TP-0184

BBI-TP-0184-102

A PHASE 1/2, OPEN-LABEL CLINICAL STUDY TO EVALUATE SAFETY AND EFFICACY OF TP-0184 TO TREAT ANEMIA WHEN ADMINISTERED TO ADULT PATIENTS WITH IPSS-R LOW OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES

Study Protocol Number:	BBI-TP-0184-102
Study Medication Name:	TP-0184
Developmental Phase:	Phase 1/2
Short Title:	A Phase 1/2 Study of Oral TP-0184 to Treat Anemia in Adults with IPSS-R Low or Intermediate Risk MDS
Indication:	Anemia in Myelodysplastic Syndrome (MDS)
Sponsor:	Sumitomo Dainippon Pharma Oncology, Inc. 640 Memorial Drive Cambridge, MA 02139
Amendment 3.0 Date	27 May 2021

SIGNATURE PAGE

Sponsor's Signatory:

The protocol has been approved by Sumitomo Dainippon Pharma Oncology, Inc.

DocuSigned by:

[redacted]

5/27/2021

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for TP-0184. I have read the protocol for Study BBI-TP-0184-102 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACT INFORMATION

Table 1: Contact Information

Role in Study	Name	Address/Email & Telephone Number
Clinical Study Leader	[redacted]	
Responsible Physician		
Drug Safety Lead		
24-Hour Emergency Contact		

2. SYNOPSIS

Name of Sponsor/Company: Sumitomo Dainippon Pharma Oncology, Inc.	
Name of Investigational Product: TP-0184	
Name of Active Ingredient: TP-0184	
Protocol Number: BBI-TP-0184-102	**Country/Region:** US
Title of Study: A Phase 1/2, Open-Label Clinical Study to Evaluate Safety and Efficacy of TP-0184 to Treat Anemia when Administered to Adult Patients with IPSS-R Low or Intermediate Risk Myelodysplastic Syndromes	
Study center(s): The study will be conducted in multiple study sites in the US.	
Phase of development: Phase 1/2	

Objectives and Endpoints:

Primary Objectives	Study Endpoints
Phase 1	
• To assess the safety and tolerability of TP-0184 • To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and recommended dose for the future expansion arms of TP-0184 in the Phase 2 part of the study	Assessment of dose limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs); type, frequency and severity of AEs and relationship of AEs to TP-0184, TP-0184 dose interruptions and dose reductions
Phase 2	
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and Transfusion-Free ≥ 8 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 8 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive) compared with the

	pretreatment transfusion number in previous 8 weeks OR Patients who are RBC transfusion-free over any consecutive 8-week (56-day) period
Phase 1	
Secondary Objectives	**Study Endpoints**
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and RBC Transfusion-Free ≥ 8 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 8 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive) compared with the pretreatment transfusion number in previous 8 weeks OR Patients who are RBC transfusion-free over any consecutive 8-week (56-day) period
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and RBC Transfusion-Free ≥ 12 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 12 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 12 weeks (consecutive) compared with the pretreatment transfusion number in previous 12 weeks OR Patients who are RBC transfusion-free over any consecutive 12-week (84-day) period
To measure time to RBC transfusion-free period	Time from first dose of TP-0184 to the first onset of a transfusion-free period for consecutive 8 weeks
To assess median duration of hemoglobin response	Duration of hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions.
To assess median duration of reduction in RBC transfusions (4 units / 8 weeks)	Duration of reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive)

To assess median duration of RBC-transfusion-free period ≥ 8 weeks	Duration of RBC transfusion-free period
To assess progression to acute myeloid leukemia (AML)	Proportion of patients progressing to AML, time to AML progression
To assess overall survival	Time from first dose of TP-0184 to death due to any cause
To establish the pharmacokinetic (PK) profile of single agent TP-0184	PK parameters of TP-0184 as single agent: C_{max}, C_{trough}, t_{max}, AUC_{τ} and possibly others
Phase 2	
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and RBC Transfusion-Free ≥ 12 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 12 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 12 weeks (consecutive) compared with the pretreatment transfusion number in previous 12 weeks OR Patients who are RBC transfusion-free over any consecutive 12-week (84-day) period
To measure time to RBC transfusion- free period	Time from first dose of TP-0184 to the first onset of a transfusion-free period for consecutive 8 weeks
To assess median duration of hemoglobin response	Duration of hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions
To assess median duration of reduction in RBC transfusions (4 units / 8 weeks)	Duration of reduction in units of ≥ 4 RBC transfusions / 8 weeks. (consecutive)
To assess median duration of RBC-transfusion-free period ≥ 8 weeks	Duration of RBC transfusion-free period
To assess changes in neutrophil count	Proportion of patients achieving hematologic improvement in neutrophil count (HI-N) over any consecutive 8-week (56-day) period and / or decrease in neutrophil count
To assess changes in platelet count	Proportion of patients achieving hematologic improvement in platelets (HI-P) over any consecutive 8-week (56-day) period and / or decrease in platelet count

To assess the safety and tolerability of TP-0184	Assessment of TEAEs; type, frequency and severity of AEs and relationship of AEs to TP-0184, TP-0184 dose interruptions and dose reductions
To determine the cardiac safety of TP-0184 administered as single agent	Assessment of the presence of symptoms of CHF (based on NYHA criteria, 12-Lead ECG abnormalities, quantification of cardiac iron by MRI, ECHO or MUGA scans, and peripheral blood cardiac markers
To characterize steady-state trough PK	TP-0184 plasma trough concentration data at various timepoints. Specifically, pre-dose (trough) samples on Cycle 1 Day 1 of Week 4 and Cycle 2 Day 1 of each Week 5, 6, 7, and 9
To assess progression to AML	Proportion of patients progressing to AML, time to AML progression
To assess overall survival	Time from first dose of TP-0184 to death due to any cause
To assess change from baseline in the Brief Fatigue Inventory	The BFI that measures the severity of fatigue based on the worst fatigue experienced during the past 24-hours
To document the percentage and outcome of patients who have achieved a hematologic response and a hematopoietic stem cell transplant (HSCT) during or following treatment with TP-0184	
Exploratory Objectives	**Endpoints**
Phase 1	
To determine pharmacodynamic effects of TP-0184 therapy	Determination of in vivo markers of ALK-2 /ALK-5 inhibition. Markers included, but not limited to: • SMAD/phospho-SMAD signaling • Markers of iron metabolism, including Hepcidin iron panel (serum iron, ferritin, transferrin, soluble transferrin receptor [STR], and total iron binding capacity [TIBC]) • Cytokines TGFβ, IL-6, CRP, EPO
To determine the cardiac safety of TP-0184	Assessment of the presence of symptoms of congestive heart failure (CHF) (based on New York Heart Association [NYHA] criteria), 12-Lead ECGs abnormalities, intensive ECG recordings taken at time of PK draws, assessment of iron

	accumulation by cardiac magnetic resonance imaging (MRI), ECHO or MUGA scans, and peripheral blood cardiac markers
To determine whether TP-0184 treatment modulates organ iron deposition	Evaluation of cardiac and hepatic iron content by MRI at baseline and during treatment with TP-0184
Metabolites of TP-0184 in patients via Phase 1 data	Profile of potential metabolites of TP-0184 in patients in Phase 1
To assess changes in neutrophil counts	Proportion of patients achieving hematologic improvement in neutrophil count (HI-N) over any consecutive 8-week (56-day) period and / or decrease in neutrophil levels
To assess changes in platelet count	Proportion of patients achieving hematologic improvement in platelets (HI-P) over any consecutive 8-week (56-day) period and / or decrease in platelet count
To assess change from baseline in the Brief Fatigue Inventory	The Brief Fatigue Inventory (BFI) that measures the severity of fatigue based on the worst fatigue experienced during the past 24 hours
Phase 2	
To determine the pharmacodynamic effects of TP-0184 therapy	Determination of in vivo markers of ALK-2 /ALK-5 inhibition Markers included, but not limited to: • SMAD/phospho-SMAD signaling • Markers of iron metabolism, including Hepcidin iron panel (serum iron, ferritin, transferrin, soluble transferrin receptor [STR], and total iron binding capacity [TIBC]) • Cytokines TGFβ, IL-6. CRP, EPO
To determine whether TP-0184 treatment modulates iron accumulation and removal in the heart and liver	Evaluation of cardiac and hepatic iron content by MRI at baseline and during treatment with TP-0184

Study Design:

This is a Phase 1/2, open-label clinical study to evaluate the preliminary safety and efficacy of TP-0184 to treat anemia when administered to adult patients with Revised International Prognostic Scoring System (IPSS-R) low or intermediate risk MDS. The recommended Phase 2 dose (RP2D) will be determined by the MTD or MAD in the Phase 1 portion of the study.

Methodology:

Phase 1 – Dose Escalation

Multiple dose levels of TP-0184, with approximately 1 to 6 patients at each level will be evaluated. There must be at least 3 DLT-evaluable patients at a specific dose level if there is a DLT observed in that level. The first cohort will receive 20 mg/day for 28 consecutive days, comprising 1 treatment cycle. Patients will receive the first dose of TP-0184 on Cycle 1 Day 1. Dose escalation is planned to proceed with provisional doses after the 20 mg dose level of 40 mg, 60 mg, 90 mg, 120 mg, 160 mg, 210 mg, and 270 mg. Further respective dose increments of up to 25% from one dose cohort to the next may occur. In order to determine the recommended Phase 2 dose, dose escalation may continue until one of the following occurs:

1. An MTD is determined.
2. An MAD is determined based on the totality of safety data and medical considerations by the study safety review committee (SRC) and sponsor.

Dose escalation will be performed using a design based on a 2-parameter Bayesian logistic regression model (BLRM). The dose recommended by the BLRM method will be treated as guidance and will be integrated with a clinical assessment of the safety adverse event information and review of clinical data, in addition to safety and PK data. Intermediate doses between planned dose levels may be explored based on safety consideration after discussion and concurrence with SRC members and Sumitomo Dainippon Pharma Oncology, Inc (SDP Oncology) clinical team. An additional cohort with a different dose schedule may be considered based on clinical judgment supported by medical observations.

Procedures for close monitoring of the DLT period and entire study have been established. In addition, an SRC will conduct scheduled meetings and will provide safety oversight of the patients, determine DLTs, and guide escalation and dose decisions.

The RP2D will be determined based upon safety, PK, PD, efficacy and other available data. Determination of the RP2D will be performed in consultation with the SRC based on safety and other data available at the time of the RP2D decision.

Phase 2 – Dose Expansion

In the Phase 2 portion of the study, the RP2D, as determined in Phase 1, will be used. Phase 2 will determine the preliminary efficacy of TP-0184 in an expansion phase of up to 60 patients.

Efficacy as assessed by response rate will be monitored using the Bayesian posterior probability to optimize the enrollment with Bayesian stopping rules.

Number of Patients/Subjects (planned):

Approximately 30 patients are planned to be enrolled in Phase 1, and approximately 10-60 patients in Phase 2.

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study:

1. A documented diagnosis of lower risk MDS (IPSS-R Low, Intermediate) according to WHO 2016 classification, de novo or secondary.
2. Bone marrow biopsy and/or aspirate performed pre-dose to assess disease status and available for review *prior* to full screening review. If the bone marrow biopsy and/or aspirate is nonproductive or nondiagnostic, the procedure must be repeated. Bone marrow biopsy/aspirate performed ≤ 12 weeks prior to baseline will not need to be repeated if results and a minimum of 6 slides are available.

3. Relapsed, refractory/resistant, intolerant, or inadequate response to ESA treatment, as defined by the following:
   - Relapse according to IWG 2006
   - Refractory/resistant – documented non-response or response that is no longer maintained to prior ESA-containing regimen, either as single agent or combination (eg, with G-CSF). ESA regimen must have been receiving either:
     - Recombinant human erythropoietin (rHu EPO) ≥ 500 IU/wk for at least 8 doses or equivalent

       OR
     - Darbepoetin alpha ≥ 300 µg Q3W for at least 4 doses or equivalent
   - Intolerant – documented discontinuation of prior ESA containing regimen, either as single agent or combination (eg, with G-CSF), at any time after introduction due to intolerance or an adverse event.
   - Inadequate response – in the absence of transfusions support, patients under ESA treatment for at least 12 weeks that do not show a rise in hemoglobin of greater than equal to 1 g/dl.
4. Patients with 5q deletions are allowed only if they have failed or are intolerant to lenalidomide treatment.
   - Failure or intolerance to lenalidomide defined as clinical and cytogenetic responses to according to the international working group 2006 MDS: (1) absence of response; (2) bone marrow progression during treatment with or without prior response; (3) secondary failure (loss of prior hematological response without bone marrow progression); or, (4) intolerance (treatment discontinuation due to AEs, with or without prior response) based on investigator judgement (Prebet 2017).
5. Previous treatment for anemia with or without RBC transfusion support:
   a. Low transfusion burden (LTb), defined as requiring less than 4 red blood cell units in the 8 weeks before treatment (and baseline hemoglobin < 9.0 g/dL)
   b. High transfusion burden (HTb), defined as requiring 4 or more red blood cell units in the 8 weeks before treatment
6. At least 12 weeks of transfusion history immediately preceding the first dose of TP-0184. This transfusion data must include hemoglobin measured prior to transfusion (pre-transfusion Hgb).
7. Informed consent for trial participation from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study related procedure.
8. At least ≥ 18 years of age.
9. An Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score ≤ 2.
10. A life expectancy of ≥ 3 months (90 days) per the treating investigator.
11. Adequate major organ function meeting the following criteria on the basis of laboratory data within 28 days of first dose, during screening. If multiple data points are available, the most recent data acquired during the 28 days screening period will be used.

   a. Serum creatinine: ≤ 1.8 x the upper limit of the normal (ULN) range.
   b. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin is ≤ 2.0 x ULN. Elevated indirect bilirubin due to post-transfusion hemolysis is allowed.
   c. Aspartate transaminase (AST) and alanine transaminase (ALT): ≤ 2.5 x ULN.
   d. Left ventricular ejection fraction (LVEF) ≥ 45% by echocardiogram or multigated acquisition (MUGA) scan.
12. All previous therapy with ESAs, G-CSF, and GM-CSF must be discontinued ≥ 14 days before Cycle 1 Day 1 dosing.
13. Twenty-eight-day washout period from prior treatment with cytotoxic chemotherapeutic agents, HMAs (hypomethylating agents), ImiDs (immunomodulatory imide drugs), luspatercept, and/or investigational drugs before study dosing for the patient begins.
14. Women of childbearing potential (WOCBP) with a negative serum or urine pregnancy test within 5 days prior to the first dose of TP-0184.
15. Non-fertile or agree to use an adequate method of contraception while on study and for 7 months after the last dose of TP-0184, and a negative pregnancy test (if female of childbearing potential) and not currently nursing; males agree to use an adequate method of contraception while on study and for 4 months after the last dose of TP-0184.
16. Ability to comply with the requirements of the entire study and accessibility for treatment and follow-up.
17. Agreement not to participate in other interventional clinical studies during participation in this trial, while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. IPSS-R high or very high risk MDS.
2. Presence of concomitant severe cardiovascular disease, congestive heart failure (CHF), myocardial infarction, angina, and/ or uncontrolled cardiac arrhythmia as determined by the investigator within 180 days of study onset.
3. Corrected QT interval (using Fridericia's correction formula) of > 465 msec in men and > 480 msec in women.
4. History of stroke, deep venous thrombosis (DVT), pulmonary or arterial embolism within 180 days prior to enrollment.
5. Presence of clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding.
   a. Iron deficiency to be determined by a bone marrow aspirate stain for iron, calculated transferrin saturation (iron/total iron binding capacity) ≤ 20%, or serum ferritin ≤ 15 µg/L.
   b. Iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks prior to enrollment, are excluded.
6. Prior allogeneic or autologous stem cell transplant.
7. Known history of diagnosis of AML.
8. Use of corticosteroids, except for subjects on a stable or decreasing dose (no greater than a 10 mg dose of prednisone or equivalent) for ≥ 2 weeks prior to enrollment for medical conditions other than MDS.

9. Evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count (reticulocyte index) of > 2% with either a positive Coombs' test or over 50% indirect bilirubin.
10. Patients with a recent diagnosis of malignancy are excluded except for those with in situ malignancies treated with curative intent (eg, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix). Patients with more advanced malignancies are allowed to enroll, provided they were treated with curative intent and have no evidence of active disease ≥ 2 years prior to Cycle 1 Day 1.
11. Patients requiring systemic antibiotics or antifungals are not eligible until they have completed the prescribed course of antibiotics or antifungals and are clinically stable. Topical antibiotics or antifungals are permitted.
12. Known HIV, active Hepatitis B, and/or active Hepatitis C infection.
13. Patients with bleeding requiring medical intervention (eg, surgical) in the past month.
14. Platelet count < 50,000/μL 50 x 10^9/L) during screening.
15. Absolute neutrophil count (ANC) < 500 /μL (0.5 x 10^9/L) during screening.
16. Women who are pregnant or breastfeeding.
17. Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second effective method of contraception during the trial and for 7 months after the last administration of study treatment.
18. Inability to undergo MRI imaging.
19. Parenchymal iron overload by screening MRI.
20. Unwillingness or inability to comply with procedures required in this protocol.
21. Have undergone recent surgery with potential to cause the impairment of gastrointestinal tract absorption or that could cause short bowel syndrome with diarrhea due to malabsorption.
22. Have known hemochromatosis at baseline or a family history of hemochromatosis.
23. Presence of any psychological, familial, sociological or geographical condition that, in the opinion of the investigator, could potentially hinder compliance with the study protocol and follow-up schedule.
24. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
25. Live vaccines within 14 days prior to first study drug administration. COVID-19 vaccines (non-live) approved by regional health authorities are allowed.
26. Medications that are known strong to moderate CYP3A4 inducers must be discontinued at least 21 days prior to first dose of study drug. Medications that are known strong to moderate CYP3A4 inhibitors must be stopped 21 days (or 5 half-lives, whichever is shorter) prior to the first dose of study drug.
27. Patients who have received medications with known or possible risk of prolonging the QT interval or inducing Torsades de Pointes within the previous 7 days.

