Clinical Study Protocol

Protocol Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study of Tamibarotene Plus Azacitidine Versus Placebo Plus Azacitidine in Newly Diagnosed Adult Patients Selected for RARA-positive Higher-risk Myelodysplastic Syndrome

Protocol Number: SY-1425-301

Amendment Number: 4.1

Compounds: Tamibarotene (formerly SY-1425) and azacitidine

Brief Title: Phase 3 Study of Tamibarotene Plus Azacitidine in Patients Selected for RARA-positive Higher-risk MDS (SELECT-MDS-1)

Study Phase: 3

Sponsor Name: Syros Pharmaceuticals, Inc.

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Amendment 1 GER (Version 1.5)	14 July 2021
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Amendment 1 BEL (Version 1.3)	28 April 2021
Amendment 1 FRA (Version 1.2)	06 April 2021
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Original Protocol (Version 1.0)	23 October 2020

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)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study of Tamibarotene Plus Azacitidine Versus Placebo Plus Azacitidine in Newly Diagnosed Adult Patients Selected for RARA-positive Higher-risk Myelodysplastic Syndrome

Brief Title: Phase 3 Study of Tamibarotene Plus Azacitidine in Patients Selected for RARA-positive Higher-risk MDS (SELECT-MDS-1)

Rationale:

Tamibarotene (formerly SY-1425) is a potent and selective agonist of retinoic acid receptor alpha (RARα), approved for the treatment of relapsed/refractory acute promyelocytic leukemia (R/R APL) in Japan. Tamibarotene is being developed in a subset of non-APL acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (HR-MDS) patients who are RARA-positive, as identified by high levels of *RARA* expression in blasts. Initial clinical data in RARA-positive R/R AML and R/R HR-MDS patients treated with single agent tamibarotene demonstrated evidence of biological activity with myeloid differentiation and blast reductions (Jurcic 2017). In newly diagnosed, unfit AML patients, tamibarotene in combination with azacitidine showed high complete response (CR) rates and a rapid onset of action in RARA-positive patients (de Botton 2022). The adverse event (AE) profile of the combination was consistent with what has been previously reported for single agent tamibarotene or single agent azacitidine in treatment of AML/MDS patients (see Investigator's Brochure [IB], VIDAZA United States Prescribing Information [USPI], VIDAZA Summary of Product Characteristics [SmPC]). Approximately 30% of AML patients (Jurcic 2017, Vigil 2017, de Botton 2022) and approximately 50% of MDS patients (data on file as of 27 May 2022) are RARA-positive. HR-MDS and AML are closely related biologically, with common cytogenetic abnormalities and gene mutations present in the blast populations in each condition (Arber 2016). Historical precedent demonstrates that active agents in AML, specifically hypomethylating agents, are active in HR-MDS, supporting the rationale for further development of the combination of tamibarotene with azacitidine in the HR-MDS patient population. Azacitidine remains the standard of care for the treatment of HR-MDS (VIDAZA USPI, VIDAZA SmPC, National Comprehensive Cancer Network [NCCN] Guidelines for MDS, Malcovati 2013), however there is opportunity to improve upon the clinical outcomes of single-agent azacitidine. In this study, newly diagnosed, RARA-positive HR-MDS patients will be randomized to therapy with tamibarotene plus azacitidine or placebo plus azacitidine.

Inclusion Criteria:

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. Patients must be RARA-positive based on the investigational assay (Section 8.6.1).
3. Patients must be newly diagnosed with HR-MDS as follows:

Diagnosis of MDS according to the World Health Organization (WHO) classification (Arber 2016) and classified by the Revised International Prognostic Scoring System (IPSS-R) risk category as:

a. Very High (risk score >6),

b. High (risk score >4.5 to 6), OR

c. Intermediate (risk score >3 to 4.5).

4. Patients must have measurable disease with bone marrow blasts >5% at the Screening Visit.

5. Patients must have Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤2.

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

   a. total bilirubin ≤3.0 × the upper limit of normal (ULN),

   b. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN, and

   c. creatinine clearance ≥30 mL/min based on the Cockcroft-Gault Glomerular Filtration Rate estimation.

7. Patients must have a serum/high-sensitivity urine 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 document.

Exclusion Criteria:

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

1. Patients are suitable for and agree to undergo allogeneic hematopoietic stem cell transplantation (HSCT) at the time of screening.

2. Patients received prior treatment for MDS with any hypomethylating agent, chemotherapy (including lenalidomide), or allogeneic HSCT, with the exception of prior treatment with growth factors or hydroxyurea. Growth factor treatment must be

discontinued at least 2 weeks prior to starting study drug. Hydroxyurea treatment must be discontinued prior to starting study drug.

3. Patients with history of cancer are excluded if they are in active treatment (with radiation, chemotherapy, antibodies, immunotherapies, or molecularly targeted therapies) or unless they are disease free for at least 2 years prior to the Screening Visit, following completion of a prior treatment. Exceptions include: localized prostate cancer treated with hormone monotherapy; localized breast cancer treated with adjuvant hormone monotherapy; or 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 $\leq$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 investigational product 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. 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.

12. Patients known to be refractory to platelet or packed red blood cell transfusions per Institutional Guidelines, or patients who refuse blood product support.

13. Patients received CCI [redacted] (see CCI [redacted] within 2 weeks prior to the first tamibarotene/placebo administration.

14. 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.

15. Patients require concurrent treatment with any investigational or approved oncology agent, other than the agents described in exclusion criterion #3.

16. Patients with ≥20% blasts in peripheral blood or bone marrow or evidence of myeloid sarcoma (extramedullary AML).

17. Patients with Grade ≥2 hypertriglyceridemia, defined as >300 mg/dL (Common Terminology Criteria for Adverse Events [CTCAE], version 5).

18. 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).

19. 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).

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

21. Patients for whom treatment with tamibarotene or azacitidine is contraindicated.

22. Patients with clinically significant cardiovascular disease, including unstable angina, acute myocardial infarction within 3 months prior to the start of study drug administration, or New York Heart Association Class III or IV congestive heart failure, cerebral vascular accident within 3 months prior to the start of study drug administration, or cardiac arrhythmia associated with hemodynamic instability.

23. **Objectives and Endpoints:**

Objectives	**Endpoints**
Primary	
• Characterize and compare the CR rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• CR, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)
Key Secondary	
• Characterize and compare the OS of tamibarotene plus azacitidine vs. placebo plus azacitidine	• OS, defined as the time from the date of randomization to the date of death due to any cause

Objectives	Endpoints
Secondary	
• Characterize and compare the TI rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• TI, defined as a period of at least 56 days with no RBC or platelet transfusion since the date of randomization to the last dose of study drug +30 days, the initiation of post-treatment therapy, or death, whichever occurs first
• Characterize and compare the ORR of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Overall response, defined as achieving CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)
• Characterize the DOCR and duration of overall response of tamibarotene plus azacitidine or placebo plus azacitidine	• DOCR, defined as the duration from the date of first documented evidence of CR to the date of documented relapse of disease, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first • Duration of overall response defined as the duration from the date of first documented evidence of CR, PR, mCR, or HI, to the date of documented disease progression, relapse of disease as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first
• Characterize the time to CR and time to initial response of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Time to CR, defined as the duration from the date of randomization to the date of the first documented evidence of CR as determined by the investigator per the modified IWG MDS criteria (Cheson 2006) • Time to initial response, defined as the duration from the date of randomization to the date of the first documented evidence of CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)
• Characterize and compare the EFS of tamibarotene plus azacitidine vs. placebo plus azacitidine	• EFS, defined as the time from the date of randomization to the date of transformation to AML or death due to any cause, whichever occurs first
• Compare changes in HRQOL of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Change in HRQOL as measured by the EORTC QLQ-30 and EQ-5D-5L
• Characterize the safety of tamibarotene plus azacitidine vs. placebo plus azacitidine	• AEs and changes in clinical laboratory values, ECG results, and vital sign measurements
Exploratory	
• Characterize and compare the cytogenetic CR rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Cytogenetic CR, defined as patients achieving cytogenetic CR (Cheson 2006), as determined by the investigator
• Characterize and compare the molecular response rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Molecular response, defined as patients achieving a reduction in variant allele frequency by next generation sequencing
• Characterize and compare the change in transfusion requirements of tamibarotene	• Transfusion requirement, defined as the frequency and amount of blood products (RBC or platelet) received

Objectives	Endpoints
plus azacitidine vs. placebo plus azacitidine	
• Characterize and compare the rate of consolidation treatment with allogeneic HSCT following treatment with tamibarotene plus azacitidine vs. placebo plus azacitidine	• The rate of consolidation with allogeneic HSCT defined as the proportion of patients who are treated with allogeneic HSCT
• Characterize the PK of tamibarotene	• Plasma concentrations of tamibarotene
• Characterize MDS molecular features associated with response and with loss of response for tamibarotene plus azacitidine vs. placebo plus azacitidine	• Clinical response and genetic mutations and/or gene expression markers at baseline, at the time of response, and loss of response

Abbreviations: AE = adverse events; AML = acute myeloid leukemia; CR = complete remission; DOCR = duration of complete remission; ECG = electrocardiogram; EFS = event-free survival; EORTC QLQ30 = European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30; EQ-5D-5L = EuroQol 5 dimensions; HI = hematologic improvement; HRQOL = health-related quality of life; HSCT = hematopoietic stem cell transplantation; IWG = International Working Group; mCR = marrow CR; MDS = myelodysplastic syndrome; ORR = overall response rate; OS = overall survival; PK = pharmacokinetic(s); PR = partial remission; RBC = red blood cell; TI = transfusion independence; vs. = versus.

Overall Design:

This is a Phase 3, multi-center, randomized, double-blind, placebo-controlled study comparing the activity of tamibarotene plus azacitidine to placebo plus azacitidine as first line of therapy in RARA-positive patients with newly diagnosed HR-MDS. Enrollment in countries in North America and Europe and in Israel is planned.

At the Pre-screening Visit, blood samples will be collected and sent to the Almac Diagnostics Laboratory for assessment of RARA biomarker to determine study eligibility. Pre-screening assessments for the RARA biomarker will be performed within 45 days of Cycle 1 Day 1 and screening assessments for all other eligibility criteria will be performed within 30 days of Cycle 1 Day 1.

Patients will be randomized 2:1 to receive either tamibarotene plus azacitidine or placebo plus azacitidine. Randomization will be stratified by the IPSS-R risk group (Intermediate, High, and Very High Risk) and by geographical region (North America, Western Europe, and Israel versus Eastern Europe); block randomization with a block size of 6 will be used.

Response will be assessed by the investigator per the modified International Working Group (IWG) MDS criteria (Cheson 2006). Bone marrow aspirates will be collected to measure response on Day 1 of Cycles 2 and 4, followed by every third cycle (7, 10, 13, etc.), with bone marrow aspirates collected at other times as clinically determined based upon clinical findings or changes in peripheral blood counts. Following the response assessment on Day 1 of Cycle 7, those in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 cycles.

