

Significant increases in both cholesterol and triglycerides have been reported with tamibarotene in patients with APL. Similarly, increases in triglycerides have been reported in patients with AML. Based upon these findings, tamibarotene should be cautiously administered to patients

with a disposition of hypertriglyceridemia such as those with diabetes mellitus, obesity, alcoholism, or abnormal lipid metabolism.

6.5.3 Sensitivity to Sodium Hydrosulfite

It is possible that tamibarotene drug substance may contain a small amount of sodium hydrosulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in individuals with asthma.

6.5.4 Interstitial Lung Disease

Interstitial lung disease has been reported in patients with APL and hepatocellular carcinoma treated with tamibarotene (frequency lower than 5%). Patients must be carefully monitored (including chest X-rays as appropriate) for interstitial lung disease. If abnormalities are observed, tamibarotene should be discontinued and appropriate treatment administered (i.e., adrenocortical steroids).

6.6 Continued Access to Study Drug After the End of the Study

At the time of study termination, if there are patients benefitting from treatment in the opinion of the investigator, the investigator should contact the medical monitor to discuss the possibility of treatment continuation.

6.7 Treatment of Overdose

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.
- Evaluate the patient to determine, in consultation with the medical monitor, whether study drug should be interrupted, reduced, or remain unchanged.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities. Note: while overdose itself is not considered to be an AE or SAE, any overdose complication will be reported as an AE or SAE.

6.7.1 Tamibarotene

There has been no experience with acute overdose of tamibarotene in humans. However, overdose with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness, and ataxia. These symptoms have resolved quickly without apparent residual effects. The sponsor does not recommend specific treatment for an overdose. Management of overdose with tamibarotene should focus on monitoring target organ function to preserve their viability and prevent complications.

6.7.2 Venetoclax

Overdose of venetoclax should be managed as described in the product label (VENCLEXTA USPI, VENCLYXTO SmPC). For patients who experience overdose of venetoclax, closely monitor and provide appropriate supportive treatment; during ramp-up phase, interrupt venetoclax and monitor carefully for signs and symptoms of tumor lysis syndrome along with other toxicities. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax. There is no specific antidote for venetoclax.

6.7.3 Azacitidine

Overdose of azacitidine should be managed as described in the product label (VIDAZA USPI, VIDAZA SmPC). One case of overdose with azacitidine was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. In the event of overdose, the patient should be monitored with appropriate peripheral blood count tests and should receive supportive treatment, as necessary. There is no known antidote for azacitidine overdose.

6.8 Concomitant Therapy

Concomitant therapy must be documented as described in Section 8.2.1.

6.8.1 Cytotoxic or Investigational Therapy

No concomitant cytotoxic or investigational therapy is allowed during the study.

6.8.2 Growth Factors

G-CSF may be administered if clinically indicated for neutropenia.

6.8.3 Oral Hydroxyurea

Concomitant hydroxyurea treatment is permitted during the study, as clinically determined. Treatment with hydroxyurea for greater than 7 consecutive days requires medical monitor approval.

6.8.4 Platelet Transfusions

Administration of platelet transfusions may be utilized throughout the study, as clinically determined.

6.8.5 Red Blood Cell Transfusions

Administration of red blood cell (RBC) transfusions may be utilized throughout the study, as clinically determined.

6.8.6 CCI and P-gp Inhibitors

Though the in vitro CCI metabolism of tamibarotene appears to be primarily due to CCI, a clinical drug-drug interaction study with CCI; Study SY-1425-102) in healthy adult study participants showed that there was no clinically significant change in tamibarotene plasma PK exposure when co-administered with itraconazole. These results demonstrate that CCI is not a major enzyme involved in the clearance of tamibarotene, and therefore, CCI should not have a clinically significant impact on tamibarotene PK exposure.

6.8.7 Antifibrinolytic

Investigators should be advised of the potential for thrombosis observed when drugs similar to tamibarotene (e.g., ATRA/tretinoin) have been combined with an antifibrinolytic. Antifibrinolytic medicines should be used with caution while on study drug.