Investigational product, dosage, schedule and mode of administration:

TP-0184, administered orally once a day, taken in the morning after an overnight fast (minimum of 6 hours) with up to 200 mL or 7 ounces of water. Study participants should wait at least 1 hour before ingesting any food, liquid (other than water), or other medications.

Duration of treatment:

The expected duration of treatment will be for 24 weeks (6 cycles). Furthermore, based on assessment of response, patients may continue to receive TP-0184 in the absence of MDS disease progression or until loss of hematological response or unacceptable toxicity.

Statistical methods:

Phase 1

Two-parameter BLRM with EWOC will be used to guide dose escalation and estimate the MTD based on occurrence of DLT during Cycle 1. The MTD with estimated posterior probability of a DLT within target toxicity interval (16%, 33%] among the admissible doses fulfilling EWOC is determined by BLRM. MTD is estimated based on observed DLTs.

After completing a given dose escalation cohort, the decision to move up to a planned cohort or not, or to adjust to a lower or slightly higher dose, will be assessed based on BLRM with EWOC and integrate all available safety data, PK and other clinical data using the BLRM method as guidance for dose escalation. A SRC will consist of the Principal Investigators, an independent cardiologist, the Safety Lead, the Statistician, and the Medical Monitor.

After completing a given dose escalation cohort, the decision to move up to the next cohort or not, or to adjust to a lower or slightly higher dose, will be decided by the SRC based on BLRM with EWOC and integration of all available safety data, PK and other clinical data using the BLRM method. The dose recommended using the BLRM method will serve as a guide and will be integrated with clinical assessment of the safety information and review of other available data to determine the actual treatment dosage.

Additional or intermediate dose levels may be explored. It is possible that potential arm with different dosing schedule is added during the Phase I study period based on safety considerations.

Determination of Recommended Dose:

The recommended dose is usually the dose with acceptable toxicity, generally defined as the dose level producing a DLT rate within the toxicity interval (16%, 33%]. Determination of the recommended dose will be performed in consultation with the SRC based on safety and other data available at the time of the recommended dose decision.

Once the recommended dose for the expansion arms is identified, the Phase 1 portion of the study will progress to Phase 2.

Phase 2:

The Phase 2 design is based on Bayesian efficacy monitoring using posterior probability criteria.

After the first 10 enrolled patients are evaluable for efficacy (Efficacy Evaluable Analysis Set), response rate monitoring using Bayesian posterior probability will be performed. If posterior probability of response rate less or equal than 5% is greater than 90% (Prob $[\theta \leq 0.05] > 0.90$), the study may be stopped for futility; if posterior probability of response rate greater or equal than 20% is greater than 80% (Prob $(\theta \geq 0.2) > 0.80$) during study enrollment, SDP Oncology has the option to stop the enrollment of Phase 2 and trigger subsequent clinical development of TP-0184. If neither criterion is met, it will continue to more fully characterize the response rate in a total of approximately 60 efficacy evaluable patients. If posterior probability of response rate greater or equal than 20% is greater than 50% (Prob $[\theta \geq 0.2] > 0.50$) at the final analysis, the current study will be

considered successful. Efficacy as assessed by response rate will be monitored using the Bayesian posterior probability to optimize the enrollment with Bayesian stopping rules.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Definitions

AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukemia
BFI	Brief Fatigue Inventory
BLRM	Bayesian logistic regression model
CHF	congestive heart failure
DLT	dose-limiting toxicities
EAS	efficacy evaluable analysis set
ECG	electrocardiography
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EPO	erythropoietin
ESA	erythropoiesis stimulating agents
EWOC	escalation with overdose control
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HNSTD	Highest Non-Severely Toxic Dose
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MDS	myelodysplastic syndromes
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PI	Principal Investigator
PK	pharmacokinetic
PTT	partial thromboplastin time
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event

SDP Oncology	Sumitomo Dainippon Pharma Oncology, Inc.
SRC	Safety Review Committee
STR	soluble transferrin receptor
TGF-β	transforming growth factor beta
TEAE	treatment-emergent adverse event
TIBC	total iron binding capacity
US	United States

5. INTRODUCTION

5.1. Disease Background

Myelodysplastic disease syndromes (MDS) is composed of a heterogeneous group of hematopoietic stem cell disorders and is characterized by dysplasia in 1 to 3 of the bone marrow cell lineages, either myeloid, megakaryocytic and/or erythroid lineages. The abnormal cells seen in MDS represent a malignant hematopoietic clone, which represses the remaining normal hematopoietic cells in the bone marrow. Patients with MDS have one or more significant peripheral blood cytopenias (anemia, leukopenia and/or thrombocytopenia).

The overall incidence of MDS in the general population is estimated to be 3 to 4 cases per 100,000 persons per year. Greater than 85% of these patients are older than 60 years at the time of diagnosis. It is also generally assumed that the incidence of MDS is underestimated due to the complexity of diagnosis. Indolent forms of MDS are often not clinically recognized or not evaluated due to patient comorbid conditions. In addition, a number of other disorders, including nutritional deficiencies, infections or medications, may cause transient cytopenias, without clonal aberrations. Bone marrow aspiration and biopsy including conventional cytogenetics is essential for diagnosis. Cytogenetic abnormalities are found in approximately 50% of MDS patients. Evaluation of peripheral blood or bone marrow for MDS-associated gene mutations may establish the presence of clonal hematopoiesis and help exclude benign causes of cytopenias, however do not in isolation establish a diagnosis of MDS.

The spectrum of MDS ranges from indolent disease in the low to intermediate risk category to severe bone marrow failure in those with high-risk disease resulting in life-threatening complications. Progression to acute myeloid leukemia (AML) occurs in about 30% of patients. The diagnosis is made by review of bone marrow aspirate revealing dysplastic marrow cellular changes that may include elevated blast counts and cytogenetic abnormalities. About 30% of patients diagnosed with low risk MDS progress to AML.

Anemia is common in patients with MDS reflecting ineffective erythropoiesis. Proinflammatory cytokines have long been implicated in the death of bone marrow progenitors in MDS (Sallman, Blood 2019; 133(10):1039-1048). Interleukin-6 and other cytokines of chronic inflammation lead to iron-restricted hematopoiesis (Hematologica 2020; 105(2): 1-13). Treatment options for anemia in MDS patients are limited (e.g., the administration of erythropoietic agents [EPO]) and are only beneficial to a sub-group of patients. As a consequence, ~ 70% of patients with low risk MDS require RBC transfusions and subsequently become transfusion dependent.

Clinical iron overload starts to develop in MDS patients before they become transfusion dependent because their ineffective erythropoiesis suppresses hepcidin production in the liver leading to unrestrained intestinal iron uptake. (Santini V PLoS ONE: 2011;6(8). However, the most important cause of iron overload in MDS is chronic transfusion therapy. While transfusion dependency by itself is a negative prognostic factor reflecting poor bone marrow function, the ensuing transfusion and dose dependent iron overload have an additional negative impact on the survival of patients with low to intermediate risk MDS due to the complications of bone marrow failure or acute leukemia (Malcovati L 2011).

The Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy trial (TELESTO) was the first placebo-controlled study evaluating outcomes using iron chelation

therapy in low risk MDS. Results presented in 2018 showed a 36.4% risk reduction in event-free survival in chelated patients, fewer cardiac and liver-related events and fewer progression events to AML compared with placebo. (Angelucci et al, Blood (2018); 132 Supplement 1: 234.)

There are 3 approved chelating agents for the treatment of iron overload (deferoxamine, deferasirox, and deferiprone). However, these agents have limited efficacy and are associated with adverse effects.

The management of anemia in MDS remains a challenging issue for hematologists/oncologists. This population is primarily elderly with significant co-morbidities making them relatively intolerant to therapy. Few therapeutic products have been approved to treat lower risk MDS. Revlimid® (lenalidomide) is approved by the United States (US) Food and Drug Administration (FDA), but only in subjects with transfusion dependent anemia due to low, or intermediate risk MDS and with a 5q deletion abnormality. The approved label for Revlimid bears a black box warning due to significant risks associated with its treatment including thrombocytopenia and neutropenia, embryofetal toxicity, and incidences of renal and hepatic toxicities (USPI Revlimid). Reblozyl® (luspatercept) was recently approved for the treatment of anemia in adult patients with very low- to intermediate MDS with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who have failed an erythropoiesis stimulating agent (ESA) and require at least 2 red blood cell units over 8 weeks. Options for treating anemia in lower risk MDS remains an unmet need.

5.2. Rationale for Study

The ineffective hematopoiesis present in MDS has long been considered to be related to inflammatory cytokines, including the TGF-β pathway associated with SMAD2/3 signaling (Herbertz 2010). The natural inhibitor of the TGF-β/SMAD2/3 signaling pathway, SMAD7, is suppressed in MDS progenitor cells due to increased miR21 expression, which in turn upregulates the TGF-β/SMAD2/3 pathway with subsequent suppression of hematopoiesis (Bhagat 2013). This leads to increased expression of myelosuppressive cytokines and decreased burst forming unit-erythroid (BFU-E) and colony forming unit- granulocyte, erythrocyte, monocyte, megakaryocyte (CFU-GEMM). These same cytokines are immunosuppressive and may also contribute to the fatigue seen in MDS patients. Blockade of the TGF-β/SMAD2/3 pathway with an TGF-βR1/ALK-5 inhibitor may improve the ineffective erythropoiesis seen in MDS and offer therapeutic benefit for the treatment of MDS.

TP-0184 is a small molecule dual inhibitor against ALK-2 and ALK-5, affecting both ALK-2-SMAD1/5/8 and ALK5-SMAD2/3 signaling pathways, respectively. In pre-clinical studies TP-0184 was shown to inhibit downstream signaling from ALK-2 kinase (by reducing phospho SMAD1/5 levels) in cancer cells treated with the ALK-2 ligand BMP2, and to block expression of hepcidin, an important regulator of iron levels, and thus erythropoiesis. Hepcidin was found to be a responsive biomarker to ALK-2 inhibition in cancer cell culture models. Hepcidin was also found to be a pharmacodynamic biomarker in in vivo studies with liver tissue and blood in the mouse model with acute inflammation or bacteria-induced anemia. Due to the lack of an appropriate in vivo model for MDS, the role of hepcidin in the anemia due to MDS is unknown. However, it may or may not play a role as a part of the ALK-2 signaling pathway effecting the anemia due to MDS. TP-0184 was also determined to be a potent inhibitor of

TGFβR1/ALK-5 ex-vivo studies. This was demonstrated by TP-0184 inhibiting downstream signaling from ALK-5 kinase by reducing SMAD2/3 phosphorylation in cancer cell lines treated with the ALK-5 ligands, TGFβ and GDF11, the growth factors leading to altered hematopoietic differentiation in MDS (Zhou L 2008). TP-0184 was found to inhibit ALK-5 pathways and SMAD2/3 phosphorylation in reporter assays at sub-micromolar to single digit micromolar concentrations. Activity of TP-0184 with in-vitro cellular models was similar to other known ALK-5 inhibitors. Though in vivo studies evaluating ALK-5 inhibition by TP-0184 have not been conducted to date, erythroid colony counts in the bone marrow and erythropoietic markers such as hemoglobin were found to be responsive biomarkers to ALK-5 inhibition in a transgenic mouse model for MDS by other ALK-5 inhibitors (eg, galunisertib) (Zhou L 2014). The in vitro and in vivo pharmacology data and the inhibitory activity of TP-0184 towards both the ALK-5 and ALK-2 signaling pathways supports the proposed evaluation of treatment of anemia in MDS patients with TP-0184.

To conclude, the inhibition of both ALK-2 and ALK-5 pathways by TP-0184 presents a potential option for the treatment of anemia due to MDS. Treatment with TP-0184 may result in the reduction of ineffective erythropoiesis and offer therapeutic benefits of improving anemia and lowering the frequency of transfusions. This, in turn, will lower the risk of iron overload.

5.3. Summary of Risks and Benefits in Humans

A full summary of risks and benefits in humans is included in Section 6, Data and Guidance for Investigators, of the Investigator Brochure.

5.4. Investigational Product Background

5.4.1. Nonclinical Studies

Twenty-eight-day repeat-dose Good Laboratory Practice (GLP) toxicology and toxicokinetic studies were conducted in rats and dogs.

Rats were given TP-0184 orally, once-daily at 0 (vehicle), 20, 50, and 150 mg/kg/day (human equivalents of 120, 300 and 900 mg/m2/day, respectively), and following the last dose a subset of rats was held for a 14-day post-treatment recovery period. Rats given 150 mg/kg/day lost weight (or gained less weight than controls). At the end of the dosing period, rats given 150 mg/kg/day had slightly higher ALT and AST compared with controls. At necropsy, liver weights were higher than controls for rats given 50 or 150 mg/kg/day. All TP-0184-treated groups exhibited mild, pan-lobular hepatocellular hypertrophy as well as lymph node sinus erythrocytosis; the incidence was dose-related. At the end of the recovery period, chemistry parameters as well as liver and lymph node morphology were normal. The Severely Toxic Dose in 10% of the animals (STD10) was determined to be greater than 150 mg/kg/day.

Dogs were given TP-0184 orally, once-daily at 0 (empty capsules), 2, 5, and 10 mg/kg/day (human equivalents of 40, 100, and 200 mg/m2/day), and following the last dose a subset of dogs was held for a 14-day post-treatment recovery period. One dog given 10 mg/kg/day was euthanized because of poor condition near the end of the study: it had pronounced clinical signs (emesis, mucoid/ soft feces, diarrhea), lost substantial weight and consumed less food, and did not respond to veterinary intervention. Emesis occurred in all treatment groups and incidence was dose-related; at 5 or 10 mg/kg/day, weight loss as well as diarrhea/ soft feces also occurred

along with decreased food consumption. During the recovery period dogs did not exhibit treatment-related clinical signs, and weight gain and food consumption were similar among control and treated groups. There were no treatment-related gross or microscopic pathologic findings. The Highest Non-Severely Toxic Dose (HNSTD) was determined to be greater than 5 mg/kg/day.

For additional details regarding these studies, please refer to the TP-0184 Investigator Brochure.

5.4.2. Clinical Studies

5.4.2.1. Study TP-0184-101 (Solid Tumor)

The first in human clinical study of TP-0184 (Tolero Study No. TP-0184-101) is ongoing in adult patients with advanced/refractory solid tumors. Since the study is still ongoing, a complete evaluation of the safety of this compound given in escalating doses has not yet been conducted.

At the start of this study, a Phase 1 first-in-human study exploring escalating dose levels of TP-0184 in patients with advanced solid tumors had already been initiated with a starting dose of 30 mg QD for 21 days. Subsequently, dosing was changed to once weekly, with a starting dose of 60 mg once weekly for 4 weeks (Amendment 2, 12 Sep 2019). The most common side effects, regardless of causality, were gastrointestinal (nausea, vomiting) and fatigue. There were no clinically significant trends of hepatic or cardiac toxicity and the safety profile was considered favorable. Preliminary PK analysis suggested dose-related increases in systemic exposure with increasing dose and longer elimination t½ than projected from preclinical PK data. Please refer to the TP-0184 Investigational Brochure for additional information.

Changes in cardiac valve status have been documented in in vivo pre-clinical studies (not human) with small molecule kinase inhibitors in the same therapeutic class as TP-0184. Following discussion with the US FDA, cardiac toxicity and hepatotoxicity were identified as Adverse Events of Special Interest (AESIs) in Study TP-0184-101. While there have been some changes in cardiac markers (BNP, NT-proBNP) observed on study, the changes have been either Grade 1 or Grade 2 in severity, and none have been associated with clinical symptoms or notable changes in ejection fraction. Thus far, no clinically significant trends of hepatic or cardiac toxicity have been reported.

5.4.2.2. Study BBI-TP-0184-102 (MDS)

Patients with MDS related anemia frequently require chronic RBC transfusions, which may cause iron overload. The potential for deposition of iron in the heart and liver may lead to organ dysfunction. Iron overload has an additional dose dependent negative impact on the survival of patients with lower risk MDS. Treatment with an ALK-2/ALK-5 inhibitor could result in improvement of anemia, resulting in fewer transfusions and may thereby reduce the risk of iron overload. The risk of potential iron deposition and its sequelae on the heart and liver is reduced by intensive cardiac and hepatic monitoring as a proactive strategy to avoid undue toxicity.