Patients will undergo response and safety evaluations throughout their study participation as detailed in the Schedule of Activities (Section 1.3). Patients may continue to receive study drug until experiencing an unacceptable toxicity, disease progression (including transformation into AML), 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.

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 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 if possible 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 5 years after discontinuation of study drug (irrespective of initiation of HSCT or other subsequent anticancer therapy) or until disease progression/relapse, death, or the occurrence of the expected number of overall survival (OS) events to support the final OS analysis, whichever occurs first. It is estimated that a final analysis of OS will occur approximately 70 months following the enrollment of the first patient.

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, the date of transformation to AML, and OS status until the expected number of OS events to support the final OS analysis is observed.

An independent data monitoring committee (IDMC) will be established and will review the data at the 2 planned interim futility analyses and the safety interims, as specified in the IDMC Charter.

Number of Patients:

Approximately CCI HR-MDS patients will be screened, with approximately CCI patients randomly assigned to tamibarotene plus azacitidine or placebo plus azacitidine.

Intervention Groups and Duration:

Patients will receive either tamibarotene plus azacitidine or placebo plus azacitidine.

- Tamibarotene/placebo will be administered at 6 mg twice per day (BID) (orally) each day on Days 8 through 28 of each 28-day treatment cycle.

- Azacitidine will be administered at 75 mg/m^2 (intravenously or subcutaneously) each day on Days 1 through 7 of each 28-day treatment 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/placebo is permitted to overlap with azacitidine on Days 8 through 9 of this alternative schedule.

Patients will receive treatment until they meet study drug discontinuation criteria, as described in the Overall Design. Patients will be followed until the number of OS events is sufficient to enable the final analysis.

Statistical Considerations

Statistical Hypotheses

Primary: CR Rate

Null hypothesis (H0): In RARA-positive patients with newly diagnosed HR-MDS, CR rate for patients in the tamibarotene plus azacitidine treatment group is the same as the CR rate for patients in the placebo plus azacitidine treatment group.

Alternative hypothesis (H1): In RARA-positive patients with newly diagnosed HR-MDS, CR rate for patients in the tamibarotene plus azacitidine treatment group is higher than the CR rate for patients in the placebo plus azacitidine treatment group.

Key Secondary: OS

Null hypothesis (H0): In RARA-positive patients with newly diagnosed HR-MDS, OS for patients in the tamibarotene plus azacitidine treatment group is the same as the OS for patients in the placebo plus azacitidine treatment group.

Alternative hypothesis (H1): In RARA-positive patients with newly diagnosed HR-MDS, OS for patients in the tamibarotene plus azacitidine treatment group is superior to the OS for patients in the placebo plus azacitidine treatment group.

Sample Size Determination

CCI patients will provide CCI power to detect the difference in CR rates between the tamibarotene plus azacitidine treatment group and the placebo plus azacitidine treatment group, with assumed CR rates of CCI versus CCI in the 2 treatment groups, respectively, a 2:1 randomization, and 1-sided alpha of CCI.

A total of CCI death events will provide CCI power to detect the difference in OS between the tamibarotene plus azacitidine treatment group and the placebo plus azacitidine treatment group, with assumed median survival of CCI months versus CCI months (hazard ratio = CCI) in the 2 treatment groups, respectively, a 2:1 randomization, and 1-sided alpha of CCI.

A total of approximately CCI patients (CCI in the tamibarotene plus azacitidine treatment group and CCI in the placebo plus azacitidine treatment group) are expected to be randomized in this study to obtain the CCI death events and final analysis time at approximately 70 months.

Primary Endpoint Analysis

CR Rate

The CR rate will be evaluated in the Intent-to-Treat (ITT) population. CR rate and 95% exact binomial confidence intervals (CIs) will be calculated by treatment group. The stratified Cochran–Mantel–Haenszel (CMH) test will be applied to compare the CR rates between the 2 treatment groups.

The point estimate of the difference of the proportions for CR rate between the 2 treatment groups will also be provided along with 95% CI.

Key Secondary Endpoint Analysis

OS

OS will be evaluated in the ITT population. The distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between 2 treatment groups using the log-rank test stratified by IPSS-R risk group (Intermediate, High, and Very High Risk) and by geographical region (North America, Western Europe, and Israel versus Eastern Europe). The hazard ratio and the corresponding 95% CI between 2 treatment groups will be estimated using the stratified Cox proportional hazards model with the same stratification factors that are used for stratified log-rank test.

Secondary Endpoint Analyses

TI Rate

TI rate (based on receiving neither red blood cell [RBC] nor platelet transfusion for a period of at least 56 days) with respective 95% exact binomial CIs will be calculated by treatment group. The stratified CMH test will be applied to compare the TI rates between the 2 treatment groups.

ORR

ORR and 95% exact binomial CIs will be calculated by treatment group. The stratified CMH test will be applied to compare the ORRs between the 2 treatment groups. The rates of CR or partial remission (PR); rates of CR, PR, or marrow CR; and the rates of hematologic improvement (HI) will also be summarized with 95% exact binomial CIs and compared between the treatment groups using the stratified CMH test.

Duration of Complete Remission (DOCR)

Kaplan-Meier estimation of median DOCR and corresponding 95% CIs will be presented by treatment group.

Duration of Overall Response

Kaplan-Meier estimation of median duration of overall response and corresponding 95% CIs will be presented by treatment group.

Time to CR

Time to CR will be summarized descriptively for the 2 treatment groups.

Time to Initial Response

Time to initial response will be summarized descriptively for the 2 treatment groups.

Event-free Survival (EFS)

Kaplan-Meier estimation of median EFS and 95% CI will be presented by treatment group. The stratified log rank test will be used to analyze the difference in EFS between treatment groups.

Change in Health-related Quality of Life (HRQOL)

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-30) and EuroQol 5 dimensions (EQ-5D-5L) test results will be summarized separately by treatment group, parameter, and visit. Additionally, the change from baseline in each parameter will be analyzed using a mixed models for repeated measures (MMRM). A by-patient listing of all EORTC QLQ-30 and EQ-5D-5L results will be provided.

Safety Analyses

The number and percentage of patients with AEs or serious adverse events (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 change in National Cancer Institute CTCAE (version 5) grade from baseline to worst grade postbaseline. Descriptive summaries will be provided for ECG and vital sign values by each visit, changes in values from baseline, and shift from baseline category to the worst post-baseline values. Prolonged QTcF intervals (>450 msec, >480 msec, and >500 msec) will be summarized by each visit. Change from baseline categories will also be summarized for measurements that represent a change >30 msec or >60 msec relative to the baseline value.

Pharmacokinetic Analysis

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

Interim Futility Analyses

There will be 2 planned interim futility analyses, one for the CR and one for OS, respectively; these will be non-binding and will be conducted by the IDMC. The IDMC may recommend terminating the study for unfavorable results at an interim analysis.

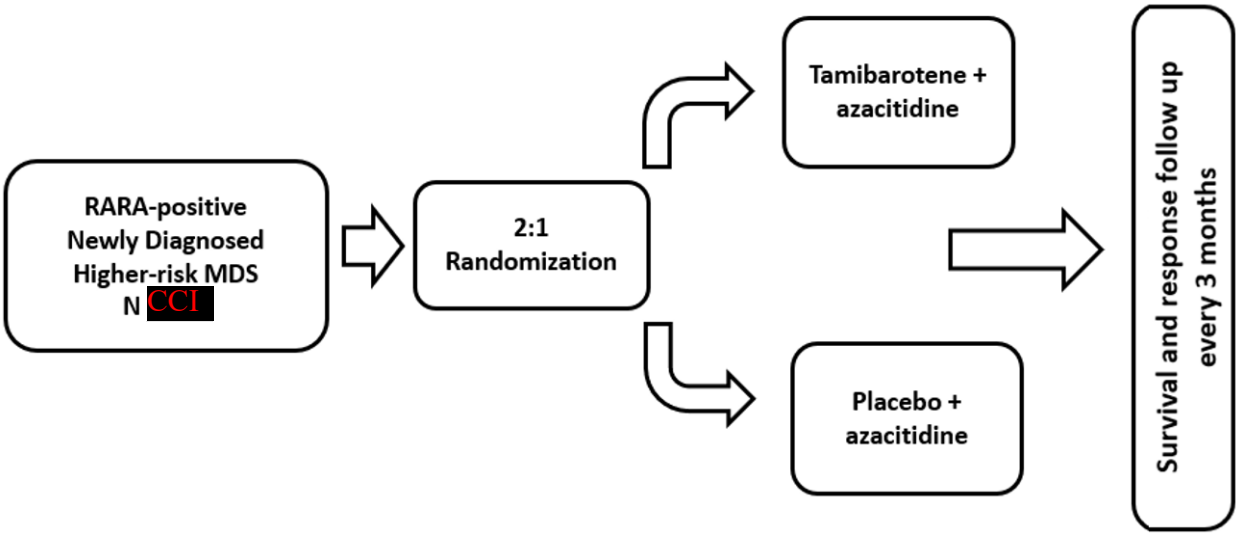
Interim Futility Analysis for CR

An interim futility analysis of the CR rate is planned when the CCI randomized patient has completed the Cycle 7 Day 1 assessment or discontinued treatment, whichever comes first. The study may be terminated at CR interim futility analysis, if the 1-sided p-value from the stratified CMH test comparing the CR rates (tamibarotene plus azacitidine treatment group versus placebo plus azacitidine treatment group) is CCI . The non-binding futility bound is derived using a Hwang-Shih-DeCani (HSD) spending function with gamma = 4 (Hwang 1990).

Interim Futility Analysis for OS

If the CR rate is statistically significant at the time of the primary efficacy analysis of the CR rates between the 2 treatment groups, an interim OS futility analysis will be conducted when approximately CCI information fraction (CCI of the total CCI events) has been observed. The study may be terminated at OS interim futility analysis if the 1-sided p-value from the stratified log rank test comparing the distribution of OS (tamibarotene plus azacitidine treatment group versus placebo plus azacitidine treatment group) is CCI . The non-binding futility bound is derived using Lan-DeMets spending function.

1.2 Schema



Abbreviations: MDS = myelodysplastic syndrome; N = number of patients; RARA = retinoic acid receptor alpha.