6.8.8 Retinoic Acid Syndrome

Patients should be carefully monitored for the development of retinoic acid syndrome (RAS). High-dose dexamethasone (i.e., 10 mg/m^2 intravenous twice daily), and supportive measures (e.g., diuretics, dialysis, mechanical ventilation) as needed, should be implemented at the earliest suspicion of RAS. Glucocorticoid therapy should continue until complete disappearance of symptoms and then tapered. Tamibarotene therapy should be temporarily discontinued until RAS is considered controlled and Grade ≤2.

6.8.9 Multivitamin and Supplements

Vitamin A supplements (>10,000 IU/day) are not allowed while on study drug.

6.8.10 Antacids and Proton Pump Inhibitors

Antacids, H_2-receptor antagonists such as cimetidine, and proton pump inhibitors such as omeprazole should be used with caution while on study drug, as exposure to tamibarotene may be increased when these products are used concomitantly. Patients must be monitored for AEs, with dose adjustments for toxicity as described in Section 6.5.

7 DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Drug Administration

If the patient discontinues treatment or study participation prior to confirmation of screening RARA results and RARA-positivity is confirmed by Cycle 1 Day 8, the patient will be enrolled (Part 1)/randomized (Part 2), and the data from Cycle 1 Day 1 until the time of study discontinuation will be captured (including AEs and the reason for discontinuation of treatment).

Enrolled (Part 1)/randomized (Part 2) patients will continue to receive study drug until they meet one of the following criteria:

- An unacceptable toxicity (AEs that would result in permanent discontinuation of study drug)
- An AE related to study drug that requires ≥28 days (1 cycle) of dose interruption of all study drugs (i.e., tamibarotene, venetoclax, and azacitidine)
- Failure to achieve a minimum response of PR following the completion of the Cycle 3 EoC response assessment
- Disease progression/relapse and not eligible for transition to Part 3
- Decision to pursue post-remission therapy (such as HSCT) or an alternative anticancer therapy
- Patient withdraws consent for further study drug (interventional therapy) administration. The site should clarify with the patient if they maintain consent to follow-up visits and calls after the end of study drug administration
- Investigator determines it is in the best interest of the patient to discontinue study drug (interventional therapy) administration

An EoT Visit should occur within 3 days of the last dose of study drug (or within 3 days of decision to permanently stop study 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. If the EoT Visit occurs ≥30 days after the last dose of study drug, it may be combined with the Safety Follow-up Visit.

Patients will continue participation in all applicable follow-up assessments according to the SoAs (Section 1.3).

7.2 Discontinuation of Study Participation by Patient's Withdrawal of Informed Consent

- If a patient withdraws consent to study participation, study drug administration will be terminated and no additional follow-up will occur. Public sources may be searched for vital status information.
- The sponsor may retain and use any data collected before withdrawal of consent for study participation.
- If a patient withdraws his/her informed consent, he/she may request destruction of any samples taken and not yet tested, and the investigator must document this in the patient's medical records.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to comply with the protocol and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have discontinued from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoAs (Section 1.3), is essential and required for study conduct.
- All pre-screening and screening evaluations must be completed by Cycle 1 Day 1 and all results reviewed by Cycle 1 Day 1, with the exception of RARA results, which must be reviewed by Cycle 1 Day 8. Minimal details of all patients screened will be captured to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized

for screening purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs (Section 1.3).

- The maximum amount of blood collected from each patient over the duration of the study is specified in the ICF.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- For all enrolled (Part 1)/randomized (Part 2) patients, any untoward medical occurrences that happen before the first dose of venetoclax/azacitidine on Cycle 1 Day 1 should be captured as a part of medical history.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoAs (Section 1.3). Unscheduled efficacy assessments during the study will also be collected in the electronic data capture (EDC) system.

8.1.1 Response Assessment

Responses are evaluated in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh (Appendix 6). Additional unscheduled hematology evaluations may be performed prior to commencement of the next treatment cycle to reflect the best AML response achieved.

In addition to on-treatment assessments, after the EoT visit, patients 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. Response assessments during Disease Follow-up visits where the bone marrow aspirates are not performed are based on hematology evaluation and physical examination findings.

Patients 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.