Study BBI-TP-0184-102 contains several measures to ensure patient safety, such as defined patient selection criteria for participation, judicious and gradual dose escalation rules, appropriate safety surveillance measures, and comprehensive dose modification guidelines to be implemented in case of treatment toxicity. In addition to physical examinations and routine laboratory testing, the medical assessments used in this study to evaluate safety include

comprehensive cardiac monitoring with intensive ECG (with QTcF assessment in Phase 1), cardiac MRIs for iron quantification, echocardiography/MUGA scans, laboratory markers for heart failure (BNP, NT-proBNP), and safety ECGs. Based on the mechanism of action of TP-0184, cardiac toxicity and hepatotoxicity events will be captured as AESIs in this study.

Liver monitoring includes liver function testing and hepatic MRIs for iron quantification. Iron panels (including ferritin) are performed frequently throughout the study per protocol.

Blood tests will also be used to explore molecular markers associated with the biology of MDS and the mechanism of action of TP-0184. These biomarkers will not be used to make therapeutic decisions on dosing or regimen management; they are only conducted for experimental purposes, to gain a better understanding of the biology of the treatment at the cellular and molecular levels, and to evidence pharmacodynamic action.

The protocol minimizes currently known risks of TP-0184 by frequent monitoring for early detection of AEs. Given the anticipated benefits of TP-0184, the safety profile of TP-0184 in patients treated in this study is considered favorable. Results of this study could contribute to a better understanding, treatment, evaluation, and management of future patients affected by MDS and anemia of cancer.

More detailed information about the known and expected benefits and risks may be found in the Investigator's Brochure.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives and Endpoints

Primary Objectives	Study Endpoints
Phase 1	
• To assess the safety and tolerability of TP-0184 • To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and recommended dose for the future expansion arms of TP-0184 in the Phase 2 part of the study	Assessment of dose limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs); type, frequency and severity of AEs and relationship of AEs to TP-0184, TP-0184 dose interruptions and dose reductions
Phase 2	
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and Transfusion-Free ≥ 8 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 8 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive) compared with the pretreatment transfusion number in previous 8 weeks OR Patients who are RBC transfusion-free over any consecutive 8-week (56-day) period

6.2. Secondary Objectives and Endpoints

Phase 1	
Secondary Objectives	**Study Endpoints**
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and RBC Transfusion-Free ≥ 8 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 8 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive) compared with the pretreatment transfusion number in previous 8 weeks OR Patients who are RBC transfusion-free over any consecutive 8-week (56-day) period

To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and RBC Transfusion-Free ≥ 12 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 12 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 12 weeks (consecutive) compared with the pretreatment transfusion number in previous 12 weeks OR Patients who are RBC transfusion-free over any consecutive 12-week (84-day) period
To measure time to RBC transfusion-free period	Time from first dose of TP-0184 to the first onset of a transfusion-free period for consecutive 8 weeks
To assess median duration of hemoglobin response	Duration of hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions.
To assess median duration of reduction in RBC transfusions (4 units / 8 weeks)	Duration of reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive)
To assess median duration of RBC-transfusion-free period ≥ 8 weeks	Duration of RBC transfusion-free period
To assess progression to AML	Proportion of patients progressing to AML, time to AML progression
To assess overall survival	Time from first dose of TP-0184 to death due to any cause
To establish the PK profile of single agent TP-0184	PK parameters of TP-0184 as single agent: C_{max}, C_{trough}, t_{max}, AUC_{τ} and possibly others
Phase 2	
To determine the effect of TP-0184 on the treatment and the hematologic improvement of anemia in terms of hemoglobin increase, reduction in RBC transfusions and RBC Transfusion-Free ≥ 12 weeks	Response rate based on composite response criteria: Hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of 12 weeks with no transfusions OR Reduction in units of ≥ 4 RBC transfusions / 12 weeks (consecutive) compared with the pretreatment transfusion number in previous 12 weeks OR

	Patients who are RBC transfusion-free over any consecutive 12-week (84-day) period
To measure time to RBC transfusion- free period	Time from first dose of TP-0184 to the first onset of a transfusion-free period for consecutive 8 weeks
To assess median duration of hemoglobin response	Duration of hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions
To assess median duration of reduction in RBC transfusions (4 units / 8 weeks)	Duration of reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive)
To assess median duration of RBC-transfusion-free period ≥ 8 weeks	Duration of RBC transfusion-free period
To assess changes in neutrophil count	Proportion of patients achieving hematologic improvement in neutrophil count (HI-N) over any consecutive 8-week (56-day) period and / or decrease in neutrophil count
To assess changes in platelet count	Proportion of patients achieving hematologic improvement in platelets (HI-P) over any consecutive 8-week (56-day) period and / or decrease in platelet count
To assess the safety and tolerability of TP-0184	Assessment of TEAEs; type, frequency, and severity of AEs, and relationship of AEs to TP-0184, TP-0184 dose interruptions and dose reductions
To determine the cardiac safety of TP-0184 administered as single agent	Assessment of the presence of symptoms of CHF (based on NYHA criteria, 12-Lead ECG abnormalities, quantification of cardiac iron by MRI, ECHO, or MUGA scans, and peripheral blood cardiac markers
To characterize steady-state trough PK	TP-0184 plasma trough concentration data at various timepoints. Specifically, pre-dose (trough) samples on Cycle 1 Day 1 of Week 4 and Cycle 2 Day 1 of each Week 5, 6, 7, and 9
To assess progression to AML	Proportion of patients progressing to AML, time to AML progression
To assess overall survival	Time from first dose of TP-0184 to death due to any cause
To assess change from baseline in the Brief Fatigue Inventory (BFI)	The BFI that measures the severity of fatigue based on the worst fatigue experienced during the past 24 hours

Hematopoietic stem cell transplant (HSCT)	To document the percentage and outcome of patients who have achieved a hematologic response and a hematopoietic stem cell transplant (HSCT) during or following treatment with TP-0184

6.3. Exploratory Objectives and Endpoints

Exploratory Objectives	Endpoints
Phase 1	
To determine pharmacodynamic effects of TP-0184 therapy	Determination of in vivo markers of ALK-2 /ALK-5 inhibition. Markers included, but not limited to: • SMAD/phospho-SMAD signaling • Markers of iron metabolism, including Hepcidin iron panel (serum iron, ferritin, transferrin, soluble transferrin receptor [STR], and total iron binding capacity [TIBC]) • Cytokines TGFβ, IL-6, CRP, EPO
To determine the cardiac safety of TP-0184	Assessment of the presence of symptoms of congestive heart failure (CHF) (based on New York Heart Association [NYHA] criteria), 12-Lead ECGs abnormalities, intensive ECG recordings taken at time of PK draws, assessment of iron accumulation by cardiac magnetic resonance imaging (MRI), ECHO or MUGA scans, and peripheral blood cardiac markers
To determine whether TP-0184 treatment modulates organ iron deposition	Evaluation of cardiac and hepatic iron content by MRI at baseline and during treatment with TP-0184
Metabolites of TP-0184 in patients via Phase 1 data	Profile of potential metabolites of TP-0184 in patients in Phase 1
To assess changes in neutrophil counts	Proportion of patients achieving hematologic improvement in neutrophil count (HI-N) over any consecutive 8-week (56-day) period and / or decrease in neutrophil levels
To assess changes in platelet count	Proportion of patients achieving hematologic improvement in platelets (HI-P) over any consecutive 8-week (56-day) period and / or decrease in platelet count
To assess change from baseline in the BFI	The BFI that measures the severity of fatigue based on the worst fatigue experienced during the past 24 hours

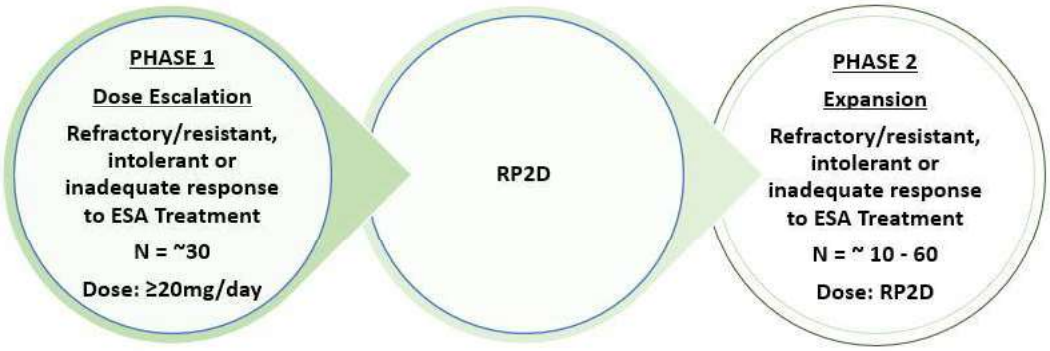
Phase 2	
To determine the pharmacodynamic effects of TP-0184 therapy	Determination of in vivo markers of ALK-2 /ALK-5 inhibition Markers included, but not limited to: • SMAD/phospho-SMAD signaling • Markers of iron metabolism, including Hepcidin iron panel (serum iron, ferritin, transferrin, STR, and TIBC) • Cytokines TGFβ, IL-6. CRP, EPO
To determine whether TP-0184 treatment modulates iron accumulation and removal in the heart and liver	Evaluation of cardiac and hepatic iron content by MRI at baseline and during treatment with TP-0184

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 1/2, open-label clinical study to evaluate preliminary safety and efficacy of TP-0184 to treat anemia when administered to adult patients with IPSS-R low or intermediate risk MDS. The recommended Phase 2 dose (RP2D) will be determined by the maximum tolerated dose (MTD) or maximum administered dose (MAD) in the Phase 1 portion of the study. The study structure is summarized in Figure 1.

Figure 1: Phase 1 and 2 Study Design in Patients with IPSS-R Low or Intermediate Risk MDS



7.1.1. Phase 1 – Dose Escalation

Multiple dose levels of TP-0184, with approximately 1 to 6 patients at each level will be evaluated. There must be at least 3 DLT evaluable patients at a specific dose level if there is a DLT observed in that level. The first dose cohort will start at 20 mg/day every day. Patients will receive their first dose of TP-0184 starting on Cycle 1 Day 1. Dose escalation is planned to proceed with patients receiving each provisional dose level of 40 mg, 60 mg, 90 mg, 120 mg, 160 mg, 210 mg, and 270 mg. Additional dose increments of up to 25% from one dose cohort to the next may occur. In order to determine the recommended Phase 2 dose, dose escalation may continue until one of the following occurs:

1. An MTD is determined.
2. An MAD is determined based on the totality of safety data and medical considerations by the SRC and sponsor.

7.1.2. Rationale for Starting Dose

The initial dose in this study is based on a thorough review of GLP toxicology studies in both rat and dog models, as well as review of the initial human data from the solid tumor study.

In these non-clinical studies, TP-0184 was administered PO daily for 28 days to rats and dogs in GLP toxicology studies. The severely toxic dose in 10% of rats (STD10) was greater than

150 mg/kg or 900 mg/m^2 body surface area (BSA), and in the dogs the HNSTD was 5 mg/kg or 100 mg/m^2 BSA. Given these data, the dog was considered the more sensitive species and per FDA and ICH guidance, the recommended safety approach of taking 1/6th of the HNSTD in dogs (16.7 mg/m^2) was calculated to determine an equivalent starting dose in humans of 30 mg/day.

At the start of this study, a Phase 1 first-in-human study exploring escalating dose levels of TP-0184 in patients with advanced solid tumors had already been initiated with a starting dose of 30 mg QD for 21 days. Subsequently, dosing was changed to once weekly, with a starting dose of 60 mg once weekly for 4 weeks (Amendment 2, 12 Sep 2019). The most common side effects, regardless of causality, were gastrointestinal (nausea, vomiting) and fatigue. There were no clinically significant trends of hepatic or cardiac toxicity and the safety profile was considered favorable. Preliminary PK analysis suggested dose-related increases in systemic exposure with increasing dose and longer elimination t½ than projected from preclinical PK data. Refer to the TP-0184 Investigational Brochure for additional information.

For the current study, a daily dosing regimen of TP-0184 daily for 28 days, without a break, is proposed. This is driven by underlying pharmacological considerations of the target which suggests continuous drug coverage/inhibition to achieve optimal activity/efficacy. However, given the longer elimination t½ observed in an ongoing first in man solid tumor study (TP-0184-101 study), a lower starting dose of 20 mg/day is proposed, to allow for continuous dosing with a 2.25-fold safety factor built in between the proposed starting dose and the 60 mg/day dose in TP-0184-101 study in which there was acceptable tolerability. Additionally, cardiac and other safety monitoring is included in the protocol for risk mitigation and to ensure ultimate safety of the patients (Section 12.1.5.4.2).

In summary, both the preclinical safety data and the ongoing clinical experiences in the TP-0184-101 study support the proposed continuous once-daily dosing regimen at 20 mg/day for this study.

7.1.3. Phase 2 – Dose Expansion

Phase 2 will determine the preliminary efficacy of TP-0184 in an expansion phase of up to 60 patients.

Preliminary efficacy as assessed by response rate will be monitored using the Bayesian posterior probability to optimize the enrollment with Bayesian stopping rules.

7.2. Planned Number of Patients

Approximately 30 patients are planned to be enrolled in Phase 1, and approximately 10-60 patients in Phase 2.

7.2.1. Patient Replacement or Addition

Patients who do not meet either of the criteria for the DLT Analysis Set, as described in Section 13.1.5, may be replaced as needed to permit dose escalation.

7.3. Treatment Assignment

7.3.1. Calculation of Dose

In Phase 1, all patients will receive the dose of TP-0184 according to the cohort in which they are enrolled (Table 3).

Table 3: Planned Dose Escalation Levels

Dose Level	Dose (Daily Schedule)
-1	10 mg
1	20 mg
2	40 mg
3	60 mg
4	90 mg
5	120 mg
6	160 mg
7	210 mg
8	270 mg

Note: An intermediate dose level between the planned dose levels may be explored. In addition, based on a safety evaluation during the escalation phase, additional dose schedules than those outlined in the table may be explored after discussion and concurrence with SRC members and SDP Oncology clinical team.

Intra-patient dose escalation is not permitted in this protocol.

In Phase 1 and 2, patients will be treated for 24 weeks (6 cycles) and based on assessment of response, continue to receive TP-0184 in the absence of MDS disease progression or until loss of hematological response or unacceptable toxicity.

Note: Loss of hematological response (lack of response or refractory to further treatment) will follow the guidelines for progression/relapse after hematological improvement by IWG Response Criteria for MDS 2006 (Appendix 6).

7.3.2. Description of Dose Escalation Study

7.3.1. Phase 1 Dose Escalation

Dose escalation will be performed using a design based on a 2-parameter BLRM (Neuenschwander 2008). The BLRM method will be applied along with the escalation with overdose control (EWOC) principle to control the risk of exposing patients to toxic doses (Babb 2013). Based on this principle, a dose level will be considered safe if the probability of excessive toxicity (ie, the probability of a DLT rate over 33% is no greater than 25%). The MTD with estimated posterior probability of a DLT within target toxicity interval (16%, 33%] among the admissible doses fulfilling EWOC is determined by BLRM. The MTD is estimated based on observed DLTs.

The use of Bayesian adaptive models for Phase 1 studies has been advocated by the European Medicines Agency's guideline on clinical trials in small populations (European Medicines Agency, 2016).

The actual dose level to be tested in the next cohort will be chosen based on the above risk assessment, using the BLRM method. The dose recommended by the BLRM method will be treated as guidance and will be integrated with a clinical assessment of the safety adverse event information and review of clinical data, including above safety and PK data. Intermediate doses between planned dose levels may be SDP Oncology explored based on safety consideration after discussion and concurrence with SRC members and SDP Oncology clinical team. The BLRM method estimates the MTD by updating the probability of observing a DLT for each dose level in the study as DLT information becomes available. An additional cohort with a different dose schedule may be considered based on clinical judgment supported by medical observations.

Procedures for close monitoring of the DLT period and entire study have been established (Section 12.1, Section 14.1). In addition, an SRC will conduct scheduled meetings and will provide safety oversight of the patients, determine DLTs, and guide escalation and dose decisions (Section 7.3.3).

7.3.2. Determination of RP2D

The RP2D is determined based upon safety, PK, pharmacodynamic, efficacy and other available data. Determination of the RP2D will be performed in consultation with the SRC members based on safety and other data available at the time of the RP2D decision. In the Phase 2 portion of the study, the RP2D, as determined in Phase 1, will be used.

7.3.3. Safety Review Committee

The SRC will consist of the Investigators, the Safety Lead, the Statistician, and the Medical Monitor, and a cardiologist consultant. The SRC will conduct scheduled meetings and will provide safety oversight of the patients, determine DLTs, and guide escalation and dose decisions. The SRC will meet after all patients in the newly escalated cohort have completed the DLT evaluation period and before proceeding with the next cohort at a higher dose level.

The SRC will review and assess all available safety data from each cohort, together with available PK and pharmacodynamic data, to determine the escalation to the next dose level cohort. The SRC will also conduct unscheduled meetings on an as needed basis to review other information that may be relevant to the conduct of this study or safety of the patients.

7.3.4. Phase 1 Study Stopping Rules

Dose escalation can be stopped earlier by a joint decision from the SDP Oncology clinical team and the Investigators during a SRC meeting, by considering the model estimations and a global assessment of the safety, PK, pharmacodynamics, and preliminary activity data.