1.3 Schedule of Activities

	Pre-screening (a) Day -45 to C1D1	**Screening (a)** Day -30 to C1D1	**Cycle 1 28 Days**				**Cycles 2+ 28 Days Each (b)**			**End of Treatment (EoT) (c)**	**Safety Follow-up (d)** 30d post EoT (±3d)	**Disease Follow-up (e)** q3mo post EoT (±14d)	**Survival Follow-up (f)** q3mo post EoT (±14d)
Study Day			D1 (g)	D2-7 (±2d)	D8 (±1d)	D22 (±1d)	D1 (±3d)	D2-7 (±2d)	D15 (±2d) (h)				
Pre-screening Informed Consent	X												
Main Informed Consent		X											
Eligibility Review (i)		X	X (i)										
Eligibility Approval Form (i)		X	X (i)										
Randomization (j)			X										
Medical History (k)		X	X										
Demographics		X											
ECOG Status		X	X				X			X	X		
Height		X											
Weight		X	X		X	X	X			X	X		
Vital Signs (l)		X	X	X (l)	X	X	X	X (l)	X	X	X		
Physical Examination (m) (n)		X	X		X (n)	X (n)	X (n)			X	X	X (n)	
Hematology (o), (p), (q)		X (p)	X		X	X	X (q)			X	X	X	

	Pre-screening (a) Day -45 to C1D1	**Screening (a)** Day -30 to C1D1	**Cycle 1 28 Days**				**Cycles 2+ 28 Days Each (b)**			**End of Treatment (EoT) (c)**	**Safety Follow-up (d)** 30d post EoT (±3d)	**Disease Follow-up (e)** q3mo post EoT (±14d)	**Survival Follow-up (f)** q3mo post EoT (±14d)
Study Day			D1 (g)	D2-7 (±2d)	D8 (±1d)	D22 (±1d)	D1 (±3d)	D2-7 (±2d)	D15 (±2d) (h)				
Serum Chemistries (o)		X	X		X	X	X			X	X		
Coagulation (o)		X	X				X			X	X		
Triglycerides, Total Cholesterol (o)		X	X				X			X	X		
Hepatitis Panel (r)		X											
Urinalysis (o)		X	X				X			X	X		
Pregnancy Test (s)		X	X				X			X	X		
Triplicate ECG (t)		X			X	X			X				
AE Monitoring (u)			X	X	X	X	X	X	X	X	X		
Prior/Concomitant Medication Review (v)		X	X	X	X	X	X	X	X	X	X		
RBC and Platelet Transfusions Recorded (w)		X	X	X	X	X	X	X	X	X	X	X	
Dosing Compliance/Diary Review					X	X	X		X	X			
HRQOL (EORTC QLQ-C30, EQ-5D-5L)		X	X				X			X	X	X	
Subsequent Anticancer Therapies (x)											X	X	X

	Pre-screening (a) Day -45 to C1D1	**Screening (a)** Day -30 to C1D1	**Cycle 1 28 Days**				**Cycles 2+ 28 Days Each (b)**			**End of Treatment (EoT) (c)**	**Safety Follow-up (d)** 30d post EoT (±3d)	**Disease Follow-up (e)** q3mo post EoT (±14d)	**Survival Follow-up (f)** q3mo post EoT (±14d)
Study Day			D1 (g)	D2-7 (±2d)	D8 (±1d)	D22 (±1d)	D1 (±3d)	D2-7 (±2d)	D15 (±2d) (h)				
Response Assessment (q), (y)							X (q), (y)			X (y)		X (y)	
Bone Marrow Aspirate		X (z)					X (aa)			X (aa)		X (bb)	
Transformation into AML							X			X		X	X
Overall Survival													X
Tamibarotene or Placebo (cc)					Dosing D8-28 of each Cycle (cc)								
Azacitidine (dd)			X	X (dd)			X	X (dd)					
Blood Sample for RARA Biomarker Test (ee)	X									X			
Blood Sample for Exploratory Research (ff)	X		X							X			
Blood Sample for CDx Development	X												
Peripheral Blood for PK (gg)					X	X							

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CBC = complete blood count; CDx = companion diagnostic; CR = complete remission; CXDX = Cycle X, Day X; D/d = day(s); ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; ECG = electrocardiogram; EDC = electronic data capture [system]; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30; EoT = End of Treatment; EQ-5D-5L = EuroQol 5 dimensions; HRQOL = health-related quality of life; HSCT = Hematopoietic stem cell transplantation; IWG = International Working Group; MDS = myelodysplastic syndrome; OS = overall survival; PK = pharmacokinetic(s); q3mo = every 3 months; RBC = red blood cell; RARA = retinoic acid receptor alpha; SAE = serious adverse event.

(a) Pre-screening assessments to ensure patients are RARA-positive will be performed within 45 days of Cycle 1 Day 1 and screening assessments for all other eligibility criteria will be performed within 30 days of C1D1. Screening assessments may occur on C1D1 but must be completed and results reviewed prior to dosing on C1D1. Screening assessments performed within 30 days of C1D1 as part of standard of care are acceptable to support eligibility review.
(b) Cycle 2 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 after the EoT Visit and if possible, 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 until disease progression/relapse, death, or the occurrence of the expected number of OS events to support the final OS analysis, whichever occurs first. Disease Follow-up Visit window is ±14 days.
(f) Patients who progress/relapse will be followed to document the start of subsequent anticancer therapy, the date of disease progression/relapse, the date of transformation to AML, and OS status by telephone (or another appropriate method) until the expected number of OS events to support the final OS analysis is observed. Survival Follow-up Visit contact window is ±14 days.
(g) C1D1 assessments must be performed prior to study drug administration.
(h) Cycles 2 through 4 only.
(i) Eligibility review and approval by Sponsor or designee (via Eligibility Approval Form) must be completed prior to randomization.
(j) Patients can be randomized earlier than C1D1, but within 72 hours of the first dose of study drug, to accommodate operational needs.
(k) For all randomized patients, any untoward medical occurrences that happen before the first dose of the study drug should be captured as a part of medical history.
(l) 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.
(m) Definitions for the "full" and "abbreviated" physical examination are provided in Section 8.2.3; both must include an assessment for the presence of extramedullary AML.
(n) Abbreviated physical examination will be performed at C1D8, C1D22, D1 of Cycles 2+, and at each Disease Follow-up Visit (see Section 8.2.3).
(o) Laboratory assessments will be performed locally.
(p) Screening hematology parameter evaluation must be performed prior to or at least 7 days following any blood product transfusion.
(q) Additional unscheduled hematology evaluations may be performed up to 2 weeks after the bone marrow aspiration, for those patients in marrow CR without full peripheral blood count recovery at the time of the bone marrow aspirate, to assess whether they meet IWG criteria for CR.
(r) See Section 10.2 for details.
(s) A pregnancy test (high-sensitivity urine or serum) must be performed for women of childbearing potential.
(t) ECGs should be performed after an approximately 10-minute rest period.
(u) AEs and SAEs will be captured from the time of the first study drug administration through the Safety Follow-up Visit.
(v) 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.
(w) All RBC and platelet transfusions received by the patient from 16 weeks prior to randomization through the Disease Follow-up period will be recorded. Per the IWG 2006 response criteria, RBC transfusions entered into the corresponding eCRF in EDC should include only those administered for a hemoglobin level of ≤9 g/dL.
(x) Subsequent anticancer therapies (including allogeneic HSCT) following EoT will be recorded.

(y) Response assessments will be performed on D1 of Cycles 2 and 4, followed by every third cycle (7, 10, 13, etc.), at the EoT Visit and at each Disease Follow-up Visit, with additional assessments performed if clinically determined. Following the C7D1 response assessment, those in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 cycles, with intervening response assessments based on hematology evaluation and physical examination findings.

(z) A screening bone marrow aspirate will be performed, with samples for local assessment of **blast count**, **cytogenetics**, **MDS-associated gene mutations**, and **immunophenotype**. A bone marrow biopsy may be performed at investigator's discretion to supplement the interpretation of the bone marrow aspirate. In addition, it is mandatory that an aspirate smear will be sent to the **Central Laboratory** for **central morphologic review**. An additional aspirate sample should be collected if possible and sent to the **Central Laboratory** for **exploratory analyses**. Bone marrow aspirate smears collected within 30 days of Cycle 1 Day 1 as a part of standard of care (pre-consent) are acceptable to support both local assessments and central review.

(aa) Response assessment bone marrow aspirates will be collected on Day 1 of Cycles 2 and 4, followed by every third cycle (7, 10, 13, etc.), and at EoT, with bone marrow aspirates collected at other times as clinically determined. Following the C7D1 response assessment, those in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 cycles. The samples for the local assessment of response (**blast count** and **cytogenetics**) are required. In addition, an aspirate smear will be collected and sent to the **Central Laboratory** for **central review**. At C4D1, C7D1, every 6 cycles thereafter, as well as at EoT, an additional aspirate sample will be collected and sent to the **Central Laboratory** for **exploratory analyses** (Section 8.6.3). A bone marrow biopsy may be performed at investigator's discretion to supplement the interpretation of the bone marrow aspirate.

(bb) Response assessment bone marrow aspirates will be collected every 3 months during the Disease Follow-up period, with bone marrow aspirates collected at other times as clinically determined. Patients in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 months. The samples for the local assessment of response (**blast count** and **cytogenetics**) are required. In addition, an aspirate smear for **central review** will be collected and sent to the Central Laboratory. An additional aspirate sample should be collected if possible and sent to the Central Laboratory for exploratory analyses (Section 8.6.3). A bone marrow biopsy may be performed at investigator's discretion to supplement the interpretation of the bone marrow aspirate.

(cc) The morning dose of tamibarotene/placebo will be taken in the clinic on C1D8, C1D22, and D15 of Cycles 2 through 4; date/time of dose should be recorded.

(dd) If dosing on Days 6 and 7 of a cycle is not possible due to logistical limitations, these doses may be delayed to Days 8 and 9. Tamibarotene/placebo is permitted to overlap with azacitidine on Days 8 through 9 of this alternative schedule. If criteria for azacitidine dose hold are met (Table 1), tamibarotene/placebo dosing may continue, unless criteria for tamibarotene/placebo hold are also met. D1 of the next treatment cycle is delayed until azacitidine dosing may resume.

(ee) Peripheral blood samples will be sent to the Almac Diagnostics Laboratory for assessment of RARA biomarker to determine study eligibility.

(ff) For evaluation of MDS molecular features associated with response to drug treatment and loss of response to drug treatment (Section 8.6.3).

(gg) The morning dose of tamibarotene/placebo will be taken in the clinic on C1D8 and C1D22; date/time of dose should be recorded. The date/time of the C1D21 evening dose of tamibarotene/placebo should also be recorded. Three PK blood samples should be obtained on C1D8 and on C1D22, and collection time/date recorded: 1) pre-dose; 2) 1 hour post-dose (±30 min); 3) 3 hours post-dose (±30 min).

2 INTRODUCTION

Tamibarotene is a potent and selective agonist of RARα, approved for the treatment of R/R APL in Japan. Tamibarotene is being developed in a subset of non-APL AML and HR-MDS patients who are RARA-positive, as identified by high levels of *RARA* expression in blasts.

2.1 Study Rationale

Initial clinical data in RARA-positive R/R AML and R/R HR-MDS patients treated with single-agent tamibarotene demonstrated evidence of biological activity with myeloid differentiation and blast reductions (Jurcic 2017). In newly diagnosed, unfit AML patients, tamibarotene in combination with azacitidine showed high CR rates and a rapid onset of action in RARA-positive patients (de Botton 2022). The AE profile of the 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). Approximately 30% of AML patients (Jurcic 2017, Vigil 2017, de Botton 2022) and approximately 50% of MDS patients (data on file as of 27 May 2022) are RARA-positive. HR-MDS and AML are closely related biologically, with common cytogenetic abnormalities and gene mutations present in the blast populations in each condition (Arber 2016). Historical precedent demonstrates that active agents in AML, specifically hypomethylating agents, are active in HR-MDS, supporting the rationale for further development of the combination of tamibarotene with azacitidine in the HR-MDS patient population. Azacitidine remains the standard of care for the treatment of HR-MDS (VIDAZA USPI, VIDAZA SmPC, NCCN Guidelines for MDS, Malcovati 2013), however there is opportunity to improve upon the clinical outcomes of single-agent azacitidine. In this study, newly diagnosed, RARA-positive HR-MDS patients will be randomized to therapy with tamibarotene plus azacitidine or placebo plus azacitidine.