8.1.2 Bone Marrow Sample Collection

A screening bone marrow aspirate will be performed, with samples collected for local assessment of blast count, cytogenetics, immunophenotype, and AML-associated gene mutations. An additional aspirate sample should be collected if possible and sent to the Central Laboratory for exploratory analyses. Bone marrow samples collected within 30 days of Cycle 1 Day 1 as a part of SOC are acceptable and in that setting a marrow would not need to be repeated for the sole purpose of gathering the exploratory sample; however, collection of the exploratory sample is encouraged. Anonymized reports will be uploaded to the EDC.

Part 1: The bone marrow aspirate samples for local assessment of response (blast count, cytogenetics, and assessment of minimal residual disease) will be collected at the EoC Visit of

Cycles 1, 2, and 3, followed by every third cycle (6, 9, 12, etc.), at the EoT Visit, and at every other visit during the Disease Follow-up period (every 6 months), with bone marrow aspirates collected at other times as clinically determined. If a patient achieves a CR/CRi at the Cycle 1 EoC Visit, the Cycle 2 EoC bone marrow aspirate is not required. Anonymized reports will be uploaded to the EDC. At each bone marrow aspirate draw, an additional aspirate sample will be collected and sent to the Central Laboratory for exploratory analyses.

Part 2 and Part 3: The bone marrow aspirate samples for local assessment of response (blast count, cytogenetics, and assessment of MRD) will be collected between Days 14 and 21 of Cycle 1, with venetoclax administration proceeding in alignment with ELN 2022 recommendations (Döhner 2022). For those with blast clearance (<5% blasts) at that initial assessment, no Cycle 1 EoC bone marrow aspirate is required. For patients with ≥5% blasts at that initial assessment, Cycle 1 EoC bone marrow aspirate will be completed. Subsequent bone marrow aspirates for all patients will be collected at the EoC Visit of Cycles 2 and 3, followed by every third cycle (6, 9, 12, etc.); at the EoT Visit; and at every other visit during the Disease Follow-up period (every 6 months), with bone marrow aspirates collected at other times as clinically determined. If a patient achieves a CR/CRi within Cycle 1 response assessment(s), the Cycle 2 EoC bone marrow aspirate is not required. Anonymized reports will be uploaded to the EDC. At each bone marrow aspirate draw, an additional aspirate sample will be collected and sent to the Central Laboratory for exploratory analyses.

Instructions for the collection and handling of the bone marrow samples will be provided separately in the Laboratory Manual.

8.1.3 Blood Product Transfusions

For all enrolled (Part 1)/randomized (Part 2) patients, all RBC and platelet transfusions received by the patient from 8 weeks prior to Cycle 1 Day 1 through the Safety Follow-up period will be recorded.

8.1.4 Overall Survival

All patients will be followed for OS every 3 months for up to 3 years after discontinuation of study drug. If the patient withdraws consent for study participation (Section 7.2) or is lost to follow-up (Section 7.3), public sources may be searched for vital status information.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

8.2.1 Prior, Concomitant, and Subsequent Medication Review

For all enrolled (Part 1)/randomized (Part 2) patients, every medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements), vaccine, and blood product used by the patient within 30 days of Cycle 1 Day 1 or at any time during the course of the study treatment, up to the Safety Follow-up Visit, must be documented, including:

- reason for use;
- dates of administration, including start and end dates;
- dosage information, including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Subsequent anticancer therapies (including HSCT) following EoT will be recorded.

8.2.2 ECOG Performance Status

A copy of the ECOG Performance Status criteria is provided in Appendix 5.

8.2.3 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, Cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.4 Vital Signs

- Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements should be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs should 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.

8.2.5 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. Fridericia formula should be used to calculate QTc. Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

ECGs should be performed after an approximately 10-minute rest period.

8.2.6 Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor, or until the Safety Follow-up Visit, whichever is first.
- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor should be notified.
- All protocol-required local laboratory tests, as defined in Appendix 2, will be conducted in accordance with local laboratory practices.
- If laboratory values from unscheduled laboratory tests performed at the institution's local laboratory require a change in patient health management or are considered clinically significant by the investigator (e.g., SAE, AE, or dose modification), then the results must be recorded in the EDC as Unscheduled Labs.

8.2.7 Pregnancy Testing

A pregnancy test (high-sensitivity urine or serum) must be performed for WOCBP at the time points listed in the SoAs (Section 1.3).