The following safety event will trigger a temporary suspension of patient enrollment to study treatment:

- The posterior probability of target toxicity at each dose level exceeds 50% and is the highest among potential dose levels.

Based on the safety review by the SRC members and the SDP Oncology clinical team, it will be determined whether the study may continue (with or without a protocol amendment) or if it must be terminated.

7.3.5. Phase 1 Individual Patient Stopping Rules

The following safety events will trigger individual patient treatment discontinuation:

- Any DLT observed during Phase 1, within 28 days after starting treatment with TP-0184 as described in Section 7.4
- Any related AEs that lead to treatment discontinuation per Section 7.4
- Evidence of disease progression based on IWG Response Criteria for MDS 2006

7.4. Dose Adjustment Criteria

Dose adjustments may be permitted for patients who experience toxicities. These toxicities will be discussed by the Investigators and Medical Monitor to determine if it would be in the best interest of the patient to continue to receive a reduced dose of TP-0184. Dose adjustments due to study drug related non-hematologic or hematologic AE severity are described in Table 4 and Table 5, respectively.

Decisions to reinstate dosing following a toxicity for which drug was held will be determined by the Investigator and Medical Monitor. In patients who receive subsequent and/or multiple treatment cycles, the TP-0184 dose may be reduced by one dose level based on the observed AE that occurred during the preceding cycle.

If further significant AEs occur during one or more cycles at the new reduced dose level, an additional dose reduction may occur (this allows for two dose reductions) EXCEPT in the first dose cohort where only one dose reduction (-1) will be permitted. If non-hematologic AE(s) > Grade 3 occur at the -1 dose the patient may be discontinued from the study pending discussion with the Investigator and Medical Monitor.

In the Phase 1 portion of the study, no dose re-escalations will be allowed for any patient who had a previous dose reduction due to AEs.

The Phase 2 treatment dosing schedule will be determined by the SRC and SDP Oncology clinical team based on the recommended Phase 2 treatment dose, and the MTD or MAD from Phase 1 safety data.

Guidelines for dose adjustments of TP-0184 following Cycle 1 and resolution of a patient's non-hematologic AE(s) to ≤ Grade 1 and/or hematologic AE(s) to baseline CTCAE Grade are provided in Table 4 and Table 5, respectively.

Table 4 Guide to TP-0184 Dose Adjustments Due to TP-0184 Related Non-Hematologic AE

Non-hematological AE Grade	Action Regarding TP-0184 Dosage
Grade 1 – non-hematologic	None - maintain current dose level
Grade 2 – non-hematologic	Results in dose delay until AE severity recovers to ≤ Grade 1. The investigator has the option to reduce dose by 1 dose level within the current or at the next cycle (beyond cycle one) with agreement of the Medical Monitor
Grade 3[a] – non-hematologic[b]	Hold, then reduce dose by 1 dose level upon recovery to ≤ Grade 1 with agreement of the Medical Monitor.
Grade 4 – non-hematologic	Discontinue treatment.

[a] Excluding brief (based on the investigator's judgment) Grade 3 vomiting or diarrhea, electrolyte abnormalities lasting less than 72 hours with optimal management.
[b]If an AE meets definition of DLT, discontinue treatment.

Table 5 Guide to TP-0184 Dose Adjustments Due to TP-0184 Related Hematologic AE

Hematologic AE Grade	Action Regarding TP-0184 Dosage
Grade 1 – hematologic	None - maintain current dose level
Grade 2 – hematologic	None - maintain current dose level
Any hematologic AE ≥ Grade 3 (except anemia or platelets and ANC decrease)	Dose delay until resolved to ≤ Grade 1 or baseline and then reduced by one dose level
Grade 4 platelets or ANC decrease	Dose delay if recovery to ≤ Grade 3 within 7 days then reduce by one dose level. Discontinue if no recovery within 7 days.
Increase of Hgb ≥ 2.0 g/dL over a duration of 2 weeks	Reduce dose by one dose level, if ΔHgb not influenced by RBC transfusions and in the absence of volume depletion (dehydration)
Hgb ≥ 11.5 g/dL, in the absence of RBC transfusion or volume depletion (dehydration)	Dose delay[a] until Hgb ≤ 11.0 g/dL

[a] Hemoglobin should be checked on a weekly basis.

Patients who are not able to be treated after a 6-week dose delay due to drug-related toxicity will, in general, be discontinued from treatment. However, for patients who have shown a beneficial response to TP-0184, consideration of treatment continuation will be discussed by the Investigator and Medical Monitor.

7.4.1. Management of Nonhematologic and Hematologic Toxicities

Nonhematologic and hematologic AEs may be treated with concomitant medications which are not prohibited in this study (Section 9.2.1), as deemed clinically indicated by the Investigator. All transfusion treatments for anemia and thrombocytopenia, and concomitant medications, must be recorded in the source and on the appropriate case report form (eCRF).

Antiemetics (ie, 5 hydroxytryptamine [5-HT3] receptor inhibitor or other antiemetic medications) are permitted according to standard practices at each investigational site.

Prophylactic antibiotic, antiviral, and/or antifungal therapy is allowed at the discretion of the Investigator and according to institutional standards.

Support with growth factors (eg, filgrastim) is not allowed except in the situation of life-threatening infections (eg, a Grade 4 sepsis with life-threatening infection with ongoing neutropenia). Whether the patient can continue TP-0184 dosing following treatment with growth factor support will be considered following discussion with the Medical Monitor.

Both onset of new hematologic and non-hematologic adverse events that are ≥ Grade 4 and considered related to study drug treatments should be discussed with the Medical Monitor to determine whether a dose reduction (Table 4 and Table 5) or treatment discontinuation should occur.

7.4.2. Dose-Limiting Toxicities

A DLT is defined as any one of the following events or abnormal laboratory value not clearly unrelated to the study drug observed within 28 days of starting treatment with TP-0184:

- Any death not clearly due to the underlying progression of disease (such as leukemic transformation)
- Any ≥ Grade 3 non hematological toxicity except for Grade 3 of nausea, vomiting, diarrhea or clinically not significant lab abnormalities lasting 72 hours or less with adequate supportive care
- New onset cardiac failure or worsening symptomatic cardiac failure based on NYHA Functional Classification (Appendix 11)
- ECHO or MUGA reduction of ejection fraction ≥ 10%
- Any Grade 4 neutropenia (absolute neutrophil count (ANC) not recovering to > 500/μL within 7 days in the absence of myelodysplasia or transformation to acute leukemia)
  - To determine progression of MDS / transformation to AML, a bone marrow biopsy / aspiration and/or peripheral blood can be performed
- Any Grade 3 thrombocytopenia associated with clinically significant bleeding or Grade 4 thrombocytopenia in the absence of myelodysplasia related marrow failure or transformation to acute leukemia
  -To determine progression of MDS / transformation to AML, a bone marrow biopsy / aspiration and/or peripheral blood can be performed
- All other hematological toxicity ≥ Grade 3 other than defined above for ANC and platelets

Note: As Grade ≤ 3 neutropenic and Grade 2 thrombocytopenic patients are included in the study, any new onset of Grade 4 neutropenia (< 500/uL neutrophils) in a patient with prior history of chronic neutropenia with infection or Grade 3 decrease in platelets (< 50K platelets) in patients with prior history of MDS-related thrombocytopenia with bleeding, will be evaluated by the SRC members and Medical Monitor in consideration as to whether a DLT has occurred. If determined that the Grade 3 or 4 hematologic AE is related only to the biology of MDS, no DLT will be declared.

Patients who experience a DLT during Cycle 1 will be discontinued from the study.

7.5. Procedures

The planned schedule of assessments, including all treatments and procedures and their timing, is presented in Table 6. Adherence to the study design requirements, including those specified in the Schedule of Assessments is essential and required for study conduct.

Table 6: Schedule of Assessments

Procedures / Tests	Pre-dose		Cycle 1				Cycle 2			Cycle 3,4		Cycle 5 and beyond	END OF TREATMENT [a]	Follow Up[b, c]
	28 D	72 Hr	D1	D2 (±1)	D8 (±1)	D15 (±1)	D1	D8 (±2)	D15 (±2)	D1	D15 (±2)	D1		
Informed consent[d]	X													
Eligibility evaluation [e]	X													
Medical history [f]	X													
Prior MDS treatments	X													
Transfusion history - 12 weeks prior to Cycle1 Day1	X													
Transfusion Data Collection and Anemia Assessment			Continuous, until 30 days after last TP-0184 dose administration or EOT visit, whichever occurs later.											
Complete physical exam	X												X	X
Abbreviated physical exam			X		X	X	X	X		X		X		
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X		X				X			X		X	X	X
ECHO or MUGA scan[g]	X						X			X		X	X	
Cardiac markers	X		X			X	X		X	X	X	X	X	X
MRI (Heart and Liver)[h]	X									X				X
NYHA classification	X		X		X	X	X	X		X		X	X	
Hematology	X[i]		X		X	X	X	X	X	X	X	X	X	X

Procedures / Tests	Pre-dose		Cycle 1				Cycle 2			Cycle 3,4		Cycle 5 and beyond	END OF TREATMENT [a]	Follow Up[b, c]
	28 D	72 Hr	D1	D2 (±1)	D8 (±1)	D15 (±1)	D1	D8 (±2)	D15 (±2)	D1	D15 (±2)	D1		
Chemistry		X			X	X	X		X	X		X	X	X
Coagulation		X					X			X		X	X	
Pregnancy test (If Applicable) [j]		X					X			X		X	X	X
Urinalysis		X					X			X		X	X	X
Iron panel (markers of iron regulation)[k]		X			X	X	X		X	X	X[k]	X	X	
Hepcidin		X					X			X		X	X	
Cytokines[l]		X					X			X[l]		X[l]	X	
SMAD-1, 2, 3, 5 and 8, in PBMCs [m]	X		X		X					X[m]		X	X	
SMAD-1, 2, 3, 5 and 8 in biopsy/aspirates [m]	X									X[m]			X	
MDS Disease Assessment [n]	X									X			X	
Prior and Concomitant medications / procedures	Continuous, until 30 days after the last dose of TP-0184 or EOT visit, whichever occurs later.													
Assessment of AEs [o,p]	From consenting through 30 days after the last dose of TP-0184.													
TP-0184 administration			X	X	X	X	X	X	X	X	X	X		
BFI	X		X				X			X		X	X	X
Ph1 Safety ECG [q]		X	X	X	X	X	X	X	X	X		X	X	X

Procedures / Tests	Pre-dose		Cycle 1				Cycle 2			Cycle 3,4		Cycle 5 and beyond	END OF TREATMENT [a]	Follow Up[b, c]
	28 D	72 Hr	D1	D2 (±1)	D8 (±1)	D15 (±1)	D1	D8 (±2)	D15 (±2)	D1	D15 (±2)	D1		
Ph1 Intensive Holter ECG monitoring[f]			X						X					
Ph1 PK			X	X	X	X	X	X	X					
Ph2 Safety ECG[g]		X				X	X	X	X	X		X	X	X
Ph2 PK						X	X	X	X	X				
Hematopoietic Stem Cell Transplant			First dose TP-0184 through Follow-up Visit											
Overall Survival			Collect for at least one year from the start of TP-0184 treatment											
MDS Progression / Transformation to AML			Collect for at least one year from the start of TP-0184 treatment											

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; BFI = Brief Fatigue Inventory; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MDS = myelodysplastic syndromes; MRI = magnetic resonance imaging; MUGA = Multiple-gated acquisition; NYHA = New York Heart Association; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics

Note: The following will be collected locally and sent to the central lab: Cardiac markers, iron panel, Hep-25, IL-6, PBMC-SMAD, BMA-SMAD, BMA-Genetic, TGF-beta-1, PK/Metabolites, Bone marrow biopsy. Refer to the Laboratory Manual for further details.

[a] If a patient discontinues study treatment, an End of Treatment visit should be conducted within 14 days (within 3 days) of the last dose of TP-0184 or within 14 days of the decision to discontinue TP-0184 treatment. If the decision is made at a regular per protocol scheduled visit, that visit may be considered the End of Treatment visit.

[b] Patients must have a safety evaluation 30 days (+ 7 days) after the last dose of TP-0184.

[c] Survival follow-up is performed every 6 months. Follow-up for progression of MDS to higher risk and / or transformation to AML and survival will continue for at least one year from start of treatment (Cycle 1 Day 1).

[d] Informed consent must be obtained prior to conduct of screening evaluations.

[e] Review all inclusion and exclusion criteria (Section 8) to determine if patient meets all eligibility criteria for enrollment into the study. Complete Eligibility Form and obtain Medical Monitor approval to enroll patient.

[f] Collect and document a complete medical and disease history including initial histologically confirmed, current diagnosis of MDS and signs and symptoms of disease, and 12 weeks of transfusion history.

[g] ECHO/MUGA scans will be performed every other cycle, such that days on which MRI scans are avoided.

[h] MRI (iron quantification) of heart and liver is acquired locally and sent to Central Imaging (refer to the study-specific Imaging Manual), and will be performed at Screening and Cycle 3 only. MRI may also be performed ad hoc if signs/symptoms of iron overload are noted. For patients continuing on treatment beyond Cycle 6, MRI will be performed every 6 cycles for the duration of treatment and at the End of Treatment visit unless performed within 6 weeks of the visit. Heart MRI will be performed as secondary monitoring to ECHO/MUGA scans.

[i] Pre-treatment counts averages at least 2 measurements, per IWG Criteria.

[j] Pregnancy testing (urine or serum) is performed for women of childbearing potential only.

[k] Iron panel (serum iron, transferrin, soluble transferrin [STR], and TIBC) is collected by local laboratories and sent to the central laboratory. Ferritin will be used as a safety parameter and analyzed by local laboratories and the other iron metabolism parameters will be exploratory. Samples will be collected at pre-dose, Cycle 1 Day 8 and Day 22, Cycle 2 Day 1 and Day 15, Cycle 3 Day 1 and Day 15, then Day 1 of subsequent cycles and EOT.

[l] CRP and EPO will be collected and analyzed at the local laboratory. IL-6 and TGF-beta1 will be collected by the local laboratory and sent to the central laboratory. Samples will be collected pre-dose, Cycle 2 Day 1, Cycle 4 Day1, Cycle 7 Day 1, then Day 1 of every 3 cycles thereafter (Cycle 10, etc.), and EOT.

[m] SMAD-1, 2, 3, 5, and 8, in PBMCs and bone marrow biopsy/ aspirates: 1) PBMC's – using peripheral blood lymphocytes drawn; predose (with biopsy) and C1D8. C3D1, C4D1, C6D1, and at EOT; 2) Bone marrow biopsy/aspirate – Pre-dose, Cycle 4 Day 1, and at EOT (if performed for assessment of MDS progression); 3) Gene mutations in bone marrow biopsy/aspirates and/or peripheral blood samples – Pre-dose and at EOT.

[n] MDS assessments according to IWG MDS 2006 (Appendix 6) include hematology and bone marrow biopsy/aspirate at Pre-dose, Cycle 4 Day 1, and at EOT (if performed for assessment of MDS progression). For patients continuing on treatment beyond Cycle 6, response assessments will be performed every 12 months. NOTE: If the bone marrow biopsy and/or aspirate is nonproductive or not diagnostic, the procedure must be repeated. Six to 8 bone marrow slides should be prepared (in addition to fresh bone marrow samples) for study analysis.

[o] Adverse events will be assessed according to the NCI CTCAE v5.0. When the grade is not available, refer to Section 12.1.6.2.3.

[p] Adverse event will be followed until either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

[q] Performed in Phase 1 Dose Escalation Only (at 6 hours after dose, and 10 minutes prior to PK collection at 6 hours).

[r] Holter ECG: Cycle 1 Day 1: Approximately 1 hour prior to TP-0184 dose through Day 2 and Cycle 2 Day 15: Approximately 1 hour prior to TP-0184 dose through Day 16. Recordings will continue through 24 hours after the Cycle 1 Day 1 dose and after the Cycle 2 Day 15 dose.

[s] Performed in Phase 2 Dose Expansion Only (prior to [but not less than 10 minutes before] any blood sample collection).