2.2 Background

2.2.1 Disease Under Study

HR-MDS is a rare orphan disease with a high unmet need for effective, tolerable therapies. The hypomethylating agent azacitidine is the standard of care for newly diagnosed HR-MDS patients. However, CR and PR rates are low (VIDAZA USPI, VIDAZA SmPC) and treatment is not curative. Thus, novel therapies that replace or augment the efficacy of azacitidine are needed to extend survival of patients with HR-MDS. Furthermore, no standard of care exists for patients who fail frontline therapy with hypomethylating agents. Thus, patients with HR-MDS have a poor prognosis and a need for more effective treatment options.

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 the presence of the t(15;17) translocation resulting in the *PML-RARA* gene 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 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 United States (US) and European Union (EU) for treatment of MDS. Azacitidine is also approved for use in AML in the EU and is widely accepted as the standard of care for treatment of AML in the US.

Additional information is available in VIDAZA label (VIDAZA USPI, VIDAZA SmPC, or as applicable).

2.3 Benefit/Risk Assessment

HR-MDS is an orphan disease with a high unmet need for effective, tolerable therapies. Allogeneic HSCT is the only potentially curative treatment for this condition.

In the ongoing SY-1425-201 study, Syros has explored the safety, pharmacokinetic (PK), pharmacodynamic, and clinical activity of tamibarotene in non-APL AML in combination with azacitidine. Clinical activity data (see IB) support the rationale for further development of the combination of tamibarotene with azacitidine in a genomically defined subset of patients characterized by overexpression of RARA in blasts. HR-MDS is biologically closely related to AML, with common mutations found across these conditions (Arber 2016), supporting the hypothesis that the combination of tamibarotene plus azacitidine will have clinical activity in those with newly diagnosed HR-MDS.

The AE profile of the 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). 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. The majority of nonhematologic AEs 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 safety profile of tamibarotene is considered to be acceptable, with the benefit to the patient primarily defined by the potential clinical utility of receiving tamibarotene plus azacitidine for the duration of the study (for patients randomized to the active combination). Both treatment arms of the randomized study contain azacitidine, which is the current standard of care for treating HR-MDS.

The risks of the underlying conditions evaluated in this study are significant and represent areas of high unmet medical need. HR-MDS is associated with the risk of infection and complications

due to persistent cytopenias. Patients undergoing treatment for HR-MDS undergo the procedural risk of repeated bone marrow aspirations, which are also required assessments in this study. The clinical activity of tamibarotene plus azacitidine, coupled with the emerging favorable safety profile of the tamibarotene plus azacitidine combination, suggests that this combination has the potential to provide a valuable treatment option for RARA-positive patients with AML, as well as those with HR-MDS.

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
Primary	
• Characterize and compare the CR rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• CR, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)
Key Secondary	
• Characterize and compare the OS of tamibarotene plus azacitidine vs. placebo plus azacitidine	• OS, defined as the time from the date of randomization to the date of death due to any cause
Secondary	
• Characterize and compare the TI rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• TI, defined as a period of at least 56 days with no RBC or platelet transfusion since the date of randomization to the last dose of study drug +30 days, the initiation of post-treatment therapy, or death, whichever occurs first
• Characterize and compare the ORR of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Overall response, defined as achieving CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)
• Characterize the DOCR and duration of overall response of tamibarotene plus azacitidine or placebo plus azacitidine	• DOCR, defined as the duration from the date of first documented evidence of CR to the date of documented relapse of disease, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first • Duration of overall response defined as the duration from the date of first documented evidence of CR, PR, mCR, or HI, to the date of documented disease progression, relapse of disease as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first
• Characterize the time to CR and time to initial response of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Time to CR, defined as the duration from the date of randomization to the date of the first documented evidence of CR as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)

Objectives	Endpoints
	• Time to initial response, defined as the duration from the date of randomization to the date of the first documented evidence of CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)
• Characterize and compare the EFS of tamibarotene plus azacitidine vs. placebo plus azacitidine	• EFS, defined as the time from the date of randomization to the date of transformation to AML or death due to any cause, whichever occurs first
• Compare changes in HRQOL of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Change in HRQOL as measured by the EORTC QLQ-30 and EQ-5D-5L
• Characterize the safety of tamibarotene plus azacitidine vs. placebo plus azacitidine	• AEs and changes in clinical laboratory values, ECG results, and vital sign measurements
Exploratory	
• Characterize and compare the cytogenetic CR rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Cytogenetic CR, defined as patients achieving cytogenetic CR (Cheson 2006), as determined by the investigator
• Characterize and compare the molecular response rate of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Molecular response, defined as patients achieving a reduction in variant allele frequency by next generation sequencing
• Characterize and compare the change in transfusion requirements of tamibarotene plus azacitidine vs. placebo plus azacitidine	• Transfusion requirement, defined as the frequency and amount of blood products (RBC or platelet) received
• Characterize and compare the rate of consolidation treatment with allogeneic HSCT following treatment with tamibarotene plus azacitidine vs. placebo plus azacitidine	• The rate of consolidation with allogeneic HSCT defined as the proportion of patients who are treated with allogeneic HSCT
• Characterize the PK of tamibarotene	• Plasma concentrations of tamibarotene
• Characterize MDS molecular features associated with response and with loss of response for tamibarotene plus azacitidine vs. placebo plus azacitidine	• Clinical response and genetic mutations and/or gene expression markers at baseline, at the time of response, and loss of response

Abbreviations: AE = adverse events; AML = acute myeloid leukemia; CR = complete remission; DOCR = duration of complete remission; ECG = electrocardiogram; EFS = event-free survival; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30; EQ-5D-5L = EuroQol 5 dimensions; HI = hematologic improvement; HRQOL = health-related quality of life; HSCT = hematopoietic stem cell transplantation; IWG = International Working Group; mCR = marrow CR; MDS = myelodysplastic syndrome; ORR = overall response rate; OS = overall survival; PK = pharmacokinetic(s); PR = partial remission; RBC = red blood cell; TI = transfusion independence; vs. = versus.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, multi-center, randomized, double-blind, placebo-controlled study comparing the activity of tamibarotene plus azacitidine to placebo plus azacitidine as first line of therapy in

RARA-positive patients with newly diagnosed HR-MDS. Enrollment in countries in North America and Europe and in Israel is planned.

At the Pre-screening Visit, blood samples will be collected and sent to the Almac Diagnostics Laboratory for assessment of RARA biomarker to determine study eligibility. Pre-screening assessments for the RARA biomarker will be performed within 45 days of Cycle 1 Day 1 and screening assessments for all other eligibility criteria will be performed within 30 days of Cycle 1 Day 1.

Patients will be randomized 2:1 to receive either tamibarotene plus azacitidine or placebo plus azacitidine. Randomization will be stratified by the IPSS-R risk group (Intermediate, High, and Very High Risk) and by geographical region (North America, Western Europe, and Israel versus Eastern Europe); block randomization with a block size of 6 will be used.

Response will be assessed by the investigator per the modified IWG MDS criteria (Cheson 2006). Bone marrow aspirates will be collected to measure response on Day 1 of Cycles 2 and 4, followed by every third cycle (7, 10, 13, etc.), with bone marrow aspirates collected at other times as clinically determined based upon clinical findings or changes in peripheral blood counts. Following the response assessment on Day 1 of Cycle 7, those in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 cycles.

Patients will undergo response and safety evaluations throughout their study participation as detailed in the Schedule of Activities (SoA; Section 1.3). Patients may continue to receive study drug until experiencing an unacceptable toxicity, disease progression (including transformation into AML), 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.

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 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 if possible 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 5 years after discontinuation of study drug (irrespective of initiation of HSCT or other subsequent anticancer therapy) or until disease progression/relapse, death, or the occurrence of the expected number of OS events to support the final OS analysis, whichever occurs first. It is estimated that a final analysis of OS will occur approximately 70 months following the enrollment of the first patient.

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, the date of transformation to AML, and OS status until the expected number of OS events to support the final OS analysis is observed.

An IDMC will be established and will review the data at the 2 planned interim futility analyses and the safety interims, as specified in the IDMC Charter.

4.2 Scientific Rationale for Study Design

Randomized, double-blind, placebo-controlled design is a well-established best practice for a Phase 3 study.

The proposed eligibility criteria are intended to ensure that only newly diagnosed, RARA-positive patients with HR-MDS are enrolled in the study. Allogeneic HSCT is the only potentially curative therapy for HR-MDS; therefore, patients who are transplant-eligible at the time of screening and agree to undergo this treatment will be excluded. Patients who received prior treatment with hypomethylating agents or chemotherapy (including lenalidomide) are excluded to avoid confounding of interpretation of the effect of study treatment.

Azacitidine is included as therapy in both the investigational and the comparator group, as it is the accepted standard-of-care treatment for patients with HR-MDS who are not transplant-eligible (VIDAZA USPI, VIDAZA SmPC). Key eligibility criteria are consistent with the current labeling for azacitidine (VIDAZA USPI, VIDAZA SmPC).

The proposed CR primary endpoint is a response-based endpoint that is a meaningful surrogate for clinical benefit in newly diagnosed HR-MDS. CR in MDS is associated with prolonged survival, transfusion independence (TI), and improved health-related quality of life in MDS (Fenaux 2009, Platzbecker 2012). Moreover, CR rate has previously been used as a primary endpoint for the approval of azacitidine and decitabine in MDS (VIDAZA USPI, VIDAZA SmPC, DACOGEN USPI).

4.3 Rationale for Dose and Regimen

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.

The dose and regimen of tamibarotene in combination with azacitidine is supported by the data from Study SY-1425-201.

The data from Study TOS-80T-003 indicate that the co-administration of CCI [redacted] has limited impact on the PK of tamibarotene. Consequently, such co-administration does not warrant dose adjustments.

Additional information is provided in the IB.

4.4 End of Study Definition

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

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

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. Patients must be RARA-positive based on the investigational assay (Section 8.6.1).
3. Patients must be newly diagnosed with HR-MDS as follows:
   Diagnosis of MDS according to the WHO classification (Arber 2016) and classified by the IPSS-R risk category as:
   a. Very High (risk score >6),
   b. High (risk score >4.5 to 6), OR
   c. Intermediate (risk score >3 to 4.5).
4. Patients must have measurable disease with bone marrow blasts >5% at the Screening Visit.
5. Patients must have ECOG Performance Status of ≤2.
6. Patients must have adequate organ function, as defined by:
   a. total bilirubin ≤3.0 × the ULN,
   b. ALT and AST ≤3 × ULN, and
   c. creatinine clearance ≥30 mL/min based on the Cockcroft-Gault Glomerular Filtration Rate estimation.