If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs; the method of recording, evaluating, and assessing causality of AEs and SAEs; and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative [LAR]).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

For all enrolled (Part 1)/randomized (Part 2) patients, AEs and SAEs will be captured from the time of the first dose of venetoclax/azacitidine on Cycle 1 Day 1 through the Safety Follow-up Visit. This will require collecting safety data for all treated patients from Cycle 1 Day 1 onward (until RARA status is confirmed) to enable timely reporting (SAEs) and capture in the eCRF (AEs) upon enrollment (Part 1)/randomization (Part 2).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

Contact information for the Pharmacovigilance group is provided in Appendix 3.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient should be used to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study drug and until 90 days after the last dose of study drug.

- If a pregnancy is reported, the investigator will record pregnancy information on the pregnancy notification form and submit it to the sponsor's designee via email at SyrosPV@primevigilance.com or Fax #: 1-855-234-6419 within 24 hours of learning of the female patient's or female partner's of male patient (after obtaining the necessary signed informed consent from the female partner) pregnancy.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The patient/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient/pregnant female partner and the infant and the information will be forwarded to the sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study patients/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female patient who becomes pregnant while participating in the study will discontinue study drug(s).

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

8.3.6.1 Disease Progression

Progression of the underlying disease, including death from progression of the underlying disease, is considered an efficacy outcome parameter and should not be captured as an AE/SAE. Documentation of the progression of disease must be obtained and recorded in the EDC.

If a patient dies of their disease during the reporting period, progressive disease (PD) and/or PD with a fatal outcome does not need to be reported as an SAE. The applicable protocol electronic case report form (eCRF) page(s) pertaining to death (End of Treatment, End of Study, Death pages) should be completed per eCRF completion guidelines.

8.3.6.2 New Cancers

The development of a new primary cancer in enrolled (Part 1)/randomized (Part 2) patients should be regarded as an AE and will generally meet at least one of the seriousness criteria (Section 10.3.2). New primary cancers are those that are not the primary reason for the administration of study drug and have developed after the patient has received at least 1 dose of study drug upon enrollment/randomization in the study. They do not include metastases of the original cancer.

Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

8.4 Pharmacokinetics

Samples will be collected from all patients in Part 1 and patients receiving triplet therapy in Part 2. Samples will be analyzed using a validated bioanalytical assay.

- Whole blood samples will be collected for measurement of plasma concentrations of tamibarotene.
- It is important that the actual date and time of each sample should be recorded.
- If a PK sample is collected outside of the schedule specified for Part 1 in the SoA (Section 1.3), this will not qualify as a protocol deviation, as long as the exact date and times of PK sample and applicable dosing are recorded.
- Unscheduled samples may be collected at additional time points during the study, if warranted (e.g., safety event evaluation) and agreed upon between the investigator and the sponsor.
- Instructions for the collection and handling of the PK samples will be provided separately.

8.5 Genetics and Pharmacogenomics

Germline genetics and pharmacogenomics are not evaluated in this study.

8.6 Biomarkers

8.6.1 RARA Biomarker Assessment

This study will be evaluating the presence of a biomarker based on the expression levels of *RARA* messenger RNA in peripheral blood mononuclear cells. The biomarker will be assessed as

"RARA-positive" or "RARA-negative" based on an investigational assay, conducted at the Almac Diagnostics Laboratory. This investigational assay will also be used to explore potential changes in the RARA biomarker associated with treatment.

8.6.2 Companion Diagnostic Assay Development

Blood samples will be used for development of companion diagnostic assays for the RARA biomarker. Samples with residual material following completion of companion diagnostic assay development may also be used for exploratory research to evaluate AML molecular features associated with response to drug treatment and loss of response to drug treatment (Section 8.6.3).

8.6.3 Molecular Markers of Tumor Response and Resistance

Blood samples will be collected for exploratory research to evaluate AML molecular features associated with response to drug treatment and loss of response to drug treatment. Bone marrow aspirates (Section 8.1.2) may also be analyzed centrally for exploratory research to evaluate genetic mutations and/or gene expression markers associated with response and loss of response.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis for Part 2

Null hypothesis (H0): In RARA-positive patients with previously untreated AML who are ineligible for standard induction therapy, the CR/CRi rate in the tamibarotene/venetoclax/azacitidine arm is the same as the CR/CRi rate in the venetoclax/azacitidine arm.