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. A documented diagnosis of lower risk MDS (IPSS-R Low, Intermediate) according to WHO 2016 classification, de novo or secondary.
2. Bone marrow biopsy and/or aspirate performed pre-dose to assess disease status and available for review *prior* to full screening review. If the bone marrow biopsy and/or aspirate is nonproductive or nondiagnostic, the procedure must be repeated. Bone marrow biopsy/aspirate performed ≤ 12 weeks prior to baseline will not need to be repeated if results and a minimum of 6 slides are available.
3. Relapsed, refractory/resistant, intolerant, or inadequate response to ESA treatment, as defined by the following:
   - Relapse according to IWG 2006
   - Refractory/resistant – documented non-response or response that is no longer maintained to prior ESA-containing regimen, either as single agent or combination (eg, with G-CSF). ESA regimen must have been either:
     - Recombinant human erythropoietin (rHu EPO) ≥ 500 IU/wk for at least 8 doses or equivalent

       OR
     - Darbepoetin alpha ≥ 300 µg Q3W for at least 4 doses or equivalent
   - Intolerant – documented discontinuation of prior ESA containing regimen, either as single agent or combination (eg, with G-CSF), at any time after introduction due to intolerance or an adverse event.
   - Inadequate response – in the absence of transfusions support, patients under ESA treatment for at least 12 weeks that do not show a rise in hemoglobin of greater than equal to 1 g/dl.
4. Patients with 5q deletions are allowed only if they have failed or are intolerant to lenalidomide treatment.
   - Failure or intolerance to lenalidomide defined as clinical and cytogenetic responses to according to the international working group 2006 MDS: (1) absence of response; (2) bone marrow progression during treatment with or without prior response; (3) secondary failure (loss of prior hematological response without bone marrow progression); or, (4) intolerance (treatment discontinuation due to AEs, with or without prior response) based on investigator judgement (Prebet 2017).
5. Previous treatment for anemia with or without RBC transfusion support:
   a. Low transfusion burden (LTb), defined as requiring less than 4 red blood cell units in the 8 weeks before treatment (and baseline hemoglobin < 9.0 g/dL)

   b. High transfusion burden (HTb), defined as requiring 4 or more red blood cell units in the 8 weeks before treatment

6. At least 12 weeks of transfusion history immediately preceding the first dose of TP-0184. This transfusion data must include hemoglobin measured prior to transfusion (pre-transfusion Hgb).
7. Informed consent for trial participation from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study related procedure.
8. At least ≥ 18 years of age.
9. An Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score ≤ 2.
10. A life expectancy of ≥ 3 months (90 days) per the treating investigator.
11. Adequate major organ function meeting the following criteria on the basis of laboratory data within 28 days of first dose, during screening. If multiple data points are available, the most recent data acquired during the 28 days screening period will be used.
    a. Serum creatinine: ≤ 1.8 x the upper limit of the normal (ULN) range.
    b. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin is ≤ 2.0 x ULN. Elevated indirect bilirubin due to post-transfusion hemolysis is allowed.
    c. Aspartate transaminase (AST) and alanine transaminase (ALT): ≤ 2.5 x ULN.
    d. Left ventricular ejection fraction (LVEF) ≥ 45% by echocardiogram or multigated acquisition (MUGA) scan.
12. All previous therapy with ESAs, G-CSF, and GM-CSF must be discontinued ≥ 14 days before Cycle 1 Day 1 dosing.
13. Twenty-eight-day washout period from prior treatment with cytotoxic chemotherapeutic agents, HMAs (hypomethylating agents), ImiDs (immunomodulatory imide drugs), luspatercept, and/or investigational drugs before study dosing for the patient begins.
14. Women of childbearing potential (WOCBP) with a negative serum or urine pregnancy test within 5 days prior to the first dose of TP-0184.
15. Non-fertile or agree to use an adequate method of contraception while on study and for 7 months after the last dose of TP-0184, and a negative pregnancy test (if female of childbearing potential) and not currently nursing; males agree to use an adequate method of contraception while on study and for 4 months after the last dose of TP-0184.
16. Ability to comply with the requirements of the entire study and accessibility for treatment and follow-up.
17. Agreement not to participate in other interventional clinical studies during participation in this trial, while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

8.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. IPSS-R high or very high risk MDS.
2. Presence of concomitant severe cardiovascular disease, congestive heart failure (CHF), myocardial infarction, angina, and/ or uncontrolled cardiac arrhythmia as determined by the investigator within 180 days of study onset.
3. Corrected QT interval (using Fridericia's correction formula) of > 465 msec in men and > 480 msec in women.
4. History of stroke, deep venous thrombosis (DVT), pulmonary or arterial embolism within 180 days prior to enrollment.
5. Presence of clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding.
    a. Iron deficiency to be determined by a bone marrow aspirate stain for iron, calculated transferrin saturation (iron/total iron binding capacity) ≤ 20%, or serum ferritin ≤ 15 μg/L.
    b. Iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks prior to enrollment, are excluded.
6. Prior allogeneic or autologous stem cell transplant.
7. Known history of diagnosis of AML.
8. Use of corticosteroids, except for subjects on a stable or decreasing dose (no greater than a 10 mg dose of prednisone or equivalent) for ≥ 2 weeks prior to enrollment for medical conditions other than MDS.
9. Evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count (reticulocyte index) of > 2% with either a positive Coombs' test or over 50% indirect bilirubin.
10. Patients with a recent diagnosis of malignancy are excluded except for those with in situ malignancies treated with curative intent (eg, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix). Patients with more advanced malignancies are allowed to enroll, provided they were treated with curative intent and have no evidence of active disease ≥ 2 years prior to Cycle 1 Day 1.
11. Patients requiring systemic antibiotics or antifungals are not eligible until they have completed the prescribed course of antibiotics or antifungals and are clinically stable. Topical antibiotics or antifungals are permitted.
12. Known HIV, active Hepatitis B, and/or active Hepatitis C infection.
13. Patients with bleeding requiring medical intervention (eg, surgical) in the past month.
14. Platelet count < 50,000/μL 50 x 10^9/L) during screening.
15. Absolute neutrophil count (ANC) < 500 /μL (0.5 x 10^9/L) during screening.
16. Women who are pregnant or breastfeeding.

17. Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second effective method of contraception during the trial and for 7 months after the last administration of study treatment.
18. Inability to undergo MRI imaging.
19. Parenchymal iron overload by screening MRI.
20. Unwillingness or inability to comply with procedures required in this protocol.
21. Have undergone recent surgery with potential to cause the impairment of gastrointestinal tract absorption or that could cause short bowel syndrome with diarrhea due to malabsorption.
22. Have known hemochromatosis at baseline or a family history of hemochromatosis.
23. Presence of any psychological, familial, sociological or geographical condition that, in the opinion of the investigator, could potentially hinder compliance with the study protocol and follow-up schedule.
24. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
25. Live vaccines within 14 days prior to first study drug administration. COVID-19 vaccines (non-live) approved by regional health authorities are allowed.
26. Medications that are known strong to moderate CYP3A4 inducers must be discontinued at least 21 days prior to first dose of study drug. Medications that are known strong to moderate CYP3A4 inhibitors must be stopped 21 days (or 5 half-lives, whichever is shorter) prior to the first dose of study drug.
27. Patients who have received medications with known or possible risk of prolonging the QT interval or inducing Torsades de Pointes within the previous 7 days.

8.3. Withdrawal Criteria

All patients have the right to withdraw at any time during treatment without prejudice. Circumstances may occur under which a patient may be permanently removed from the study. The criteria used to justify withdrawal of a patient are described in Section 8.3.1.

An End of Treatment (EOT) visit will be conducted following permanent discontinuation of treatment with TP-0184 for any reason, except in the case of consent withdrawal by patient. The EOT visit will be conducted within 14 (± 3) days of treatment discontinuation, or within 14 days of the decision to discontinue TP-0184 treatment, as detailed in the Schedule of Assessments (Table 6).

If the patient withdraws consent for disclosure of future information, SDP Oncology may retain and continue to use any data collected before a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records, as well as notify SDP Oncology.

In the event of a treatment discontinuation, the assessments for the EOT visit and End of Study (EOS) visit, as detailed in Table 6, should be completed wherever possible.

8.3.1. Reasons for Treatment Discontinuation

A patient may be discontinued from TP-0184 treatment for any of the following reasons:

- In Phase 1, patient experiences a DLT during Cycle 1
- Failure to achieve a hematologic response. Patients not demonstrating evidence of hematologic response after the first 6 cycles (24 weeks) of treatment will be considered for treatment discontinuation, although with permission of the Medical Monitor and Investigator, TP-0184 study treatment may continue if clinically indicated and provided there is no evidence of Grade 4 toxicity.
- Grade 4 toxicity not responding to supportive measures and without a response to treatment
- The occurrence of any other AE, concurrent illness or laboratory abnormality which, in the opinion of the Investigator, warrants treatment discontinuation
- Patient noncompliance, defined as refusal or inability to adhere to the study schedule
- At the request of the patient, Investigator, SDP Oncology, or regulatory authority
- Patient is lost to follow-up
- Patient becomes pregnant while on study
- Patient begins another treatment for their disease
- Patient death
- Patient withdrawal of consent.

8.3.2. Follow-up for Patients Discontinued from Treatment

In the event of a permanent discontinuation of treatment, the patient will be followed up for 30 (+ 7) days after administration of the last dose of treatment for safety assessments.

Follow-up for progression of MDS to higher risk and / or transformation to AML and survival will continue every 6 months for at least one year from start of treatment (Cycle 1 Day 1) with TP-0184.

8.3.3. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the Investigator or designee.

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 and 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.

9. TREATMENT OF PATIENTS

9.1. Description of TP-0184

Refer to Section 10 for a description of TP-0184, and to Section 7.3 for TP-0184 administration details.

9.2. Concomitant Medications

Concomitant therapies are any new or existing medications or therapy received by the patient including:

- All drugs, including but not limited to, prescription, over-the-counter, birth control pills/patches/hormonal devices, and homeopathic preparations.
  Note: All previous treatments with ESAs, G-CSF and GM-CSF must be discontinued ≥ 14 days before Cycle 1 Day 1 dosing.
- Nondrug therapies, including but not limited to, thermal/laser/radiation procedures, vitamins, herbal medicines/supplements.

During the Screening process (within 28 days prior to the anticipated first TP-0184 dose), information on all prior and current medications, therapies, and procedures will be recorded. Concomitant medications, therapies, and procedures will also be recorded during the study. All prior and concomitant treatments will be recorded in the source documents and appropriate eCRF along with the diagnosis or reason for use.

Patients on the study will be permitted to receive non-live COVID-19 vaccinations that are authorized for use by the Health Authorities of the country/region.

The therapies used for the treatment of an AE are to be linked to an AE and documentation of the AE must also be completed (refer to Section 12.1.6).

9.2.1. Prohibited Medications and Therapies

The following medications and therapies are prohibited during the treatment with TP-0184:

- Antileukemic therapy (chemotherapy, radiation therapy, immunotherapy)
- Growth factor support, including G-CSF, -GM-CSF, TPO, ESA's
  - Allowing a patient to remain on treatment following administration of growth factor for a Grade 4 sepsis with life-threatening infection and ongoing neutropenia, will be considered after discussion with the Medical Monitor.
- Initiation of iron chelation therapy (oral or injectable) following enrollment.
  - Patients receiving iron chelators at stable or decreasing doses for at least 8 weeks prior to entering the study will be allowed to continue with this treatment.
- Herbal/alternative supplements
- Immune suppressive agents
- Live vaccines within 14 days prior to first study drug administration, during the study, and for approximately 3 months after the last dose of study drug.
- Medications that are known strong or moderate CYP3A4 inhibitors or inducers (Appendix 8), as preliminary in vitro reaction phenotyping data suggested that TP-0184 is metabolized predominately by CYP3A4.

- Medications with known or possible risk of prolonging QT or inducing Torsades de Pointes (TdP) one week prior to and during intensive ECG Holter monitoring at both Cycle 1 Day 1-Day 2 and Cycle 2 Day 15-16. Refer to Appendix 9 for the list of prohibited medication with known or possible risk of QT or TdP (which was revised on 31 Mar 2021 from the website, https://crediblemeds.org/new-drug-list/, generated on 17 Apr 2021). As the website updates its list periodically, please refer to the website (https://crediblemeds.org/new-drug-list/) for a most updated list.

9.3. Treatment Compliance

The dose of TP-0184 to be dispensed will be determined by the patient's cohort assignment. Patients will receive a pill pack with a 28-day supply of TP-0184 capsules at Day 1 of each cycle. The dispensed number of capsules and dose will be recorded in an accountability log to be periodically reviewed by SDP Oncology.

Patients will also be given a Study Drug Dosing Diary and will be asked to record the date, time, number of capsules taken, fasting, if a dose was missed, and the reason for any change in dosing. Patients will be instructed to bring their diary along with all unused study drug and empty packs to each follow-up clinic visit. The diary will be reviewed by the designated study personnel and a capsule count will be performed to ensure dosing compliance.

9.4. Randomization

Not applicable.

9.5. Blinding

Not applicable, as this is an open-label study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The study drug, TP-0184, is supplied by SDP Oncology as a drug/excipient powder blend in hard gelatin capsules for oral administration and is manufactured under current Good Manufacturing Practices for investigational use.

TP-0184 capsules are formulated in 5, 25, and 125 mg strengths that are color-coded. The 5 mg strength comes in a size "3" Swedish orange, hard gelatin capsule. The 25 mg strength comes in a size "3" Dark green, hard gelatin capsule. The 125 mg strength comes in a size "0" Brown, hard gelatin capsule. They are packaged as follows:

- For 5 mg and 25 mg:
  - packaged in 200 cc HDPE bottle with approximately 2 g of polyester coil
- For 125 mg:
  - packaged in 400 cc HDPE bottle with approximately 2 g of polyester coil

10.2. Study Drug Packaging and Labeling

The label and package for the drug product will be prepared in accordance with current regulatory requirements.

10.3. Study Drug Storage

The TP-0184 capsules should be stored as per the storage statement on the investigational product label.

10.4. Study Drug Dispensing and/or Administration

Depending on the assigned dose level, the different combinations of the above-mentioned capsule strengths will be dispensed to the patient. To help the patient take the correct dose (number of capsules and capsule strength) for their dose level, the authorized staff at the study sites will dispense the correct number of capsules and capsule strength from the supplied bottles of TP-0184 into a 28-day pill package for each day of the week.

If there is concern about risk of exposure to SARS-CoV-2, home delivery of TP-0184 may be implemented to protect patients from coming to the study sites. In all cases, requirements under FDA regulations for maintaining required storage conditions and accountability remain; these requirements must be addressed and documented.

Further instructions regarding the dispensing of pill packages to patients is outlined in the Pharmacy Manual.

10.5. Study Drug Accountability

An accurate and current accounting of the dispensing of the study drugs for each patient will be maintained on an ongoing basis by a member of the study site staff in a drug accountability log or equivalent document and will be verified by the SDP Oncology study monitor. All drug supplies, including unused study drug, must be accounted for. A final inventory of the total amount of drug received at each study site against the amount used and returned must be

recorded in the study drug accountability log or an equivalent document. Inventory and dispense records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time.

10.6. Study Drug Handling and Disposal

TP-0184 will be provided by SDP Oncology to study sites as an investigational drug. The Investigator or designee will inventory and acknowledge receipt of all shipments of study drugs. The study drugs must be kept in a locked area with access restricted to designated study personnel. Destruction of unused study drug will be handled by the sites or returned to an authorized depot for destruction.

11. PHARMACOKINETIC, PHARMACODYNAMIC, AND BIOMARKER ASSESSMENTS

11.1. Pharmacokinetic Assessments

Blood samples will be collected by local laboratories and analyzed by the central laboratory to measure plasma concentrations of TP-0184 and possibly its metabolites at the time points outlined in Table 6, Table 7, and Table 8.

Sample preparation and process will be described in this study's Laboratory Manual. The PK parameters to be assessed include:

- C_{max} = maximum observed plasma concentration
- C_{trough} = Trough plasma concentrations
- t_{max} = time to C_{max} (peak time)
- AUC_{τ} = AUC within a dosing interval
- Additional parameters may be determined

Table 7 Phase 1 PK Sampling Schema with ECG

	Cycle 1						**Cycle 2**			
	C1D1	**C1D2**	**C1D4**[a] (±1)	**C1D8** (±1)	**C1D15** (±1)	**C1D22** (±1)[a]	**C2D1**	**C2D8** (±2)	**C2D15** (±2)	**C2D16** (±2, same as C2D15)[a]
Intensive Holter ECG monitor	X[b]								X[b]	
Safety ECG	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	
PK Blood Sample Collection Time										
Pre-dose (-1h)	X	X	X	X	X	X	X	X	X	X
2-hour post (±10 min)	X		X	X					X	
4-hour post (±10 min)	X		X	X					X	
6-hour post (±15 min)	X		X	X					X	
8-hour post (±20 min)	X		X	X	X	X	X	X	X	
10-hour post (±20 min)	X			X					X	

[a] These assessments are optional.

[b] Apply the Holter monitor prior to first pre-dose PK blood draw and start recording approximately 1 hour prior to the first dose.

[c] Perform Safety ECG at 6 hours after dose, and 10 minutes prior to PK collection at 6 hours.

Note: Safety ECGs will be performed prior to PK blood sampling

Table 8 Phase 2 PK Sampling Schema

	Cycle 1	Cycle 2			Cycle 3
	C1D22 (±1)	**C2D1**	**C2D8** (±2)	**C2D15** (±2)	**C3D1**
Safety ECG	X	X	X	X	X
PK Blood Draw Time					
Pre-dose	X	X	X	X	X

Note: Safety ECGs should be performed prior to (but not less than 10 minutes) **any** blood sample collection.

Plasma concentrations of TP-0184 and possibly metabolites will be summarized by descriptive statistics, including mean, n, standard deviation, coefficient of variation, minimum, maximum, and median. TP-0184 and/or metabolite concentration data may also be analyzed in conjunction with data from other studies, reported in the associated clinical study report (CSR), other CSRs or separately. Prior to analysis of study samples, the assay sensitivity, specificity, linearity, and reproducibility will be documented.