7. Patients must have a serum/high-sensitivity urine 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 document.

5.2 Exclusion Criteria

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

1. Patients are suitable for and agree to undergo allogeneic HSCT at the time of screening.

2. Patients received prior treatment for MDS with any hypomethylating agent, chemotherapy (including lenalidomide), or allogeneic HSCT, with the exception of prior treatment with growth factors or hydroxyurea. Growth factor treatment must be discontinued at least 2 weeks prior to starting study drug. Hydroxyurea treatment must be discontinued prior to starting study drug.

3. Patients with history of cancer are excluded if they are in active treatment (with radiation, chemotherapy, antibodies, immunotherapies, or molecularly targeted therapies) or unless they are disease free for at least 2 years prior to the Screening Visit, following completion of a prior treatment. Exceptions include: localized prostate cancer treated with hormone monotherapy; localized breast cancer treated with adjuvant hormone monotherapy; or 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 investigational product 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. 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.

12. Patients known to be refractory to platelet or packed red blood cell transfusions per Institutional Guidelines, or patients who refuse blood product support.

13. Patients received CCI [redacted] (see CCI [redacted]) within 2 weeks prior to the first tamibarotene/placebo administration.

14. 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.

15. Patients require concurrent treatment with any investigational or approved oncology agent, other than the agents described in exclusion criterion #3.

16. Patients with ≥20% blasts in peripheral blood or bone marrow or evidence of myeloid sarcoma (extramedullary AML).

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

18. 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 Fridericia formula (QTcF).

19. 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).

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

21. Patients for whom treatment with tamibarotene or azacitidine is contraindicated.

22. Patients with clinically significant cardiovascular disease, including unstable angina, acute myocardial infarction within 3 months prior to the start of study drug administration, or New York Heart Association Class III or IV congestive heart failure, cerebral vascular accident within 3 months prior to the start of study drug administration, or cardiac arrhythmia associated with hemodynamic instability.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. 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.

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

Intervention Name	**Tamibarotene**	**Tamibarotene-matched Placebo**	**Azacitidine**
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tamibarotene-matched tablet	Reconstituted as solution or suspension
Unit Dose Strength(s)	2-mg tablets	Not applicable	100-mg single-use vials

Intervention Name	Tamibarotene	Tamibarotene-matched Placebo	Azacitidine
Dosage Level and Regimen	6 mg twice per day (BID); Days 8 through 28 of each 28-day treatment cycle See Section 6.2.1 for details of dose administration.	3 tablets that match tamibarotene BID; Days 8 through 28 of each 28-day treatment cycle See Section 6.2.1 for details of dose administration.	75 mg/m^2 once per day; Days 1 through 7 of each 28-day treatment 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. See Section 6.2.2 for details of dose administration.
Route of Administration	Oral	Oral	Intravenous or subcutaneous
Use	Experimental	Placebo comparator	Background intervention
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	As regionally applicable
Packaging and Labeling	Study drug will be provided in bottles. Each bottle will be labeled as required per country requirement.	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.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Tamibarotene/Placebo

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 to 30°C) and should not be removed from the bottles until immediately before administration.

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

Only patients enrolled in the study may receive tamibarotene/placebo and only authorized site staff may supply or administer it. All tamibarotene/placebo 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/placebo accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

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

6.2.2 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 should be stored at room temperature (15°C to 30°C). Refer to the azacitidine package insert approved by your National Regulatory Agency/Competent Authority for complete details, as applicable (e.g., VIDAZA USPI, VIDAZA SmPC).

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization will be double-blinded and will be performed on Cycle 1 Day 1 using an interactive response system.[1]

Approximately CCI patients with HR-MDS will be randomly assigned to study drug. Patients will be randomized 2:1 to receive either tamibarotene plus azacitidine or placebo plus azacitidine. Randomization will be stratified by the IPSS-R risk group (Intermediate, High, and Very High Risk). In addition, stratification of analyses by geographical region (North America, Western Europe, and Israel versus Eastern Europe) will be performed, as there may be differences in available supportive care treatments and in access to subspecialty consultants and specialized hospital care among these regions. Block randomization with a block size of 6 will be used.

All patients, investigators, pharmacist(s) performing drug preparation, and site staff will be blinded to treatment assignment.

Personnel responsible for the bioanalysis of the tamibarotene concentrations in plasma will be provided with the randomization code in order to identify samples for analysis. The results will not be shared with the sponsor until the study is unblinded.

[1] Patients can be randomized earlier than Cycle 1 Day 1, but within 72 hours of the first dose of study drug, to accommodate operational needs.

In addition, at the time of CR futility analysis, preliminary PK analysis will be performed by designated contract research organization (CRO), the limited personnel from the CRO will have access to the unblinded PK data to build the population PK model.

The interactive response system will be programmed with blind-breaking instructions.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If necessary, for patient safety, the investigator may unblind the patient's intervention assignment immediately, without prior discussion with the sponsor. The investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a patient's intervention assignment, unless this could delay emergency treatment for the patient. Maintaining the blinded treatment assignment will preserve integrity of the study data. If a patient's intervention assignment is unblinded without discussion with the sponsor, the sponsor must be notified within 24 hours of this occurrence. The date and reason that the blind was broken will be recorded.

Sponsor safety staff may unblind the study drug assignment for any patient with a SAE if necessary. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's study drug assignment, may be sent to the investigators in accordance with local regulations and/or sponsor policy. Contact information for the Pharmacovigilance group is provided in Appendix 3.

6.4 Study Drug Compliance

Tamibarotene/placebo 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/placebo 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 applicable study visit (Section 1.3). 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 1 and Table 2 must be followed to adjust tamibarotene/placebo or azacitidine 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 azacitidine (see most current VIDAZA USPI/VIDAZA SmPC, or applicable locally approved labeling).

Table 1: Dose Modifications

Adverse Events (AEs)	Dosage Modification
Hematologic toxicity	The dose of azacitidine should be modified as described in the most current VIDAZA USPI/VIDAZA SmPC or applicable locally approved labeling. If Grade 4 hematologic toxicity does not resolve after azacitidine dose modifications have been attempted, the dose of tamibarotene may be CCI [redacted].
Retinoic acid syndrome (RAS)[a]	Hold tamibarotene/placebo until RAS is considered controlled and Grade ≤2. See Section 6.8.9 for additional information on monitoring and treatment of RAS.
Grade 4 hypertriglyceridemia	Hold tamibarotene/placebo until AE resolves to Grade ≤1 or baseline. Tamibarotene/placebo 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/placebo will be CCI [redacted] Dosing may be CCI [redacted] 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 CCI [redacted].
Grade ≥3 non-hematologic toxicity (excluding hypertriglyceridemia and serum electrolyte and renal toxicity)	Hold tamibarotene/placebo, if AE is deemed related to tamibarotene and not resolved with supportive care, until AE resolves to Grade ≤1 or baseline. Tamibarotene/placebo 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 CCI [redacted]. Dosing may be CCI [redacted] if the AE remains Grade ≤1 or at baseline for 14 days. If Grade ≥3 non-hematologic toxicity does not resolve after dose modification to tamibarotene/placebo has been attempted, azacitidine may be held until AE resolves to Grade ≤1 or baseline. If attribution is unclear, follow tamibarotene dose modification first. If AE does not resolve, azacitidine modifications may be attempted next.

Abbreviations: SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information.
Note: Tamibarotene administration should not be resumed in the case of ≥28-day dose delay due to treatment-related AEs.
[a] Also referred to as differentiation syndrome.

Table 2: Dose Reductions of Tamibarotene/Placebo

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

6.5.1 Dose Delay and Toxicity-related Discontinuation Guidelines

If criteria for tamibarotene/placebo dose hold are met (Table 1), azacitidine dosing may continue, unless criteria for azacitidine hold are also met.

If criteria for azacitidine dose hold are met (Table 1), tamibarotene/placebo dosing may continue, unless criteria for tamibarotene/placebo hold are also met. Day 1 of the next treatment cycle is delayed until azacitidine dosing may resume.

If implementation of dose modification guidelines described in Table 1 (including dose holds and reductions) was not sufficient to adequately manage toxicity, the relevant study drug(s) should be discontinued. Discontinuation of only tamibarotene/placebo or only azacitidine while continuing administration of the other study drug 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 1 are insufficient to adequately manage toxicity and discontinuation of both tamibarotene/placebo and azacitidine is required, the patient should have an EoT Visit.

6.5.2 Phototoxicity

Tamibarotene did not demonstrate phototoxic potential in Neutral Red Uptake Phototoxicity Assay (see IB). Furthermore, phototoxicity has not been reported in clinical studies of tamibarotene to date.

6.5.3 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.

6.6 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

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.

One case of overdose with azacitidine was reported during clinical trials (VIDAZA USPI, VIDAZA SmPC). 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 blood count tests and should receive supportive treatment, as necessary. There is no known antidote for azacitidine 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 or whether the dose should be reduced.
- 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.

6.8 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

Growth factor treatment must be discontinued at least 2 weeks prior to starting study drug. Short-term use of myeloid growth factor is allowable for treatment of life-threatening infections.

6.8.3 Thrombopoietin Receptor Agonists

Thrombopoietin receptor agonists must be discontinued prior to starting study drug and are not allowed during the study.

6.8.4 Oral Hydroxyurea

Hydroxyurea treatment must be discontinued prior to starting study drug and is not allowed during the study.

6.8.5 Platelet Transfusions

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

6.8.6 Red Blood Cell Transfusions

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

6.8.7 CCI

CCI are not allowed to be administered during the study as they may reduce exposure of tamibarotene.

Though the in vitro CCI-mediated metabolism of tamibarotene appears to be primarily due to CCI, a clinical drug-drug interaction study with itraconazole (a 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 plasma PK exposure.

A list of CCI is included in CCI

6.8.8 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.

6.8.9 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/placebo therapy should be temporarily discontinued until RAS is considered controlled and ≤Grade 2.

6.8.10 Multivitamin and Supplements

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

6.8.11 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

Patients will continue to receive study drug until they meet one of the following criteria:

- An unacceptable toxicity, including AEs that would result in permanent discontinuation of study drug (Section 6.5)
- An AE related to study drug that requires ≥28 days (1 cycle) of dose interruption of both tamibarotene/placebo and azacitidine
- Failure to achieve a minimum response of HI in at least 1 cell lineage following the completion of the Cycle 7 Day 1 response assessment
- Disease progression/relapse
- Pregnancy
- Decision to pursue post-remission therapy (such as HSCT) or an alternative anticancer therapy; consolidation treatment with HSCT following the receipt of study drug is permissible.
- 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 if possible 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 SoA (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 their 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 SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

- All pre-screening and screening evaluations must be completed and results reviewed prior to dosing on Cycle 1 Day 1. 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 SoA (Section 1.3). Screening hematology parameter evaluation must be performed at least 7 days following any blood product transfusion.