Alternative hypothesis (H1): In RARA-positive patients with previously untreated AML who are ineligible for standard induction therapy, the CR/CRi rate in the tamibarotene/venetoclax/azacitidine arm is higher than the CR/CRi rate in the venetoclax/azacitidine arm.

The level of significance for the analysis of the primary endpoint is 1-sided at 0.05.

Adjustments for multiplicity will not be performed.

9.2 Sample Size Determination

Up to approximately CCI patients will be treated in Part 1. The actual number of tamibarotene dose levels explored in combination with venetoclax/azacitidine, and the number of patients treated at each dose regimen, will vary depending on the totality of evaluated data (including safety, dose modifications, and tamibarotene PK data) from patients treated with the tamibarotene/venetoclax/azacitidine combination. With CCI patients treated, there is approximately CCI% probability of observing at least 1 AE with an event rate of CCI%. With CCI patients treated, there is approximately CCI% probability of observing at least 1 AE with an event rate of CCI%.

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

9.3 Analysis Sets

For the purposes of the analyses, the following analysis sets are defined:

Part 2 Modified Intent-to-treat (mITT) Population	All RARA-positive patients who are randomized in Part 2 starting treatment from Cycle 1 Day 1. Treatment groups for this analysis set will be determined according to the treatment assignment at the time of randomization.
Part 1 Safety Population	All enrolled RARA-positive patients who have received any amount of study drug (tamibarotene, venetoclax, or azacitidine)
Part 2 Safety Population	All randomized RARA-positive patients 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 patients received.
Part 2 Per-protocol Population	All patients in Part 2 mITT Population who are considered to be sufficiently compliant with the protocol. Specific criteria for this population will be defined in the statistical analysis plan.
PK Evaluable Population	All patients who are have received at least 1 dose of tamibarotene and have at least 1 quantifiable PK concentration comprise the PK evaluable analysis population.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.4.1 General Considerations

The level of significance for the analysis of the Part 2 primary endpoint is 1-sided at 5%. All secondary and exploratory endpoints for Part 1 and Part 2 will 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.

Frequency distributions will be used for categorical variables and appropriate summary statistics (i.e., mean, median, and range) for quantitative/continuous variables.

Additional details of the analyses will be provided in the SAP.

9.4.2 Primary Endpoint

Part 1

The number and percentage of patients with AEs, including AEs leading to dose modifications or discontinuations, and SAEs will be summarized. Laboratory values and changes in values from baseline will be summarized descriptively by visit, and shift tables will be provided showing changes in NCI CTCAE (version 5) grade from baseline to worst grade postbaseline. Descriptive summaries will be provided for ECG and vital sign values, changes in values from baseline, and categorical summaries. The number and percentage of patients with dose modifications will be summarized.

Part 2

Patients will be assessed for the primary endpoint of CR/CRi from the time of Cycle 1 Day 1 until the initiation of non-study drug therapy or until time of disease progression/relapse. CR/CRi rate and 95% exact binomial CIs will be calculated by treatment group in the mITT Population. Patients who do not have a post-baseline response assessment will be considered non-responders and included in the denominator when calculating the response rate analysis. In addition, patients who do not achieve a response and 1) die, 2) have a transplant, 3) experience prolonged treatment interruption requiring permanent withdrawal of study drug, and/or 4) start a new systemic therapy will also be considered non-responders. The Fisher's exact test will be applied to compare the CR/CRi rates between the 2 treatment groups. The analysis of the CR/CRi rate is planned for the time when the last patient has completed the Cycle 3 EoC response assessment or discontinued treatment earlier.

9.4.3 Secondary Endpoints

Part 1

The estimated ORR will be provided with corresponding 95% exact binomial CIs. Patients who do not have a post-baseline response assessment will be considered non-responders and will be included in the denominator.

Part 2

The number and percentage of patients with AEs, including AEs leading to dose modifications or discontinuations, and SAEs will be summarized. Laboratory values and changes in values from baseline will be summarized descriptively by visit, and shift tables will be provided showing changes in NCI CTCAE (version 5) grade from baseline to worst grade postbaseline. Descriptive summaries will be provided for ECG and vital sign values, changes in values from baseline, and categorical summaries. The number and percentage of patients with dose modifications will be summarized.