11.2. Assessment of Pharmacodynamics and Biomarkers

Peripheral blood and bone marrow samples will be collected by local laboratories and analyzed by the central laboratory at protocol-specific time points (Table 6) to assess the effects of TP-0184. The samples will be used to determine any possible correlation between the rate of erythropoietic efficacy response, clinically positive bone marrow biopsy/ aspirate results, drug plasma concentration and biomarkers for TP-0184.

The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Biomarker assessments may be used to assess and generate prognostic, predictive, or surrogate biomarker signatures. These assessments may be explored in the context of MDS or related conditions or drugs of similar class. The results from these analyses are exploratory in nature and may not be included in a CSR. Analyses will include evaluating genetic mutations and other biomarkers associated with MDS.

- Exploratory biomarkers include, but are not limited to:
  - Hepcidin in serum
  - Iron metabolism in serum: (eg, serum iron, transferrin, STR, and TIBC)
  - Cytokine panel including: CRP, EPO, IL-6, TGF-β1 in serum and/or plasma
  - Signal transduction pathways inhibited by TP-0184, including phosphorylation of SMAD-1, 2, 3, 5 and 8, in PBMCs and bone marrow biopsy / aspirate mononuclear pellet
  - Gene mutations associated with MDS and/or associated with signal transduction pathways inhibited by TP-0184 in bone marrow biopsy / aspirate and/or peripheral blood samples

Additional exploratory analyses may be performed if useful in the interpretation of the data and/or to assist SDP Oncology in planning future studies.

12. ASSESSMENTS OF SAFETY AND EFFICACY

12.1. Assessment of Safety

12.1.1. Safety Parameters

12.1.2. Assessment for Study Eligibility

All screening evaluations must be completed and reviewed with the Medical Monitor to confirm that potential patients meet all eligibility criteria. Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 6.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

12.1.3. Informed Consent

Informed consent will be obtained for each participant/potential participant in this trial, in accordance with World Medical Association Declaration of Helsinki (DoH) and ICH-Good Clinical Practice (GCP) Section 16.3. The investigational site is responsible for ensuring that all local policies are followed.

Additionally, SDP Oncology may require that participants/potential participants be informed of any new information that may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations, a participating Investigator (as defined on the Delegation of Authority list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. SDP Oncology recognizes that in many centers, other personnel (as designated on the Delegation of Authority list) also play an important role in this process. It is acceptable for the Principal Investigator to delegate the responsibility for conducting the consent discussion.

SDP Oncology allows the use of translators in obtaining an informed consent. Provision of translators is the responsibility of the local investigational site. Investigational sites should follow applicable local policies when procuring or using a translator for this purpose.

If a subject is unable to read, then informed consent may be obtained by having the consent form read and explained to the subject. This process must be thoroughly documented.

12.1.1. MDS Disease Confirmation

MDS diagnosis confirmation at screening requires the collection of peripheral blood, bone marrow biopsy and aspirate. Bone marrow biopsy and/or aspirate performed ≤ 12 weeks prior to baseline will not need to be repeated if results and a minimum (ie, 6-8) slides are available. If > 12 weeks since last bone marrow response assessment, a fresh peripheral blood, bone marrow biopsy and/or aspirate sample will be required to confirm the patient's diagnosis per WHO Classification System 2016 (Appendix 3 and Appendix 4). If the bone marrow biopsy and/or aspirate is nonproductive or not diagnostic, the procedure must be repeated. Six to 8 bone

marrow slides should be prepared in addition to fresh bone marrow samples (see Laboratory Manual).

12.1.2. Prior Transfusion History

Transfusion history must be available and collected for a minimum of 12 weeks immediately preceding the first dose of TP-0184. The records must include: the type of transfusion received (eg, RBC, platelets), number of units, reason for transfusion, date of transfusion, and pre-transfusion Hgb value or, if the patient received platelets, platelet count prior to transfusion.

12.1.3. Prior Concomitant Medications and Procedures

Information on all concomitant therapies, medications, and procedures will be recorded in the source documents and appropriate eCRF along with the diagnosis or reason for use.

12.1.4. Pregnancy Testing

Pregnancy testing is performed at the screening visit and will be repeated at subsequent cycles and treatment discontinuation, per institutional standard of care, for WOCBP only.

WOCPB and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in the eligibility criteria. Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

Contraceptive Guidance and Collection of Pregnancy Information can be found in Appendix 5.

12.1.5. On-treatment Transfusions

The number of RBC and platelet transfusions received, and the date received will be recorded. The hemoglobin and platelet count prior to the transfusion will also be recorded.

12.1.5.1. Demographics and Medical/MDS Disease History

The following patient information will be collected:

- Date of birth, sex, race and ethnicity
- Relevant medical history (including recent surgical history), as well as other current medical conditions
- MDS disease history (initial histologically confirmed and current diagnosis of MDS, signs and symptoms of disease, date of diagnosis, and WHO and /or IPSS-R classification at original diagnosis)
- Prior treatments for MDS, including ESAs, HMAs, EMAs (erythroid maturation agents), ImiDs, and/or investigational drugs. These therapies will be recorded in the source documents and appropriate eCRF.

12.1.5.2. Vital Signs

Temperature, heart rate, respiratory rate, height, weight, and systolic and diastolic blood pressure will be assessed. Blood pressure and pulse measurements should be preceded by at least

5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

12.1.5.3. Physical Examinations

Physical examinations will be performed as specified in Table 6. A complete physical examination performed during the screening will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.

An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). An abbreviated exam may also be performed at additional time if an AE- or symptom-directed.

12.1.5.4. Electrocardiogram

12.1.5.4.1. Intensive ECG Monitoring

An ambulatory 12-Lead ECG recording device (Holter monitor) will be supplied to patients receiving TP-0184 in Phase 1 of the study. This device will capture and digitally record continuous ECGs. Please reference study specific Holter ECG Acquisition Manual.

Patients are to be resting for 10 minutes prior to, and 10 minutes after the designated ECG capture windows, which are to precede each PK blood draws, as specified in Table 6.

The continuous digital ECG data will be stored electronically and transmitted by the study site to the ECG central laboratory.

Up to 10 ECGs will be extracted from the digital recordings by the ECG central laboratory from each of the 5-minute time windows preceding each PK blood draw.

12.1.5.4.2. Safety ECG Assessments

Triplicate 12-Lead ECGs will be performed at the study site as specified in Table 6.

The following ECG parameters will be recorded on the eCRF: heart rate, PR interval, QRS duration, QT and QTc (preferably QTcF) and any abnormalities noted. The investigator will review the results and assess as normal or abnormal.

12.1.5.5. Clinical Safety Laboratory Assessments

See Table 9 for the list of clinical laboratory tests to be performed. All protocol-required laboratory assessments must be conducted as outlined in Table 6 and in the study specific Laboratory Manual.

Table 9: Assessments of Clinical Safety Laboratory Parameters

Assessments	Samples Collected and Analyzed by Local laboratories

Hematology[a]	• White blood cell (WBC) count with manual differential
	  ○ Neutrophils
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils
	  ○ Blasts
	  ○ Atypical lymphocytes
	• Platelet Count
	• Reticulocytes
	• Reticulocyte hemoglobin concentration
	• Erythrocyte Sedimentation Rate
	• Hyperchromic red cells
	• Hemoglobin
	• Hematocrit
	• Red blood cell (RBC) Count
	• RBC Indices:
	  ○ Mean corpuscular volume (MCV)
	  ○ Mean corpuscular hemoglobin (MCH)

Chemistry	• Albumin
	• Blood urea nitrogen (BUN)
	• Ferritin
	• Creatinine
	• Uric acid
	• Glucose
	• Potassium
	• Sodium
	• Chloride
	• Calcium
	• Bicarbonates
	• Magnesium
	• Phosphorus
	• Triglycerides
	• Aspartate Aminotransferase (AST)
	• Alanine Aminotransferase (ALT)
	• Alkaline phosphatase
	  ○ Fractionation of the alkaline phosphatase isoenzymes
	• LDH
	• Total and direct bilirubin
	• Total Protein
	• Amylase/Lipase
	• Iron
	• Transferrin
	  ○ Soluble Transferrin Receptor (STR)
	  ○ Total Iron Binding Capacity (TIBC)

Urinalysis	• Color • Specific gravity • pH • Bilirubin • Ketones

Assessments	Samples Collected and Analyzed by Local laboratories
	• Glucose • Occult blood (hemoglobin) • Leukocyte esterase • Protein • Urobilinogen • Nitrites • White blood cells • Red blood cells • Casts • Crystals • Bacteria
Coagulation	• PT/INR • PTT • Fibrinogen
Pregnancy test	Serum or Urine
Cytokine panel	• C-reactive protein • Erythropoietin

[a] Pre-treatment counts averages at least 2 measurements per IWG Criteria.

All laboratory assessments (protocol or not protocol-specified) that are considered clinically significant by the investigator as defined in Section 12.1.6.3.5 must be recorded in the applicable eCRFs (ie, AEs). All laboratory tests with values considered clinically significant during participation in the treatment phase of the study or within 30 days after the last dose of TP-0184 should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and captured in the eCRF.

12.1.6. Adverse Events and Serious Adverse Events

12.1.6.1. Definitions

12.1.6.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study patient administered an investigational agent that does not necessarily have a causal relationship with the treatment administered. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the investigational agent, whether or not considered related to the investigational agent. An AE can arise from any use of the drug, and from any route of administration, formulation or dose, including an overdose.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigations (eg, laboratory results, x-ray findings). See Section 12.1.6.3.5 for further guidance on clinically significant laboratory findings.

Pregnancy is not an AE; however, if a female patient or partner of a male patient becomes pregnant during the conduct of the study, the Investigator must notify SDP Oncology according to the procedures provided in Section 12.1.6.4.4

12.1.6.1.2. Adverse Reactions and Suspected Adverse Reactions

All noxious and unintended responses to an investigational agent related to any dose should be considered adverse drug reactions. Suspected adverse reactions are any AEs for which there is a reasonable possibility that the investigational agent caused the AE. Adverse reactions may also include medication errors and uses outside of what is foreseen in the protocol, including misuse, abuse, and overdose (intentional or unintentional) of the investigational agent.

12.1.6.1.3. Serious Adverse Event

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience
  - Note: "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event as it occurred; it does not refer to an event that might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless the hospitalization is for the following:
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF).
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience
- Results in congenital anomaly or birth defect
- Results in persistent or significant disability or incapacity
- Is considered to be an important medical event.

  Note: Important medical events are those that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

12.1.6.2. Procedures for Eliciting, Recording, and Reporting Adverse Events

12.1.6.2.1. Eliciting and Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit.

All AEs occurring from the signing of informed consent until 30 days after the last dose of investigational therapy will be recorded in the eCRF.

An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

All SAEs occurring from the signing of informed consent through 30 days after the last investigational agent administration will be reported to SDP Oncology or designee as outlined in Section 12.1.6.3.

At each required visit during the study, all AEs that have occurred since the previous visit must be reviewed. The Investigator or appropriate designee must determine if the AE is serious or non-serious.

12.1.6.2.2. Relationship to Investigational Agent

A medically qualified Investigator must assess the relationship of any AE to the use of the investigational agent, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between investigational agent exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known mechanism of action or toxicities associated with the investigational product.
- **Dechallenge**: the AE resolved or improved with decreasing the dose or stopping use of the investigational agent. Judgment should be used if multiple products are discontinued at the same time.
- **Rechallenge**: the AE recurred or worsened upon re-exposure to the investigational agent.

The causal relationship between the investigational agent and the AE will be assessed using one of the following categories:

- **Not Related**: An AE is not associated with the investigational agent if, for example:
  - Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of the investigational agent); or
  - Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).
- **Related**: An AE is attributed to the investigational agent if, for example:
  - There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of investigational agent); or
  - The AE is more likely explained by the investigational agent than by another cause (ie, the AE shows a pattern consistent with previous knowledge of the investigational agent or the class of the investigational agent.
  - The event improved on dechallenge and/or re-occurred upon rechallenge (if applicable).

12.1.6.2.3. Adverse Event Severity

The severity of AEs will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v5.0. For events not specifically found in CTCAE, the following definitions will be used to estimate grade of severity:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," (outlined in Section 12.1.6.1.3 which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

12.1.6.2.4. Assessment of Expectedness

The Reference Safety Information for assessing the expectedness of an AE in this study is to be the section identified as the Reference Safety Information in the most recent TP-0184 Investigator's Brochure.

12.1.6.3. Specific Instructions for Recording Adverse Events on the eCRF

12.1.6.3.1. Diagnosis Versus Signs and Symptoms

If a diagnosis is known at the time of reporting, the diagnosis rather than the individual signs and symptoms should be recorded in the eCRF (eg, record only hepatitis rather than elevated transaminases, bilirubin, jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up and should replace the individual signs and/or symptoms as the event term on the eCRF.

12.1.6.3.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF (eg, dehydration secondary to diarrhea).

12.1.6.3.3. Medication Errors, Misuse and Abuse of Investigational Agent

Overdose, medication error, misuse and abuse are defined as follows:

- *Overdose*: refers to the administration of a quantity of investigational agent given per administration or cumulative, which is above the maximum dose according to the protocol. Clinical judgment should always be applied.
- *Medication error*: refers to an unintentional error in dispensing or administration of the investigational agent not in accordance with the protocol.
- *Off-label use*: relates to situations where the investigational agent is intentionally used for medical purpose not in accordance with the protocol.
- *Misuse*: refers to situations where the investigational agent is intentionally and inappropriately used not in accordance with the protocol.
- *Abuse*: corresponds to the persistent or sporadic, intentional excessive use of the investigational agent, which is accompanied by harmful physical or psychological effects.
- *Occupational exposure*: refers to the exposure to the investigational agent as a result of one's professional or non-professional occupation.

Overdoses, medication errors, abuse or misuse regardless of whether there was an associated AE will be collected as part of investigational agent dosing information and/or as a protocol violation, as required.

Any AE associated with an overdose, medication error, misuse or abuse of study drug should be recorded on the AE eCRF with the diagnosis of the AE.

12.1.6.3.4. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF. If a persistent AE becomes more severe in severity, it should be recorded as a new AE on the eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. Each individual instance of a recurrent AE should be recorded on an SAE Report Form and/or AE eCRF.

12.1.6.3.5. Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be recorded on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form and/or eCRF. Abnormal laboratory values assessed as not clinically significant (NCS) should be documented as such in the source document.

Abnormal laboratory values will be reported as an AE if the laboratory result:

- Requires an adjustment in the investigational agent(s) or discontinuation of treatment
- Meets seriousness criteria
- Requires additional testing or surgical intervention
- Is associated with accompanying symptoms

12.1.6.3.6. Cancers

The development of cancer (including AML) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 12.1.6.1.3).

12.1.6.3.7. Adverse Event of Special Interest

An adverse event of special interest (AESI) is a non-serious AE, SAE, or occurrence that is designated to be of special interest and must be reported to SDP Oncology or designee in the same manner and on the same timelines as SAEs, as described in Section 12.1.6.4.

The following events are considered AESIs for this study:

- Cardiac toxicity
- Hepatotoxicity

12.1.6.3.8. COVID-19

Because much is still unknown about how SARS-CoV-2 affects the human body, patients who have tested positive for COVID-19 will be identified and relevant information collected. All patients should provide documentation of any testing for COVID-19, if available, along with the test results, at screening for enrollment and/or during the study. Prior test results should be reported, if available, for any patient who has previously tested positive for COVID-19 SARS-CoV-2 titers (antiviral immunoglobulin G [IgG] and immunoglobulin M [IgM]). (Long 2020) These data will be entered into the patient's study-specific record.

Any patient-reported illness of COVID-19 during the study should be recorded as an AE. If a patient reports infection with COVID-19, the investigator may discuss with the Medical Monitor whether the patient can continue on study.

12.1.6.3.9. Deaths

All events leading to the clinical outcome of death occurring during the SAE reporting period (from the signing of the informed consent through 30 days after the last investigational agent administration) are to be reported to Sponsor or designee as an SAE and recorded on the AE eCRF.

12.1.6.4. Reporting of Expedited Safety Observations by the Investigator Including Serious Adverse Events

12.1.6.4.1. Immediate Reporting of Serious Adverse Events by Investigator to Sponsor

All SAEs, from the signing of informed consent through 30 days after last dose, including SAEs from screen failures, will be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event, even if the experience does not appear to be related to the investigational agent.

Serious AEs should be communicated on an SAE report form as follows:

SDP Oncology Pharmacovigilance Department Contacts	
Email:	BBISafety@bostonbiomedical.com
Fax:	(617) 674-8660

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented on a follow-up form. All follow-up information must be reported in the same timelines as initial information.

At any time after completion of the AE reporting period (ie, 30 days post-treatment), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to the investigational agent, the event must be reported to the Sponsor or designee.

12.1.6.4.2. Immediate Reporting of Occupational Exposure, Adverse Events of Special Interest, Overdose, or New Cancers

Cardiac toxicity and hepatotoxicity are AESIs, and therefore immediately reportable events, even if the events do not meet SAE criteria.

All AESIs will be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, whether or not the event is serious, even if the experience does not appear to be related to investigational agent. Adverse Events of Special Interest should be communicated on the SAE Report Form, as described above for SAEs.

Any **occupational exposure** or exposure of an individual not enrolled in the study to the investigational medicinal product must be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event, even if the exposure does not result in an AE. Unintentional exposures should be communicated on the SAE Report Form, as described above for SAEs.