- 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 randomized patients, any untoward medical occurrences that happen before the first dose of the study drug should be captured as a part of medical history.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (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 per the modified IWG MDS criteria (Cheson 2006). A copy of the criteria is provided in Appendix 8. Note that resolution of dysplasia is not required for achievement of an IWG response. Physical examinations (Section 8.2.3) are scheduled at the time of all response assessments and include an assessment for the presence of extramedullary AML. Additional unscheduled hematology evaluations may be performed up to 2 weeks after the bone marrow aspiration, for those patients in marrow CR without full peripheral blood count recovery at the time of the bone marrow aspirate, to assess whether they meet IWG criteria for CR based on the results of this additional hematology evaluation. The CR date is assigned as the date of marrow sampling or peripheral count recovery, whichever is later.

In addition to on-treatment assessments, patients who have not progressed/relapsed will enter the Disease Follow-up period, during which response assessments will be performed every 3 months for response assessment until disease progression/relapse, death, or the occurrence of the expected number of OS events to support the final OS analysis, 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, the date of transformation to AML, and OS status until the expected number of OS events to support the final OS analysis is observed.

8.1.2 Bone Marrow Sample Collection

A screening bone marrow aspirate will be performed, with samples for local assessment of blast count, cytogenetics, MDS-associated gene mutations, and immunophenotype. A bone marrow biopsy may be performed at investigator's discretion to supplement the interpretation of the bone marrow aspirate. In addition, it is mandatory that an aspirate smear will be sent to the Central Laboratory for central morphologic review. An additional aspirate sample should be collected if possible and sent to the Central Laboratory for exploratory analyses.

Bone marrow aspirate smears collected within 30 days of Cycle 1 Day 1 as a part of standard of care (pre-consent) are acceptable to support both local assessments and central review.

Response assessment bone marrow aspirates will be collected on Day 1 of Cycles 2 and 4, followed by every third cycle (7, 10, 13, etc.), and at EoT, with bone marrow aspirates collected at other times as clinically determined. Following the Cycle 7 Day 1 response assessment, those in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 cycles. The samples for the local assessment of response (blast count and cytogenetics) are required. In addition, an aspirate smear will be collected and sent to the Central Laboratory for central review. At Cycle 4 Day 1, Cycle 7 Day 1, every 6 cycles thereafter, as well as at EoT, an additional aspirate sample will be collected and sent to the Central Laboratory for exploratory analyses (Section 8.6.3). A bone marrow biopsy may be performed at investigator's discretion to supplement the interpretation of the bone marrow aspirate.

During the Disease Follow-up period, the response assessment bone marrow aspirates will be collected every 3 months during the Disease Follow-up period, with bone marrow aspirates collected at other times as clinically determined. Patients in CR may have the frequency of bone marrow aspirates for response assessment reduced to every 6 months. The samples for the local assessment of response (blast count and cytogenetics) are required. In addition, an aspirate smear for central review will be collected and sent to the Central Laboratory. An additional aspirate sample should be collected if possible and sent to the Central Laboratory for exploratory analyses (Section 8.6.3). A bone marrow biopsy may be performed at investigator's discretion to supplement the interpretation of the bone marrow aspirate.

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

8.1.3 Hematologic Improvement

Baseline hemoglobin and platelet values will be collected at the Screening Visit. The screening hematology parameter evaluation must be performed prior to or at least 7 days following any blood product transfusion (see Appendix 8).

8.1.4 Transformation to AML

A diagnosis of AML (per WHO; Vardiman 2009, Arber 2016) is defined by either:

- ≥20% blasts in the peripheral blood or bone marrow

OR

- development of myeloid sarcoma

8.1.5 Blood Product Transfusions

All RBC and platelet transfusions received by the patient from 16 weeks prior to randomization through the Disease Follow-up period will be recorded.

8.1.6 Overall Survival

All patients will be followed for OS every 3 months until the expected number of OS events to support the final OS analysis is observed. 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 SoA (Section 1.3).

8.2.1 Prior, Concomitant, and Subsequent Medication Review

Every medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements), vaccines, and blood products 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 and an assessment for the presence of extramedullary AML. The skin examination should

include monitoring for cancerous and pre-cancerous lesions and appropriate referral to dermatologic evaluation and care, as clinically indicated.

- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, Cardiovascular system, and abdomen (liver and spleen) and an assessment for the presence of extramedullary AML. The skin examination should include monitoring for cancerous and pre-cancerous lesions and appropriate referral to dermatologic evaluation and care, as clinically indicated.

- 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 SoA (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).

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.

Emergency unblinding procedures are described in Section 6.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be captured from the time of the first study drug administration through the Safety Follow-up Visit.

All SAEs will be recorded and reported to the sponsor or designee immediately without undue delay 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 immediately without undue delay and 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.

Germany only: AEs and SAEs will be captured from the time of the first study drug administration through the Safety Follow-up Visit.

All SAEs will be recorded and reported to the sponsor or designee immediately without undue delay, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor immediately without undue delay.

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 6 months after the last dose of study drug for female patients and 90 days after the last dose of study drug for male patients.

- 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 PPD or Fax #: PPD 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.

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.

8.3.6.2 New Cancers

The development of a new primary cancer 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 in the study. They do not include metastases of the original cancer or diagnosis of AML in a patient previously diagnosed with MDS.

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

If a new cancer is detected, patients should be referred to appropriate care and long-term follow-up.

8.4 Pharmacokinetics

Samples will be collected from all patients. Placebo samples will not be analyzed. Samples from the patients receiving tamibarotene 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 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 at the Pre-screening Visit as “RARA-positive” based on an investigational assay, conducted at the

Almac Diagnostics Laboratory. The investigational assay will be repeated at the EoT Visit to explore potential changes in the RARA biomarker associated with treatment.

8.6.2 Companion Diagnostic Assay Development

Blood samples collected at the Pre-screening Visit 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 MDS molecular features associated with response to drug treatment (Section 8.6.3).

8.6.3 Molecular Markers of Tumor Response and Resistance

Blood samples and bone marrow aspirates will be collected for exploratory research to evaluate MDS molecular features associated with response to drug treatment and loss of response to drug treatment. Consent will be requested to retain residual samples for future research that may be conducted following the completion of this study. Consent for this future research is not required to participate in this study.

8.7 Health-related Quality of Life

Patient-reported health-related quality of life will be evaluated to determine the impact of the addition of tamibarotene to the standard of care azacitidine treatment. The patients will be evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (Appendix 9) and EuroQol 5 dimensions (Appendix 11) tools. These questionnaires are to be self-administered by the patient and reviewed by the site for completeness. If any questions were incomplete, the site should encourage the patient to complete any missing information.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

Primary: CR

Null hypothesis (H0): In RARA-positive patients with newly diagnosed HR-MDS, CR rate for patients in the tamibarotene plus azacitidine treatment group is the same as the CR rate for patients in the placebo plus azacitidine treatment group.

Alternative hypothesis (H1): In RARA-positive patients with newly diagnosed HR-MDS, CR rate for patients in the tamibarotene plus azacitidine treatment group is higher than the CR rate for patients in the placebo plus azacitidine treatment group.

Key Secondary: OS

Null hypothesis (H0): In RARA-positive patients with newly diagnosed HR-MDS, OS for patients in the tamibarotene plus azacitidine treatment group is the same as the OS for patients in the placebo plus azacitidine treatment group.

Alternative hypothesis (H1): In RARA-positive patients with newly diagnosed HR-MDS, OS for patients in the tamibarotene plus azacitidine treatment group is superior to the OS for patients in the placebo plus azacitidine treatment group.

Multiplicity Adjustment

The study will be claimed positive when the primary endpoint (CR rate) is statistically significant. To maintain the overall type I error among the primary endpoint and the key secondary endpoint, the CR rate will be tested at 1-sided alpha of CCI, and if it is significant, OS will be tested at 1-sided alpha of CCI.

9.2 Sample Size Determination

CCI patients will provide CCI power to detect the difference in CR rates between the tamibarotene plus azacitidine treatment group and the placebo plus azacitidine treatment group, with assumed CR rates of CCI versus CCI in the 2 treatment groups, respectively, a 2:1 randomization, and 1-sided alpha of CCI.

A total of CCI death events will provide CCI power to detect the difference in OS between tamibarotene plus azacitidine treatment group and the placebo plus azacitidine treatment group, with assumed median survival of CCI months versus CCI months (hazard ratio = CCI) in the 2 treatment groups, respectively, a 2:1 randomization, and 1-sided alpha of CCI.

A total of approximately CCI patients (CCI in the tamibarotene plus azacitidine treatment group and CCI in the placebo plus azacitidine treatment group) are expected to be randomized in this study to obtain the CCI death events and final analysis time at approximately 70 months.

9.3 Analysis Sets

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

Intent-to-treat Population	All patients who are randomized. Treatment groups for this analysis set will be determined according to the treatment assignment at the time of randomization.
Safety Population	All patients who are randomized and have received any amount of study drug (tamibarotene/placebo or azacitidine). Treatment groups for this population will be determined according to the actual treatment the patients received.
Per-protocol Population	All patients who are randomized and are considered to be sufficiently compliant with the protocol. Specific criteria for this population will be defined in the statistical analysis plan, and the exclusion of patients from this population will be based on blinded review of the clinical data.
Pharmacokinetic (PK) Evaluable Population	All patients who are randomized and have received at least 1 dose of tamibarotene and have at least 1 quantifiable PK concentration.

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, key secondary, and secondary endpoints.

9.4.1 General Considerations

When applicable, analyses will be stratified by IPSS-R risk group (Intermediate, High, and Very High Risk) and by geographical region (North America, Western Europe, and Israel versus Eastern Europe).

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

Complete Remission

CR will be determined by the investigator per the modified IWG MDS criteria (Cheson 2006). Per the IWG MDS criteria responses must last at least 4 weeks. Instructions for the assessment of IWG response including the provision of a 2-week window for unscheduled hematology evaluations to meet the IWG criteria of CR are provided in Section 8.1.1.

The CR will be evaluated in the Intent-to-Treat (ITT) population. CR rate and 95% exact binomial confidence intervals (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 stratified Cochran–Mantel–Haenszel (CMH) test will be applied to compare the CR rates between the 2 treatment groups, stratified by IPSS-R risk group (Intermediate, High, and Very High Risk) and by geographical region (North America, Western Europe, and Israel versus Eastern Europe). The final analysis of CR is planned for the time when all 190 patients have completed the Cycle 7 Day 1 response assessment or discontinued treatment, whichever comes first. Patients with missing response assessment data will be considered as a failure to achieve CR, including patients who have died, withdrew consent, or started a new treatment prior to achieving a CR.

The point estimate of the difference of the proportions for CR rate between the 2 treatment groups will also be provided along with 95% CI.

9.4.3 Key Secondary Endpoint

Overall Survival

OS, defined as the time from the date of randomization to the date of death due to any cause, will be analyzed in the ITT population. Patients who do not die at the time of a data cutoff date

(interim and/or final) will be censored at the last date the patient is known to be alive or at the analysis cutoff date, whichever is earlier.

The distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between 2 treatment groups using the log-rank test stratified by IPSS-R risk group (Intermediate, High, and Very High Risk) and by geographical region (North America, Western Europe, and Israel versus Eastern Europe). The hazard ratio and the corresponding 95% CI between the 2 treatment groups will be estimated using the stratified Cox proportional hazards model with the same stratification factors that are used for stratified log-rank test. OS will be displayed by Kaplan-Meier curves. The 25th percentile, median, and 75th percentile OS and the 95% CI will be provided for each treatment group. The 12-month and 24-month OS rates will be estimated using the Kaplan-Meier method.

Table 3: Estimands (Primary and Key Secondary)

Objectives	Estimand Category				
	Treatment	**Population**	**Variable/Endpoint**	**Intercurrent Event; Strategy**	**Population Level Summary**
CR: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in CR in RARA-positive newly diagnosed HR-MDS patients	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	CR, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)	Treatment discontinuation; Treatment policy Patients who die, withdraw consent, or start a new anticancer treatment before achieving a response; Composite strategy	• CR rate by treatment arm • Difference in proportion of CR rate between two treatment arms
OS: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in overall survival in RARA-positive newly diagnosed HR-MDS patients	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	OS, defined as the time from the date of randomization to date of death from any cause	Treatment discontinuation; Treatment policy Initiation of HSCT or other subsequent anticancer therapy; Treatment policy	Kaplan-Meier estimate of OS and hazard ratio

Abbreviations: CR = complete remission; HR-MDS = higher-risk myelodysplastic syndrome; HSCT = hematopoietic stem cell transplantation; IPSS-R = Revised International Prognostic Scoring System; ITT = intent-to-treat; IWG = International Working Group; RARA = retinoic acid receptor alpha; OS = overall survival; WHO = World Health Organization.

9.4.4 Secondary Endpoints

Transfusion Independence

TI, defined as a period of at least 56 days with no RBC or platelet transfusion since the date of randomization to the last dose of study drug +30 days, the initiation of post-treatment therapy, or death, whichever occurs first.

TI rate (based on receiving neither RBC nor platelet transfusion for a period of at least 56 days) with respective 95% exact binomial CIs will be calculated by treatment group. The stratified CMH test will be applied to compare the TI rates between the 2 treatment groups.

Overall Response

Overall response, defined as achievement of CR, PR, marrow CR (mCR), or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006).

Overall response rate (ORR) and 95% exact binomial CIs will be calculated by treatment group. The stratified CMH test will be applied to compare the ORRs between the 2 treatment groups. The rates of CR or PR; rates of CR, PR, or marrow CR; and the rates of HI will also be summarized with 95% exact binomial CIs and compared between the treatment groups using the stratified CMH test.

Overall response may also be analyzed in line with the updated IWG response criteria (Zeidan 2023).

Duration of Complete Remission

DOCR, defined as the duration from the date of first documented evidence of CR to the date of documented relapse of disease, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first.

Kaplan-Meier estimation of median DOCR and corresponding 95% CIs will be presented by treatment group.

Duration of Overall Response

Duration of overall response defined as the duration from the date of first documented evidence of CR, PR, mCR, or HI, to the date of documented disease progression, relapse of disease as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first.

Kaplan-Meier estimation of median duration of overall response and corresponding 95% CIs will be presented by treatment group.

Time to CR

Time to CR, defined as the duration from the date of randomization to the date of the first documented evidence of CR as determined by the investigator per the modified IWG MDS criteria (Cheson 2006).

Time to CR will be summarized descriptively for the 2 treatment groups.

Time to Initial Response

Time to initial response, defined as the duration from the date of randomization to the date of the first documented evidence of CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006).

Time to initial response will be summarized descriptively for the 2 treatment groups.

EFS

EFS, defined as the time from the date of randomization to the date of transformation to AML or death due to any cause, whichever occurs first.

Kaplan-Meier estimation of median EFS and 95% CI will be presented by treatment group. The stratified log rank test will be used to analyze the difference in EFS between treatment groups.

Change in HRQOL

EORTC QLQ-30 and EQ-5D-5L test results will be summarized separately by treatment group, parameter, and visit. For EORTC QLQ-30, results for global health status, each of the five functional scales (physical, role, emotional, cognitive, and social functioning), and each of the eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea) will be summarized. The scores for global health status, functional scales and symptom scales will be calculated and standardized using the methods described in The EORTC QLQ-C30 Scoring Manual (3rd Edition) (Fayers 2001). For EQ-5D-5L, results for overall health and each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarized.

Descriptive statistics will be presented for observed values and changes from baseline by parameter at each visit where the questionnaires were scheduled to be collected per the clinical study protocol. Change from baseline in important parameters will be analyzed using MMRM. The model will include treatment, visit, and treatment-by-visit interaction as fixed effects and baseline as covariate. An unstructured covariance matrix will be used to model the between- and within-patient errors.

The Kenward-Roger method will be used to estimate the degrees of freedom. Treatment least squares means (LSMs) will be estimated within the framework of the MMRM using type 3 sums of squares. Differences in LSM between treatment groups (and associated standard errors and 95% CI) will be used for statistical inference. The LSM difference, standard error, and 95% CI and will be reported for each parameter and visit.

A by-patient listing of all EORTC QLQ-30 and EQ-5D-5L results will be provided.

Safety Analyses

Adverse Events

The number and percentage of patients with AEs or 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 change in National Cancer Institute (NCI) CTCAE (version 5) grade from baseline to worst grade postbaseline.

Laboratory Tests

Changes from baseline will be analyzed for each scheduled post-baseline visit for chemistry and hematology parameters. Where applicable, chemistry and hematology laboratory determinations will be categorized according to NCI CTCAE (Version 5) grades, and shift from baseline NCI CTCAE grades to worst post-baseline grades will be assessed.

Vital Signs

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

Changes from baseline in systolic and diastolic blood pressure results will also be presented as box plots by visit and for each treatment group.

ECG

A shift from baseline category to the worst post-baseline category (Normal, Abnormal NCS, Abnormal CS) summary will be presented by treatment group and total. Prolonged QTcF intervals (>450 msec, >480 msec, and >500 msec) will be summarized by each visit. Change from baseline categories will also be summarized for measurements that represent a change >30 msec or >60 msec relative to the baseline value.

Change from baseline in QTcF interval results will also be presented as box plots by visit and for each treatment group.

All AE data, vital sign data and ECG data will be listed.

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

Table 4: Estimands (Secondary)

Secondary Objectives	Estimand Category				
	Treatment	**Population**	**Variable/Endpoint**	**Intercurrent Event; Strategy**	**Population Level Summary**
TI: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in TI	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	TI, defined as a period of at least 56 days with no RBC or platelet transfusion since the date of randomization to the last dose of study drug +30 days, the initiation of post-treatment therapy, or death, whichever occurs first	Treatment discontinuation; Treatment policy Patients who die, withdraw consent, or start a new anticancer treatment before achieving a response; Composite strategy	TI rate by treatment arm
Overall Response: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in overall response	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	Overall response, defined as achieving CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)	Treatment discontinuation; Treatment policy Patients who die, withdraw consent, or start a new anticancer treatment before achieving a response; Composite strategy	Overall response rate by treatment arm

Secondary Objectives	Estimand Category				
	Treatment	**Population**	**Variable/Endpoint**	**Intercurrent Event; Strategy**	**Population Level Summary**
DOCR: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in duration of complete remission	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	DOCR, defined as the duration from the date of first documented evidence of CR to the date of documented relapse of disease, as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first	Treatment discontinuation; Treatment policy Initiation of HSCT or other subsequent anticancer therapy; Treatment policy	Kaplan-Meier estimate of DOCR
Duration of Overall Response: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in duration of overall response	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	Duration of overall response defined as the duration from the date of first documented evidence of CR, PR, mCR, or HI, to the date of documented disease progression, relapse of disease as determined by the investigator per the modified IWG MDS criteria (Cheson 2006), or death due to any cause, whichever occurs first	Treatment discontinuation; Treatment policy Initiation of HSCT or other subsequent anticancer therapy; Treatment policy	Kaplan-Meier estimate of duration of overall response

Secondary Objectives	Estimand Category				
	Treatment	**Population**	**Variable/Endpoint**	**Intercurrent Event; Strategy**	**Population Level Summary**
Time to CR: Characterize the time to CR and time to initial response of tamibarotene plus azacitidine vs. placebo plus azacitidine	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	Time to CR, defined as the duration from the date of randomization to the date of the first documented evidence of CR as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)	Treatment discontinuation; Treatment policy Patients who die, withdraw consent, or start a new anticancer treatment before achieving a response; Composite strategy	Summary statistics (n, mean, median, min, max)
Time to Initial Response: Characterize the time to initial response of tamibarotene plus azacitidine vs. placebo plus azacitidine	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	Time to initial response, defined as the duration from the date of randomization to the date of the first documented evidence of CR, PR, mCR, or HI as determined by the investigator per the modified IWG MDS criteria (Cheson 2006)	Treatment discontinuation; Treatment policy Patients who die, withdraw consent, or start a new anticancer treatment before achieving a response; Composite strategy	Summary statistics (n, mean, median, min, max)

Secondary Objectives	Estimand Category				
	Treatment	**Population**	**Variable/Endpoint**	**Intercurrent Event; Strategy**	**Population Level Summary**
EFS: To demonstrate the superiority of tamibarotene plus azacitidine compared to placebo plus azacitidine in event free survival	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	EFS, defined as the time from the date of randomization to the date of transformation to AML or death due to any cause, whichever occurs first.	Treatment discontinuation; Treatment policy Initiation of HSCT or other subsequent anticancer therapy; Treatment policy	Kaplan-Meier estimate of EFS
Change in HRQOL: Compare changes in HRQOL of patients treated with tamibarotene plus azacitidine vs. placebo plus azacitidine	Tamibarotene plus azacitidine versus placebo plus azacitidine	RARA-positive patients with newly diagnosed HR-MDS according to the WHO classification, classified by the IPSS-R risk category as intermediate, high, or very high risk	Observed and change from baseline for EORTC QLQ-30 and EQ-5D-5L parameters	Treatment discontinuation; Treatment policy Patients who die, withdraw consent, or start a new anticancer treatment; Composite strategy	Summary of Estimate of change from baseline for EORTC QLQ-30 and EQ-5D-5L parameters from Linear mixed model

Abbreviations: AML = acute myeloid leukemia; CR = complete remission; DOCR = duration of complete remission; EFS = event-free survival; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30; EQ-5D-5L = EuroQol 5 dimensions; HI = hematologic improvement; HR-MDS = higher-risk myelodysplastic syndrome; HRQOL = health-related quality of life; = hematopoietic stem cell transplantation; HSCT = IPSS-R = Revised International Prognostic Scoring System; IWG = International Working Group; max = maximum; min = minimum; mCR = marrow CR; PR = partial remission; RARA = retinoic acid receptor alpha; RBC = red blood cell; TI = transfusion independence; vs. = versus; WHO = World Health Organization.

9.4.5 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.

9.4.6 Timing of Efficacy Analysis

The primary analysis for CR will occur when all CCI randomized subjects have completed the Cycle 7 Day 1 assessment or discontinued treatment, whichever comes first. The analysis for OS for the Key Secondary endpoint will be performed when approximately CCI OS death events have been observed.