Table 7: Estimands

Objective	Estimand Category	Estimand			
		Variable	Analysis Set	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 patients	Primary	CR/CRi	mITT	• New anti-cancer therapy: while on treatment • Treatment discontinuation: treatment policy	CR/CRi percentage by treatment arm
	Supplementary	CR/CRi	PP	• New anti-cancer therapy: while on treatment • Treatment discontinuation: treatment policy	CR/CRi percentage by treatment arm

Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRi = CR with incomplete blood count recovery; mITT = modified intent-to-treat; PP = per protocol; RARA = retinoic acid receptor alpha.

The difference in CR/CRi rate between the 2 treatment groups and corresponding 95% CIs will be calculated.

CR rate and 95% exact binomial CIs will be calculated by treatment group. Patients who do not have any post-baseline response assessment will be considered as non-responders and will be included in the denominator. The Fisher's exact test will be applied to compare the CR rates between the 2 treatment groups.

CR/CRh rate and 95% exact binomial CIs will be calculated by treatment group. Patients who do not have any post-baseline response assessment will be considered as non-responders and will be included in the denominator. The Fisher's exact test will be applied to compare the CR/CRh rates between the 2 treatment groups.

Kaplan-Meier estimation of median duration of CR, median duration of CR/CRi, and median duration of CR/CRh and respective 95% CIs will be presented by treatment group.

Time to CR, time to CR/CRi, and time to CR/CRh will be summarized descriptively for the 2 treatment groups.

ORR rate and 95% exact binomial CIs will be calculated by treatment group. Patients who do not have a post-baseline response assessment will be considered as non-responders and will be included in the denominator. The Fisher's exact test will be applied to compare the ORR rates between the 2 treatment groups.

9.4.4 Exploratory Endpoints

Concentration-time data for tamibarotene will be included in the Clinical Study Report as listings; no formal non-compartmental analysis will be performed.

Analyses of the other exploratory endpoints will be described in the SAP.

9.5 Interim Analysis

An interim futility analysis of the CR/CRi rates is planned in Part 2 for the first 40 treated RARA-positive patients and will be performed after the 40th randomized patient has received approximately 3 months of study drug or has discontinued treatment due to disease progression, withdrawal of consent, or death. 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 >0.428. The non-binding futility bound is derived using an HSD spending function with gamma = -2 (Hwang 1990).

Administrative interim analyses may be performed after approximately 25%, 50%, and 75% (20, 40, and 60) patients have had 3 cycles of treatment. No multiplicity adjustments are needed since the study will not be stopped for efficacy until the primary analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the currently approved protocol and any other study agreements and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - (EU) No 536/2014
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to the safety and welfare of patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study and adherence to all applicable regulations

10.1.2 Informed Consent Process

- A Pre-screening ICF and a Main ICF will be used in this study, as shown in the SoAs (Section 1.3). Patients who begin Cycle 1 Day 1 prior to enrollment (Part 1)/randomization (Part 2) must use the Main ICF.

- The investigator or his/her representative will explain the nature of the study to the patient/LAR and answer all questions regarding the study.

- Patients must be informed that their participation is voluntary. Patients/LARs will be required to sign an IRB/IEC-approved ICF that meets the requirements of 21 CFR 50 and 56, local regulations, ICH guidelines, and Health Insurance Portability and Accountability Act requirements, where applicable.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).

- Patients must be re-consented to the most current IRB/IEC-approved version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the patient/LAR.

10.1.3 Confidentiality and Data Protection

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Syros. However, authorized regulatory officials, IRB/IEC personnel, and Syros and its authorized representatives are allowed full access to the records.

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.

- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for their data to be used as described in the informed consent.

- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4 Committees Structure

10.1.4.1 Independent Data Monitoring Committee

There will be no formal IDMC. The sponsor will provide oversight of safety and tolerability at regularly scheduled intervals (and ad hoc if needed) via SRT meetings as detailed in the SRT Charter. In addition, regularly scheduled reviews of safety and tolerability will be performed by the sponsor in collaboration with the study investigators in Part 1 of the study. These reviews will inform the dose of tamibarotene to be combined with venetoclax/azacitidine in Part 2 of the study. Administrative interim analyses will be performed by the sponsor personnel or designee.