Any **overdose** to the investigational medicinal product must be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event, even if the overdose does not result in an AE. Overdose should be communicated on the SAE Report Form, as described above for SAEs.

Any **new cancers** must be reported to Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event. New cancers should be communicated on the SAE Report Form, as described above for SAEs.

12.1.6.4.3. Reporting COVID-19 Infections

Suspected or confirmed COVID-19 infections, including asymptomatic infections and positive COVID-19 tests are AESIs and therefore immediately reportable events, even if the events do not meet SAE criteria.

Serious COVID-19 events will be reported on an SAE Report form within 24 hours of the investigator's awareness, according to Section 12.1.6.4.1.

Nonserious COVID-19 events will be reported on a COVID-19 Report form within 5 calendar days of the investigator's awareness, to the same email/fax for reporting SAEs described in Section 12.1.6.4.1.

Updates or follow-up information for COVID-19 events should be reported on an SAE Report form (serious events) or a COVID-19 Report form (nonserious events) within the same timelines as the initial reports.

12.1.6.4.4. Reporting Pregnancies

If a female patient or the female partner of a male patient becomes pregnant during the course of study, the Investigator must report the pregnancy to the Sponsor or designee using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event.

If not all information on the Pregnancy Reporting Form is available at the time of the initial report, follow-up Pregnancy reports will be completed and submitted within **24 hours** of becoming aware of the new information. The Investigator is required to follow up on the pregnancy until it has completed. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within **24 hours** of becoming aware. SAEs associated with the pregnancy, including fetal death, miscarriage or congenital anomalies, must be reported as a serious adverse event according to Section 12.1.6.4.

If the female partner of a male patient becomes pregnant, the Investigator must obtain consent to collect pregnancy information from the pregnant partner (including the status of the newborn, if applicable).

12.1.6.4.5. Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations.

12.1.6.4.6. Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any suspected adverse drug reaction that is both serious and unexpected, or any finding that suggests a significant risk for patients, in accordance with local laws and regulations. The Investigator will promptly inform his/her IRB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

12.2. Assessment of Efficacy

12.2.1. Assessment of MDS Disease

Assessments of the patient's MDS disease will be performed by collection of peripheral blood, bone marrow biopsy and aspirate samples. If the bone marrow biopsy and aspirate are nonproductive or not diagnostic, the procedure must be repeated. Six to 8 bone marrow slides should be prepared (in addition to fresh bone marrow samples) and sent to the designated pathology laboratory for assessment. The patient's disease assessment will be done according to International Working Group Response Criteria for MDS 2006 (Appendix 6).

12.2.2. Survival

Survival status will be collected every 6 months for at least one year from the first dose of TP-0184 treatment (Cycle 1 Day 1).

12.2.2.1. ECOG Performance Status

Standard criteria as defined by the ECOG Scale of Performance Status (Appendix 7) will be considered for assessing the patient's level of activities, mobility, and functioning abilities.

12.2.2.2. ECHO/MUGA

ECHO or MUGA scan will be performed as primary cardiac monitoring to assess LVEF, as specified in Table 6. If an ECHO or MUGA have been obtained within 6 weeks of EOT, they do not need to be repeated.

12.2.2.3. MRI Imaging

Cardiac and hepatic imaging by MRI for quantification of iron will be performed as specified in the Schedule of Assessments. The MRI may also be performed ad hoc if signs/symptoms of iron overload are noted. Please reference study specific MRI Acquisition Manual.

12.2.2.4. New York Heart Association Classification

The NYHA (Appendix 11) provides a simple way of classifying the extent of heart failure. It classifies patients in 1 of 4 categories based on their limitations during physical activity; the limitations/symptoms are with regard to normal breathing and varying degrees in shortness of breath and or angina pain.

12.2.3. Patient Reported Outcomes

The Brief Fatigue Inventory (BFI; see Appendix 10) is a brief participant-reported questionnaire that measures the severity of fatigue based on the worst fatigue experienced during the past 24 hours. The severity of fatigue is assessed using an 11-point numeric scale, with 0 = no fatigue and 10 = fatigue as bad (Mendoza 1999). Patients will complete a paper version of this questionnaire at screening, Day 1 of each cycle, at EOT and follow-up.

13. STATISTICS

13.1. Statistical Methods

Detailed methodology for the statistical analyses of the data collected in this study will be documented in the statistical analysis plan (SAP), which will be maintained by SDP Oncology. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

13.1.1. Determination of Sample Size

13.1.2. Phase 1

The exact sample size for Phase 1 (dose escalation part) cannot be specified in advance due to the dynamic features of BLRM study design. Approximately 30 patients are planned to be enrolled in Phase 1.

13.1.3. Phase 2

A total of 10 to 60 patients will be enrolled into Expansion Phase 2. After the first 10 enrolled patients are evaluable for efficacy (Efficacy Evaluable Analysis Set), response rate monitoring using Bayesian posterior probability will be performed. If posterior probability of response rate less or equal than 5% is greater than 90% (Prob ($\theta \leq 0.05$) > 0.90), the study may be stopped for futility; if posterior probability of response rate greater or equal than 20% is greater than 80% (Prob ($\theta \geq 0.2$) > 0.80) during study enrollment, SDP Oncology has the option to stop the enrollment of Phase 2 and trigger subsequent clinical development of TP-0184. If neither criterion is met, it will continue to more fully characterize the response rate in a total of approximately 60 efficacy evaluable patients. If posterior probability of response rate greater or equal than 20% is greater than 50% (Prob ($\theta \geq 0.2$) > 0.50) at the final analysis, the current study will be considered to be successful.

13.1.4. Randomization and Stratification

There is no randomization in this study.

13.1.5. Analysis Datasets

The safety analysis set (SAS) is defined as all patients who receive at least one dose of study drug (TP-0184) and will be used for safety analysis and related time to event analyses if applicable.

The DLT analysis set (DAS) is defined as patients evaluable for the determination of dose escalation in Phase 1 who met either one of the following criteria:

1. Experienced a DLT during the first 28 days (the DLT evaluation period)
2. Completed the DLT evaluation period and received at least 80% of planned doses.

Patients who did not meet either of the above criteria are not evaluable for the dose escalation assessment and may be replaced as needed to permit dose escalation. The DAS will be used for DLT related analysis.

The efficacy evaluable analysis set (EAS) is defined as all patients who have baseline data of Hemoglobin value, number of transfusions received in previous 12 weeks before study treatment, have received at least 1 dose of TP-0184, and have at least 1 available post baseline response assessment as per the composite endpoint criteria. The EAS will be used for analyses of response rate and related efficacy analyses.

Pharmacokinetic evaluable analysis set is defined as all treated patients in the trial with sufficient and adequate PK sample data as determined by SDP Oncology.

13.1.6. Handling of Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For patient reported outcomes data, primarily missing data imputation will be based on published instrument specific methods. Other missing data imputation method such as Last Observation Carry Forward (LOCF) and mixed model may be explored as sensitivity analyses for patient reported outcomes data.

13.1.7. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, sex, race, weight, baseline disease characteristics, and other parameters, as appropriate.

13.1.8. Data Analyses

13.1.8.1. Phase 1

Two-parameter Bayesian logistic regression model (BLRM) with EWOC will be used to guide dose escalation and estimate the MTD based on occurrence of DLT during Cycle 1. MTD with estimated posterior probability of a DLT within target toxicity interval (16%, 33%] among the admissible doses fulfilling EWOC is determined by BLRM. MTD is estimated based on observed DLTs.

After completing a given dose escalation cohort, the decision to move up to the next cohort or not, or to adjust to a lower or slightly higher dose, will be decided by the SRC based on BLRM with EWOC and integration of all available safety data, PK, and other clinical data using the BLRM method. The dose recommended using the BLRM method will serve as a guide and will be integrated with clinical assessment of the toxicity information and review of other available data to determine the actual treatment dosage.

Additional or intermediate dose levels may be explored after the discussion and concurrence of SRC and SDP Oncology clinical team. It is possible that potential arm with different dosing schedule is added during the Phase I study period based on safety considerations.

13.1.8.2. Determination of Recommended Dose

The recommended dose is usually the dose with acceptable toxicity, generally defined as the dose level producing a DLT rate within the toxicity interval (16%, 33%]. Determination of the

recommended dose will be performed in consultation with the SRC based on safety and other data available at the time of the recommended dose decision.

Once the recommended dose for the expansion arms is identified, the Phase 1 portion of the study will progress to Phase 2.

13.1.8.3. Phase 1 Study Stopping Rule

Dose Escalation can be stopped earlier by a joint decision from SDP Oncology and the Investigators during an SRC meeting, by considering the model estimations and a global assessment of the safety, PK, pharmacodynamics, and preliminary clinical data.

The following safety event will trigger a temporary suspension of patient enrollment to study treatment if the posterior probability of target toxicity at each dose level exceeds 50% and is the highest among potential dose levels.

Based on the safety review with the SRC, SDP Oncology will determine whether the study may continue (with or without a protocol amendment) or if it must be terminated.

13.1.8.4. Phase 1 DLT Analysis

The DLT will be summarized by dose level using DAS for patients in Phase 1. By-patient listing of the DLTs will also be provided.

13.1.9. Phase 2

Bayesian posterior probability of response rate will be estimated continuously. The study may be stopped early for futility (Prob ($\theta \leq 0.05$) > 0.90) or efficacy (Prob ($\theta \geq 0.2$) > 0.80) during the enrollments starting from 10 enrolled efficacy evaluable patients. Study will be considered to be successful if Prob ($\theta \geq 0.2$) > 0.50 at the final analysis (N=~60).

13.1.9.1. Efficacy Analysis

13.1.9.1.1. Phase 1 Efficacy Analysis

Phase 1 efficacy endpoints will be analyzed using Phase 1 Efficacy Analysis Set.

Efficacy analysis at Phase 1 will be conducted using similar methods defined in Phase 2 portion unless otherwise specified (details in Section 13.1.9.1.2).

Overall survival for Phase 1 is defined as the time from the date of initial dosing at same dose level or one dose level lower than RP2D to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. Overall survival will be analyzed based on Phase 1 SAS patients.

13.1.9.1.2. Phase 2 Efficacy Analysis

13.1.9.1.2.1. Response Rate

Response rate is defined as the proportion of patients who achieves response according to the composite endpoint criteria for a consecutive period of 8 weeks (Appendix 1). Response rate will be estimated with 2-sided 95% exact binomial confidence intervals based on EAS.

13.1.9.1.2.2. 12-Week Response Rate

The 12-Week response rate is defined as the proportion of patients who achieves response according to the composite endpoint criteria for a consecutive period of 12 weeks (Appendix 1). The 12-Week response rate will be estimated with 2-sided 95% exact binomial confidence intervals based on the EAS.

13.1.9.1.2.3. Time to RBC transfusion-free analysis

Time to RBC transfusion-free period is defined as the time from the date of initial dosing at RP2D to first documentation of a transfusion-free period for patients who have one or more transfusion-free periods. Transfusion-free period is defined as the period that a patient becomes transfusion-free for consecutive 8 weeks or longer after treatment of TP-0184. Kaplan-Meier (K-M) survival curve and K-M median (estimate), along with 2-sided 95% CIs, will be provided.

13.1.9.1.2.4. Duration of Hemoglobin Response

Duration of hemoglobin response is defined as the time from the date of first documentation of a hemoglobin response to the date of first documentation of progression of hemoglobin response for hematologic responders. Hemoglobin response is defined as an increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions; hemoglobin progression is defined as a change from baseline < 1.5 g/dL of the hemoglobin or the start of one or more transfusions.

The K-M survival curve and K-M median (estimate), along with 2-sided 95% CIs will be provided.

13.1.9.1.2.5. Duration of Reduction in RBC Transfusion for 8 Weeks Analysis

High transfusion burden patient with reduction in RBC transfusion for 8 weeks is defined as high transfusion burden patients (baseline ≥4U transfusions) patients with change from baseline of equal or more than 4 units transfusions in consecutive 8 weeks in EAS.

Duration of reduction in RBC transfusions for 8 weeks is defined as the time from the assessment date of consecutive 8 weeks with reduction from baseline of RBC transfusions >= 4 units to the assessment date of the reduction from baseline < 4 units or increased transfusions frequencies from baseline within a consecutive 8 weeks. For high transfusion burden patient with reduction in RBC transfusion.

The K-M survival curve and K-M median (estimate), along with 2-sided 95% CIs will be provided.

13.1.9.1.2.6. Duration of RBC Transfusion-Free Period ≥ 8 weeks

RBC transfusion-free period ≥ 8 weeks patient is defined as a patient who maintains RBC transfusion-free during consecutive 8 weeks or longer in EAS.

Duration of RBC transfusion-free period ≥ 8 weeks is defined as the time from the assessment date of consecutive 8 weeks without any RBC transfusions to the assessment date of the first documented transfusion in the following visits for RBC transfusion-free period ≥8 weeks patients.

The K-M survival curve and K-M median (estimate), along with 2-sided 95% CIs will be provided.

13.1.9.1.2.7. Changes in Neutrophil Count

Hematologic improvement in neutrophil count (HI-N) is defined as patients achieving over any consecutive 8-week (56-day) period and / or decrease in neutrophil levels in EAS.

Change in neutrophils analysis will provide summary statistics of the proportion of patients with hematologic improvement in neutrophil count with 2-sided 95% exact binomial confidence intervals using EAS.

13.1.9.1.2.8. Changes in Platelet Count

Hematologic improvement in platelet count (HI-P) is defined as patients achieving hematologic improvement in platelets over any consecutive 8-week (56-day) period and / or decrease in platelet levels in EAS.

Change in platelet count analysis will provide summary statistics of the proportion of patients with hematologic improvement in platelet count with 2-sided 95% exact binomial confidence intervals using EAS.

13.1.9.1.2.9. Progression to AML

Progression to AML is defined follow the guidelines by IWG Response Criteria for MDS 2006 (Appendix 6).

Summary statistics of the proportion of patients progressing to AML will be estimated with 2-sided 95% exact binomial confidence intervals based on EAS.

13.1.9.1.2.10. Time to Progression to AML

Time to progression to AML is defined as the time from the date of initial dosing at RP2D to the date of first documented progression to AML using EAS.

The K-M survival curve and K-M median (if estimable), along with 2-sided 95% CIs will be provided.

13.1.9.1.2.11. Overall Survival

Overall survival is defined as the time from the date of initial dosing at RP2D to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. Overall survival will be analyzed based on SAS patients whose initial dosing is RP2D.

The KM survival curve and K-M median (if estimable), along with 2-sided 95% Cis will be provided.

13.1.9.1.2.12. Hematopoietic Stem Cell Transplant Analysis

Hematopoietic stem cell transplant (HSCT) patients are defined as patients achieving a hematologic response and an HSCT in EAS. Summary statistics of the proportion of

hematopoietic stem cell transplant patients will be estimated with 2-sided 95% exact binomial confidence intervals among hematologic response in EAS.

13.1.9.1.2.13. MRI Imaging Analysis

Summary statistics will be provided based on MRI quantitative results by cohort, study, and overall patients. By-patient listings will be provided.

13.1.9.2. Safety Analysis

13.1.9.2.1. Phase 1 Safety Analysis

All safety analyses will be performed on the safety analysis set in Phase 1. Adverse event listings and tabulated summaries of TEAEs will be generated for each dose level, and for all Phase 1 patients. Treatment-emergent AEs are AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug. Additionally, AESIs, SAEs, the number of patients enrolled, the number of patients evaluable for dose escalation, number of patients with DLTs, and TP-0184 dose interruption and reduction due to TEAEs will be described for each dose level and for all Phase 1 patients.

Descriptive statistics for the actual values and changes from baseline of vital signs, weight, ECOG scores will be tabulated by scheduled time point by each dose level, and for all Phase 1 patients. ECHO or MUGA scans, cardiac markers, and other test results will be analyzed using proper statistical methods for each dose level, and for all Phase 1 patients.

13.1.9.2.2. Phase 2 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, SAEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- TEAEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs
- The most commonly reported TEAEs (i.e., those events reported by ≥ 10% of patients in any treatment group)
- SAEs
- AESI

A listing of TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values and changes from baseline of vital signs, weight, ECOG scores will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE v.5 grade from baseline to the worst post baseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst post baseline values, may be used to understand the TP-0184 safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) Drug Dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TP-0184.

13.1.9.3. Pharmacokinetics and Biomarkers

Pharmacokinetic parameters including C_{max}, C_{trough}, t_{max}, and AUC_{τ}, will be estimated using standard noncompartmental methods. Other parameters may also be computed. Actual sample collection times will be used rather than scheduled (nominal) collection times, where available (Table 7 and Table 8). Data obtained from the current study may be modeled, either singularly or in conjunction with data from other studies (for example, for population PK analyses).

Exploratory endpoints including biomarker analysis will be summarized using mean, standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures for the potential biomarker parameters (Section 11.2). The correlations of biomarker results with pharmacokinetic parameters and measures of efficacy may be explored, if deemed appropriate.