9.5 Interim Analyses

There will be 2 planned interim futility analyses, one for the CR and one for OS, respectively; these will be non-binding and will be conducted by the IDMC. The IDMC may recommend terminating the study for unfavorable results at an interim analysis.

Interim Futility Analysis for CR

An interim futility analysis of the CR rate is planned when the CCI randomized patient has completed the Cycle 7 Day 1 assessment or discontinued treatment, whichever comes first. The study may be terminated at CR interim futility analysis, if the 1-sided p-value from the stratified CMH test comparing the CR rates (tamibarotene plus azacitidine treatment group versus placebo plus azacitidine treatment group) is CCI . The non-binding futility bound is derived using a HSD spending function with gamma = -4 (Hwang 1990).

Interim Futility Analysis for OS

If the CR rate is statistically significant at the time of the primary efficacy analysis of the CR rates between the 2 treatment groups, an interim OS futility analysis will be conducted when approximately CCI information fraction (CCI of the total CCI events) has been observed. The study may be terminated at OS interim futility analysis if the 1-sided p-value from the stratified log rank test comparing the distribution of OS (tamibarotene plus azacitidine treatment group versus placebo plus azacitidine treatment group) is CCI . The non-binding futility bound is derived using Lan-DeMets spending function.

The details about the futility and efficacy stopping boundaries at interim analysis and final analysis for CR rate and OS endpoints are specified in Table 5 and Table 6.

Table 5 Planned Stopping Boundaries for CR Futility Analysis and FA

Endpoint	Look	IF	Number of Subjects	Boundary (1-sided p-value)	Minimum Critical Difference of CR Rate at the Boundary
CR rate	Futility	0.5	CCI	CCI	0.0045
	FA	1	CCI	CCI	0.1349

Abbreviations: CR = complete remission; FA = final analysis; IF = information fraction.

Table 6 Planned Stopping Boundaries for OS Futility Analysis and FA

Endpoint	Look	IF	Number of Events	Boundaries (1-sided p-value)	Approx. Observed Hazard Ratios at the Boundary
OS	Futility	0.249	CCI	CCI	1.261
	FA	1	CCI	CCI	0.78

Abbreviations: FA = final analysis; IF = information fraction; OS = overall survival.

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 SoA (Section 1.3).

- 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.

United Kingdom only:

- A Pre-screening ICF and a Main ICF will be used in this study, as shown in the SoA (Section 1.3).

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

- Patients must be informed that their participation is voluntary. Patients 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.

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, 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 and by inspectors from regulatory authorities.

10.1.4 Committees Structure

10.1.4.1 Independent Data Monitoring Committee

An IDMC will be established and will review the data at the 2 planned interim futility analyses and the safety interims, as specified in the IDMC Charter. The IDMC will be comprised of 3 clinicians, one of whom will be the Chair, and one statistician (see IDMC Charter for additional details). The IDMC will meet approximately every 4 months to review the safety data from the study and ad hoc if needed based on request from sponsor.

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 electronic case report forms (eCRFs) via EDC. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

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

- The investigator must permit study-related monitoring, audits, 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 site desires to destroy any study documentation or such other documents, site shall notify sponsor of such desire and 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 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/placebo 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 investigator shall promptly inform the patient 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 SoA (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

Laboratory 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	Prothrombin time or international normalized ratio		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]		

Laboratory Tests	Parameters
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Hepatitis panel testing may include the following tests, as needed, to rule out an active or chronic hepatitis B or active hepatitis C virus (HCV) infection: HCV antibody test, nucleic acid test for HCV RNA, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody (total), and hepatitis B core antibody (IgM)
[a] Local high-sensitivity urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.	

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 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. • Progressive disease (PD), including death from PD, is considered an efficacy outcome parameter and should not be captured as an AE/SAE. Documentation of PD must be obtained and recorded in the eCRF. Until a diagnosis of PD is made, signs and symptoms that meet the AE criteria should be reported as specific AEs, regardless of whether PD is suspected.

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 National Cancer Institute CTCAE, version 5.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 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 post-mortem 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 PPD or Fax #: PPD immediately without undue delay and within 24 hours of receipt of the information. The investigator may also be asked by the sponsor to provide clarification or additional information. ***Germany only:*** The investigator will submit any updated SAE data to the sponsor's designee via email at PPD or Fax #: PPD immediately without undue delay from 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 PPD or Fax #: PPD immediately without undue delay and 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. ***Germany only:*** An SAE Report form will be completed and submitted to the sponsor's designee via email at PPD or Fax #: PPD immediately without undue delay from 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 immediately without undue delay and 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. ***Germany only:*** 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 immediately without undue delay from 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.

Patients must be willing and able to comply with the use of 2 methods of birth control (including a barrier method) for WOCBP and male patients.

Male patients with a partner who is a WOCBP must agree to use a condom combined with an additional contraceptive method that together result in a failure rate of <1% per year (see Section 10.4.2). Contraception use must be continued for at least 90 days after the last dose of study drug. Men should not donate sperm during this timeframe. Tamibarotene has been reported to cause abnormalities in spermatogenesis in nonclinical studies in rats and dogs. In addition, adverse reactions with azacitidine use on male fertility have been documented in animals. Consequently, male patients should consider banking sperm before tamibarotene is administered.

WOCBP patients are required to use highly effective contraceptive measures, as defined in Section 10.4.2. Contraception use must be continued for at least 6 months after the last dose of study drug. Women should not donate ova during this timeframe.

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 postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - 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.
  - 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 study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - 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.

- 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:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy
    d. 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. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        i. 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.
        ii. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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: CCI [redacted]

The table below is prepared to provide examples and is not intended to be exhaustive.

CCI [redacted]

10.7 Appendix 7: Criteria for Determination of MDS IPSS-R Risk Category

MDS Cytogenetic Scoring System (IPSS-R)

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
Very Good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very Poor	Complex: >3 abnormalities

MDS Prognostic Score Values (IPSS-R)

	Score Value						
Prognostic Variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	**Very Good**	**-**	**Good**	**–**	**Inter-mediate**	**Poor**	**Very Poor**
Marrow Blasts (%)	≤2	-	>2 - <5	-	5-10	>10	-
Hemoglobin (g/dL)	≥10	-	8 - <10	<8	-	-	-
Platelet Count (× 10^9/L)	≥100	50 - <100	<50	-	-	-	-
Absolute Neutrophil Count (× 10^9/L)	≥0.8	<0.8	-	-	-	-	-

MDS IPSS-R Prognostic Risk Category and Risk Score (Sum of Prognostic Score Values)

Risk Category	Overall Risk Score
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-65. Epub 2012 Jun 27.

10.8 Appendix 8: IWG Response Criteria for MDS

Hematologic Improvement

The IWG criteria for HI define specific responses of cytopenias in the 3 hematopoietic lineages: erythroid (HI-E), platelet (HI-P), and neutrophil (HI-N). The HIs are measured in patients with pretreatment abnormal values: hemoglobin level less than 110 g/L (11 g/dL) or RBC-transfusion dependence, platelet count less than 100×10^9/L or platelet-transfusion dependence, and absolute neutrophil count less than 1.0×10^9/L.

Response Criteria and Progression Definitions for Myelodysplasia

Response Criteria[a]	***Peripheral Blood***				***Bone Marrow Blasts (BMB) (%)***	***Other***
	Hemoglobin (g/dL)	**Neutrophils per (L)**	**Platelets per (L)**	**Blasts (%)**		
Complete Remission (CR)	≥11	$\geq 1.0 \times 10^9$	$\geq 100 \times 10^9$	0	≤5	Normal maturation of all cell lines, persistent dysplasia will be noted
Partial Remission (PR)					Decreased by ≥50% from baseline, but >5%	All CR criteria if abnormal before treatment except BMB
Marrow CR (mCR)	If hematologic improvement (HI) response, note in addition to marrow CR				decreased by ≥50% from baseline, and ≤5%	
Stable Disease						Failure to achieve PR & no evidence of progression for >8 weeks
Failure						Death during treatment, or disease progression: worsening cytopenia, increase in % BM blasts, progression to a more advanced MDS FAB subtype
Relapse after CR or PR						At least one of the following: Return to pretreatment BMB % Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb ≥1.5g/dL or transfusion dependence

Cytogenetic Response	**Evaluation**
Complete	Disappearance of chromosomal abnormality with no appearance of new ones
Partial	≥50% reduction of chromosomal abnormality

Disease Progression, patients with:	**Evaluation Criteria:**
<5% bone marrow blasts 5%-<10% bone marrow blasts 10%-<20% bone marrow blasts For all categories	≥50% increase to >5% bone marrow blasts ≥50% increase to >10% bone marrow blasts ≥50% increase to ≥20% bone marrow blasts At least 50% decrease from maximum remission/response in granulocytes or platelets or reduction in Hgb by ≥2 g/dL or transfusion dependence

[a] Response must last at least 4 weeks.

Response Criteria for Hematologic Improvement for Myelodysplasia

Hematologic Improvement	**Response Criteria (Response Lasting 8 Weeks)**
Erythroid response (pretreatment <11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of red blood cell (RBC) transfusions by an absolute number of at least 4 RBC transfusions/8 week compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet Response (pretreatment <100 × 10^9/L)	Absolute increase of ≥30 × 10^9/L if starting with >20 × 10^9/L platelets Increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Neutrophil Response (pretreatment <1 × 10^9/L)	At least a 100% increase and an absolute increase >0.5 × 10^9/L
Progression or relapse after HI in the absence of another explanation	At least one of the following: At least 50% decrease from maximum response levels in granulocytes or platelets; Reduction in Hgb by ≥1.5 g/dL; Transfusion dependence.

Adapted from: Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425. Epub 2006 Apr 11.

10.9 Appendix 9: European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (Sample)

10.10 Appendix 10: EuroQol 5 Dimensions (Sample)

10.11 Appendix 11: Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ART	Anti-retroviral therapy
AST	Aspartate aminotransferase
ATRA	All-trans retinoic acid
BID	Twice per day
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CR	Complete remission/complete response
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DOCR	Duration of complete response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture (system)
EFS	Event-free survival
EORTC QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30
EoT	End of treatment
EQ-5D-5L	EuroQol 5 dimensions
EU	European Union
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HCV	Hepatitis C virus
HI	Hematologic improvement
HIV	Human immunodeficiency virus
HR-MDS	Higher-risk myelodysplastic syndrome
HRQOL	Health-related quality of life
HRT	Hormonal replacement therapy

Abbreviation	Definition
HSD	Hwang-Shih-DeCani
HSCT	Hematopoietic stem cell transplantation
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
IPSS-R	Revised International Prognostic Scoring System
ITT	Intent-to-Treat
IWG	International Working Group
LSM	Least squares mean
mCR	Marrow CR
MDS	Myelodysplastic syndrome
MMRM	Mixed models for repeated measures
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic(s)
PR	Partial remission/partial response
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
SoA	Schedule of Activities
SmPC	Summary of Product Characteristics
TI	Transfusion independence
ULN	Upper limit of normal

Abbreviation	Definition
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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