10.1.5 Dissemination of Clinical Study Data

Dissemination of the clinical study data will occur in alignment with Syros policies and any applicable local regulations.

10.1.6 Data Quality Assurance

- All patient data relating to the study will be recorded/uploaded in eCRFs via EDC. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The site shall retain all study documentation and any other documents required to be retained by applicable law for the longer of (i) 2 years after the marketing authorization approval or termination of the program or (ii) such longer period as required by applicable law. After the end of such period, if the site desires to destroy any study documentation or such other documents, the site shall notify the sponsor of such desire and the sponsor shall have 30 days after receipt of such notice to, at its option, either take custody of any study documentation or other documents the site proposes to destroy or allow the site to destroy such study documentation or other documents.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, based on what is required in the SoA. Also, current medical records must be available for monitoring.

- The source records are typically the patient's medical chart and other sources, such as tamibarotene dosing diary.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable compared to the source documents; that the safety and rights of patients are being protected; and that the study is being conducted as outlined in Section 10.1.1.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first patient pre-screened.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion at that site. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination:
  - Discontinuation of further study drug development
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the investigator

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the patients and should assure appropriate patient therapy and/or follow-up.

10.1.9 Publication Policy

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements. The publication of study results will be governed by the applicable clinical trial agreement between the sponsor and the study site and investigator (as applicable).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory as specified in the SoAs (Section 1.3) and Section 8.2.6.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Protocol-Required Safety Laboratory Tests

Lab Tests	Parameters		
Hematology	Platelet Count Hemoglobin White blood cell (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 and white blood cells, leukocyte esterase, ketones, and nitrite		
Pregnancy testing	• Highly sensitive serum or urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[a]		
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)		

NOTES:

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

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: 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.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Medical conditions present prior to the first dose of study drug that are being treated at baseline will be captured as medical history unless the frequency, severity, or character of the condition worsens during the study (after the first dose of any study drug), for which the condition would then be captured as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

10.3.2 Definition of SAE

An SAE is defined as any serious AE that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Similarly, any planned hospitalization, such as for blood sampling for PK assessments, is not considered an AE or criterion for seriousness. Note: Complications that occur during hospitalization are AEs and if a complication prolongs hospitalization, then the event is serious.

d. Results in persistent or significant disability/incapacity

e. Is a congenital anomaly/birth defect

f. Other important medical events:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.
- Examples of such events include intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the Pharmacovigilance group in lieu of completion of the SAE required form.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The investigator will make an assessment of severity (Grades 1 through 5) for each AE and SAE reported during the study using NCI CTCAE, version 5.

Note: It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 10.3.2.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- Related assessment is reported when a "reasonable possibility" of a relationship between study drug administration and AE exists. "Reasonable possibility" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Pharmacovigilance group. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Pharmacovigilance group. It is helpful if the investigator includes the rationale for the assessment as being causally related, or not causally related, in the transmission of the SAE data.

- The investigator may change his/her opinion of causality based upon follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the Pharmacovigilance group with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor's designee via email at SyrosPV@primevigilance.com or Fax #: 1-855-234-6419 within 24 hours of receipt of the information. The investigator may also be asked by the sponsor to provide clarification or additional information.

10.3.4 Reporting of SAEs

SAE Reporting to Pharmacovigilance Group

- An SAE Report form will be completed and submitted to the sponsor's designee via email at SyrosPV@primevigilance.com or Fax #: 1-855-234-6419 within 24 hours of the investigator's first knowledge of the event, even if the experience does not appear to be related to study drug.
- The initial SAE Report form must be as complete as possible, including details of the current illness and SAE and an assessment of the relationship between the event and the study drug. Additional information relating to a previously reported SAE must also be reported within 24 hours of the investigator's first knowledge of information. The investigator may also be asked by the sponsor to provide clarification or additional information.
- If the investigator becomes aware of an SAE considered related to study drug by the investigator occurring more than 30 days after the last dose of study drug, the SAE must be reported as described above.

10.3.5 Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committees, and Institutional Review Board

The sponsor will determine the expectedness for each reported SAE based on the appropriate reference safety information per local requirements. The sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs per local requirements. The sponsor or designee shall notify the investigator of serious, related, and unexpected AE(s) per local country requirements.

The investigator will notify the appropriate IRB/IEC of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The investigator must keep records of all AE information on file, including correspondence with the sponsor and IRBs/IECs.

10.4 Appendix 4: Contraceptive and Barrier Guidance

Contraceptive use by men and women should be consistent with description below or with local requirements (as defined in local informed ICF) for those participating in clinical studies.

Tamibarotene has been reported to cause abnormalities in spermatogenesis in nonclinical studies in rats and dogs. Patients who are fertile must agree to use 2 methods of birth control including a barrier method (e.g., latex condom, diaphragm, or cervical cap) combined with an intrauterine device (IUD) or birth control pills while taking tamibarotene. Contraception use must be continued for at least 90 days after the last dose of study drug for men and 6 months for women. Men/women should not donate sperm or ova during this timeframe. Male patients should consider banking sperm before tamibarotene is administered.

10.4.1 Definitions

Woman of Childbearing Potential

Women in the following categories are considered to be of childbearing potential (fertile):

1. Following menarche.
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below).
    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        i. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
        ii. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before Cycle 1 Day 1.
    b. Permanent sterilization methods (for the purpose of this study) include:
        i. Documented hysterectomy
        ii. Documented bilateral salpingectomy
        iii. Documented bilateral oophorectomy

iv. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

c. If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Woman of Nonchildbearing Potential

Women in the following categories are considered NOT to be of childbearing potential:

1. Premenopausal female with permanent infertility due to one of the following:

   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

2. Postmenopausal female

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before Cycle 1 Day 1.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

As published in Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55.

10.6 Appendix 6: Response Criteria for AML

Responses are evaluated as summarized below, in alignment with ELN AML criteria (Döhner 2017) and Bloomfield 2018 for CRh.

Response Category	**Definition**			
	ANC (/µL)	*Platelets (/µL)*	*Bone Marrow Blasts (%)*	*Comment*
CR without MRD (CR_{MRD-})	≥1,000	≥100,000	<5	All CR criteria met and absence of MRD as accessed by multiparameter flow cytometry, qPCR, or next generation sequencing
Complete Remission (CR)	≥1,000	≥100,000	<5	Absence of circulating blasts and blasts with Auer rods; absence of EMD
CR with incomplete hematologic recovery (CR_i)	<1,000 -or	<100,000	<5	All CR criteria met except either neutrophils or platelets not recovered
CR with partial hematologic recovery (CR_h)	>500	>50,000	<5	All CR criteria met except ANC and platelets with partial recovery of peripheral counts
Morphologic leukemia-free state (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.
Partial Remission (PR)	≥1,000	≥100,000		≥50% decrease from baseline, with decrease to 5-25
Stable disease	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 (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.			

Abbreviations: ANC = absolute neutrophil count; EMD = extramedullary disease; MRD = minimal residual disease; qPCR = quantitative polymerase chain reaction; WBC = white blood cell.

[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.

10.7 Appendix 7: Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse event
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
ART	Anti-retroviral therapy
AST	Aspartate aminotransferase
ATRA	All-trans retinoic acid
BID	Twice daily
CHF	Congestive heart failure
CI	Confidence interval
CR	Complete remission
CRh	CR with partial hematologic recovery
CRi	CR with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interaction
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EF	Ejection fraction
ELN	European LeukemiaNet
EoC	End of Cycle
EoT	End of Treatment
EU	European Union
FEV_1	Forced expiratory volume in one second
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating growth factor
HCV	Hepatitis C virus

Abbreviation	Definition
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HRT	Hormonal replacement therapy
HSCT	Hematopoietic stem cell transplantation
HSD	Hwang-Shih-DeCani
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally authorized representative
mITT	Modified intent-to-treat
MLFS	Morphologically leukemia-free state
NCI	National Cancer Institute
ND	Newly diagnosed
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
QTcF	QTc interval calculated using Fridericia formula
RARα	Retinoic acid receptor alpha
RAS	Retinoic acid syndrome
RBC	Red blood cell
RNA	Ribonucleic acid
R/R	Relapsed/refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	Standard of care
SRT	Safety Review Team
ULN	Upper limit of normal
US	United States

Abbreviation	Definition
USPI	United States Prescribing Information
WBC	White blood cell
WOCBP	Women of childbearing potential

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