13.1.9.4. Patient-reported Outcomes

Patient-reported outcome assessments using BFI will be analyzed to determine any measurable changes in the severity of fatigue based on the worst fatigue score experienced during the past 24-hours. The analysis will be performed using proper statistical methods for collected scores using SAS in Phase 2. Missing items in BFI scores will be handled based on each individual assessment and according to the developer's guidelines. Investigation of missing patterns and details of imputation will be discussed in the SAP. Similar analyses will be performed using BFI assessments in Phase 1 if data is applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a monitor from SDP Oncology or a representative will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of SDP Oncology or its representatives. This will be documented in a Clinical Study Agreement between SDP Oncology and the investigator.

During the study, a monitor from SDP Oncology or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to SDP Oncology.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to SDP Oncology and those SAEs that met criteria for reporting have been forwarded to the IRB.
- The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

During the COVID-19 public health emergency, traditional on-site monitoring might be difficult for reasons such as: (1) sites may not be able to accommodate monitoring visits (eg, due to staffing limitations or site closures) or (2) monitors may not be able to travel to trial sites. When planned on-site monitoring visits are not possible, the reason should be documented and available for review by SDP Oncology and during FDA inspections. On-site monitoring visits may be replaced with remote monitoring visits during the COVID-19 public health emergency (Food and Drug Administration, January 2021).

14.2. Audits and Inspections

Authorized representatives of SDP Oncology, a regulatory authority, an Independent Ethics Committee, or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an SDP Oncology audit or inspection is to systematically and independently examine all study-related activities and documents to

determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact SDP Oncology immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board/Independent Ethics Committee

The investigator must obtain IRB or IEC approval for the study. Initial IRB/IEC approval of the protocol and all materials approved by the IRB/IEC for this study, including the patient ICF and any recruitment materials must be maintained by the study site/investigator and made available for inspection by the study monitor or any regulatory authorities with an interest in this study.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, SDP Oncology may conduct a quality assurance audit. Refer to Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to SDP Oncology before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. SDP Oncology will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Good Clinical Practice, applicable regulatory requirements and the SDP Oncology's policy on Bioethics.

16.3. Informed Consent

The Principal Investigator(s) at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures. If an informed consent cannot be obtained and documented from a prospective trial participant (or legally authorized representative) as signed paper copy, the consent form may be provided electronically by the Investigator/designee.

Where a prospective trial participant (or legally authorized representative) is unable to print the informed consent document provided electronically by the Investigator/designee, an electronic signature process is not available, and the prospective trial participant must meet time-sensitive eligibility criteria, the investigator may consider using the alternative process to satisfy FDA requirements for obtaining and documenting informed consent and IRB approved process. (Food and Drug Administration, January 2021)

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

17. DATA HANDLING AND RECORDKEEPING

17.1. Data Protection

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the FDA, as well as that of any other applicable regulatory agency(ies), will be granted direct access to the study patient's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patient to the extent permitted by laws and regulations. In any presentation of the results of this study or in publications, the patient's identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act and applicable national and/or local laws and regulations regarding personal data protection.

17.2. Inspection of Records

SDP Oncology will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. If on-site monitoring visits are not possible SDP Oncology will be allowed to do remote monitoring to maintain oversight of the clinical site.

17.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for SDP Oncology or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

The publication policy for the study will be described in the clinical study agreement. To avoid disclosures that could jeopardize proprietary rights, the investigator agrees to give SDP Oncology the right to review all manuscripts, abstracts, and presentations related to this study prior to their submission for publication or presentation. SDP Oncology may use these data now and in the future for presentation or publication at SDP Oncology's discretion or for submission to government regulatory agencies.

Authorship among Investigators generally will be based on the extent of significant contribution, including scientific and clinical, to the publication.

19. LIST OF REFERENCES

Bach DH, Park HJ, Lee SK. The Dual Role of Bone Morphogenetic Proteins in Cancer. Mol Ther Oncolytics 2017;8:1–13.

Bhagat TD, Zhou L, Sokol L, et al. miR-21 mediates hematopoietic suppression in MDS by activating TGF-β signaling. Blood. 2013 Apr 11;121(15):2875-81. Zhou L, et al. Blood 2008;112(8):3434-43.

Brunning RD, Bennett JM, Flandriin G, et al. Pathology and genetics of tumors and hematopoietic and lymphoid tissues. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumors, Lyon (France). IARC Press 2001: 63-73

Dixon SJ, Stockwell BR. The role of iron and reactive oxygen species in cell death. Nat Chem Biol 2014;10(1):9–17.

Han HJ, Jain P, Resnick AC. Shared ACVR1 mutations in FOP and DIPG: Opportunities and challenges in extending biological and clinical implications across rare diseases. Bone 2018;109:91–100.

Herbertz S, Sawyer JS, Stauber AJ, et al. Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth factor-beta signaling pathway. Drug Des Devel Ther. 2015 Aug 10; 9:4479-99

Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nature Medicine 2020; 26:845-848

Fenaux P, Platzbecker U, Mufti G, Garcia-Manero G, Buckstein R, Santini V, Díez-Campelo M, Finelli C, Cazzola M, Ilhan O, Sekeres M, Falantes J. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. January 9, 2020. N Engl J Med 2020; 382:140-151

Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). Haematologica. 2011 Oct;96(10):1433-40.

Martelotto LG, Baslan T, Kendall J, Geyer FC, Burke KA, Spraggon L, et al. Whole-genome single-cell copy number profiling from formalin-fixed paraffin-embedded samples. Nat Med 2017;23(3):376–385.

Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 1999;85:1186–96)

Pacifici M, Shore EM. Common mutations in ALK2/ACVR1, a multi-faceted receptor, have roles in distinct pediatric musculoskeletal and neural orphan disorders. Cytokine Growth Factor Rev 2016;27:93–104.

Prebet T, Toma A, Cluzeau T, et al. Outcome of patients treated for myelodysplastic syndromes without deletion 5q after failure of lenalidomide therapy. Oncotarget 2017; Vol. 8(23):37866-37874.

Singh B, Arora S, Agrawal P, Gupta SK. Hepcidin: a novel peptide hormone regulating iron metabolism. Clin Chim Acta 2011;412(11-12):823–830.

Sun CC, Vaja V, Babitt JL, Lin HY. Targeting the hepcidin-ferroportin axis to develop new treatment strategies for anemia of chronic disease and anemia of inflammation. Am J Hematol 2012;87(4):392–400.

Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med. 2014 Apr;20(4):408-14.

Taylor KR, Vinci M, Bullock AN, Jones C. ACVR1 mutations in DIPG: lessons learned from FOP. Cancer Res 2014;74(17):4565–4570.

Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute myeloid leukemia: rationale and important changes. Blood 2009;114(5):937-51.

Zhao B, Pritchard JR. Inherited Disease Genetics Improves the Identification of Cancer-Associated Genes. PLoS Genet 2016;12(6):e1006081.

Zhao N, Zhang AS, Enns CA. Iron regulation by hepcidin. J Clin Invest 2013;123(6):2337–2343.

Zhou L, McMahon C, Bhagat T, et al. Reduced SMAD7 leads to overactivation of TGF-beta signaling in MDS that can be reversed by a specific inhibitor of TGF-beta receptor I kinase. Cancer Res. 2011 Feb 1;71(3):955-63

Zhou L, Nguyen AN, Sohal D, Ying Ma J, Pahanish P, Gundabolu K, et al. Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS. Blood 2008;112(8):3434–3443.

20. APPENDICES

APPENDIX 1. CONSIDERATION OF RESPONSE FOR COMPOSITE ENDPOINT

Patient population	Hemoglobin increase ≥ 1.5 in the absence of transfusion / 8 weeks	RBC transfusion free / 8 weeks	Reduction in units of ≥ 4 RBC transfusions / 8 weeks
High transfusion burden (≥ 4U transfusion)	X	X	X
Low transfusion burden (1-3 U transfusion)	X	X	

APPENDIX 2. BLRM STATISTICAL METHODS

17.2.1 Introduction

In the Dose Escalation part of the study, an adaptive Bayesian logistic regression model (BLRM) with EWOC will be used to guide dose escalation and estimate the MTD(s) based on occurrence of DLT during Cycle 1. This appendix provides details on the statistical model, prior definition and operating characteristics in order to illustrate the performance of the design in estimating the MTD under various dose-toxicity relationships through simulations. Finally, hypothetical dose escalations scenarios will be presented to illustrate the dose allocation in first cohorts of the study.

20.1.1. Dose Escalation Method

17.2.2.1 Statistical Model

The DLT-dose relationship in the Dose Escalation part of the study is described by a 2-parameter logistic model:

$$logit\left(\pi_{(d)}\right) = \log(\alpha) + \beta \log(d/d^*), \alpha > 0, \beta > 0$$

where

$logit\left(\pi_{(d)}\right) = \log\left(\frac{\pi_{(d)}}{1-\pi_{(d)}}\right)$ and $\pi_{(d)}$ is the probability of a DLT at dose d. Doses are rescaled as d/d^* with reference dose $d^* = 90\ mg$ of TP-0184. As a consequence, α is equal to the odds of toxicity at d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

The MTD is the highest drug dosage that is unlikely (< 25% posterior probability) to cause DLT in more than 33% of the treated patients in the first cycle of TP-0184 treatment.

20.1.1.1. Planned Dose Escalation Levels

This study currently plans and expects to complete dose escalation with the following provisional dose levels:

Table 10 Planned Dose Escalation Levels

Dose Level	Dose (Daily Schedule)
-1	10 mg
1	20 mg
2	40 mg
3	60 mg
4	90 mg
5	120 mg
6	160 mg
7	210 mg
8	270 mg

Note: An intermediate dose level between the planned dose levels may be explored. In addition, based on safety during the escalation phase, additional dose schedules than those outlined in the

table may be explored after discussion and concurrence with SRC members and SDP Oncology clinical team.

Intra-patient dose escalation is not permitted in the protocol.

20.1.1.2. Prior Specifications

The bivariate normal prior for the BLRM parameters with a reference dose level of 90 mg is obtained as follows:

The following noninformative prior for (log(α), log(β)) was used:

- The mean of log(α) was set to -0.847 and mean of log(β) was set to 0.913 to allow the median DLT rate to be around 1%.
- The standard deviation of log(α) was set to 1.275, and the standard deviation of log(β) to 0.482, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between log(α) and log(β) was set to -0.9.

Table 11 Prior Parameters for Bivariate Normal Distribution of Model Parameters

Parameters	Means	Standard Deviations	Correlation
$\log(\alpha), \log(\beta)$	(-0.847, 0.913)	(1.275, 0.482)	-0.9

Table 12 Prior Distribution Summaries Derived from Priors in Table 11

TP-0184 Dose (mg)	Prior Probabilities Pr(DLT) is in Interval:			Mean	SD	Quantiles		
	(0, 0.16]	(0.16, 0.33]	(0.33, 1]			2.5%	50%	97.5%
20	0.8685	0.0744	0.0571	0.06784	0.13677	0	0.0101	0.5253
40	0.7191	0.1414	0.1395	0.13674	0.18611	0.00026	0.05436	0.6946
60	0.5463	0.2089	0.2448	0.21414	0.21583	0.00324	0.1354	0.77793
90	0.2602	0.282	0.4578	0.34556	0.22766	0.03638	0.3026	0.84387
120	0.0303	0.2178	0.7519	0.48932	0.20034	0.15282	0.47701	0.87993
160	0	0.0119	0.9881	0.66399	0.14196	0.37032	0.67276	0.91269
210	0	1e-04	0.9999	0.80101	0.09715	0.57776	0.81558	0.95098
270	0	0	1	0.88234	0.06829	0.72003	0.89404	0.98476

Note: Bold doses indicate not meeting the overdose control criterion (more than 25% chance of over-dosing) with the prior information only.
Abbreviation: DLT = dose-limiting toxicity.

20.1.1.3. Dose Recommended by the BLRM Method

The dose allocation will start at the dose of 20 mg. Patients will be included by cohort of 1 to 6 patients. There must be at least 3 DLT evaluable patients at a specific dose level if there is a DLT observed in that level. After each cohort of patients is completed, the dose recommendation by the model will be based on posterior summaries including the mean, median, standard deviation, 95% credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- (0, 16%]: under-dosing
- (16%, 33%]: targeted toxicity
- (33%, 100%]: over-dosing

Following the principle of EWOC, after each cohort of patients the recommended dose by the model is the one with the highest posterior probability of the DLT rate falling in the targeted toxicity interval (16%, 33%] among the admissible doses fulfilling EWOC, i.e., it is unlikely (< 25% posterior probability) that the DLT rate at the dose falls in the over-dosing interval.

17.2.2 Final Recommendation and Stopping Rules

Dose escalation will continue until identification of the MTD(s) or suitable lower dose for recommended phase 2 dose(s) (the RP2D). This will occur when the following conditions are met:

1. At least 6 patients have been treated at this dose.
2. This dose satisfies one of the following conditions:
   a. The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
   b. A minimum of 12 patients have already been treated on the trial.
3. It is the dose recommended for patients, by review of all clinical data by patients of the end of cohort meeting. Of note, the Dose Escalation part could be stopped earlier by a joint decision from the Sponsor and the Investigators during an SRC meeting, by considering the model estimations and a global assessment of the safety, PK, pharmacodynamics, and preliminary activity data.

17.2.3 Operating Characteristics

17.2.3.2 Introduction

This section presents the operating characteristics illustrating the precision of the design in estimating the MTD under various assumed true dose-toxicity relationship.

17.2.3.3 True Dose-DLT Scenarios

Simulations were performed on several true toxicity-dose relationships:

4. non-decreasing and finally reaching plateau
5. linear increasing (no plateau)
6. constant
7. increase steadily at the first beginning, and then increase much faster

Table13 True Underlying DLT Probabilities

	TP-0184 Dose Level (mg)							
Dose-limiting Toxicity (DLT) Scenarios	**20**	**40**	**60**	**90**	**120**	**160**	**210**	**270**
A	0.05	0.1	0.2	0.3	0.33	0.45	0.56	0.7
B	0.05	0.1	0.2	0.3	0.35	0.65	0.8	0.9
C	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
D	0.05	0.1	0.15	0.2	0.25	0.25	0.35	0.35

17.2.3.4 Simulation Parameters

For each dose-DLT scenario, 5,000 clinical trial replications were generated using R software version 3.6.0 on a x86-64 architecture on a Windows OS. The Markov chain Monte Carlo (MCMC) estimation is obtained using R packages rjags and R2WinBUGS with 2,000 burn-in and 12,000 iterations on 2 chains (6,000 each). The seed used for MCMC estimation is 1 for chain 1 and 2 for chain 2.

Maximum number of patients of 30 was used. However, during the study, more patients may be added. The dose allocation rule used in the simulations is identical to the rule presented in Section 20.1.1.3, ie, dose having the highest posterior probability of the DLT rate falling in the targeted interval (16%, 33%] among the admissible doses fulfilling EWOC.

20.1.1.3.1. Evaluation Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance of the design under each true dose-DLT relationship. The following metrics were:

- Probability of recommending as the MTD:
  - An under-toxicity dose level, i.e., a dose with true probability of DLT in the under-toxic interval (0%, 16%] (Sponsor risk)
  - A targeted-toxicity dose level, i.e., a dose with true probability of DLT in the targeted-toxicity interval (16%, 33%] (correct final decision)
  - An over-toxicity dose level, i.e., a dose with true probability of DLT in the over toxicity interval (33%, 100%] (patient risk)
- Average number of patients per trial exposed at:
  - An under-toxicity dose level, as defined above
  - A targeted-toxicity dose level, as defined above
  - An over-toxicity dose level, as defined above
- Summary of the total number of patients per trial (mean, first quartile, median, third quartile)
- Average total number of DLTs observed per trial

20.1.1.3.2. Operating Characteristics of the Design

Operating characteristics of the final design are reviewed to investigate performance of the model under each true dose-DLT scenario.

Table 14 summarizes the results from the simulations performed.

Table 14: Summary Metrics of the Simulations Performed

DLT scenario	Probability of Recommending a Dose with true Pr(DLT)			No MTD Recommended	Average Number of Patients Per Trial Receiving a Dose with True Pr(DLT)			Average Number of Patients	
	(0, 0.16]	(0.16, 0.33]	(0.33, 1]		(0, 0.16]	(0.16, 0.33]	(0.33, 1]	Per Trial (Q1-Median-Q3)	Experiencing a DLT per Trial
A	0.038	0.771	0	0.19	0.3	10.3	0	21.3 (22-22-26)	5
B	0.105	0.487	0.201	0.207	0.9	5.2	1.8	20.8 (22-22-26)	5
C	0.015	0	0	0.985	0.3	0	0	26.2 (30-30-30)	0.1
D	0.181	0.326	0.303	0.19	1.8	3	5.4	21.1 (22-22-26)	4.7

Abbreviations: MTD = maximum tolerated dose; P(DLT) = DLT rate; Q1= the first quartile; Q3= the third quartile.

17.2.4 Hypothetical Dose Allocation Scenarios in Early Cohorts

Aside from the overall operating characteristics studied above, the design should make reasonable decisions during a study based on the observed DLTs. After completion of a given dose level, the dose allocation for the subsequent dose level will depend on the recommendation of the model and medical review of all available data.

Some scenarios to illustrate on-study dose allocation are presented in Table 15. These scenarios assume that each dose level has 3 or more evaluable patients and the next recommended dose is based on the rule defined in Section 20.1.1.3, with the provisional doses specified in Table 15. However, during the study it may be possible to add new provisional dose levels.

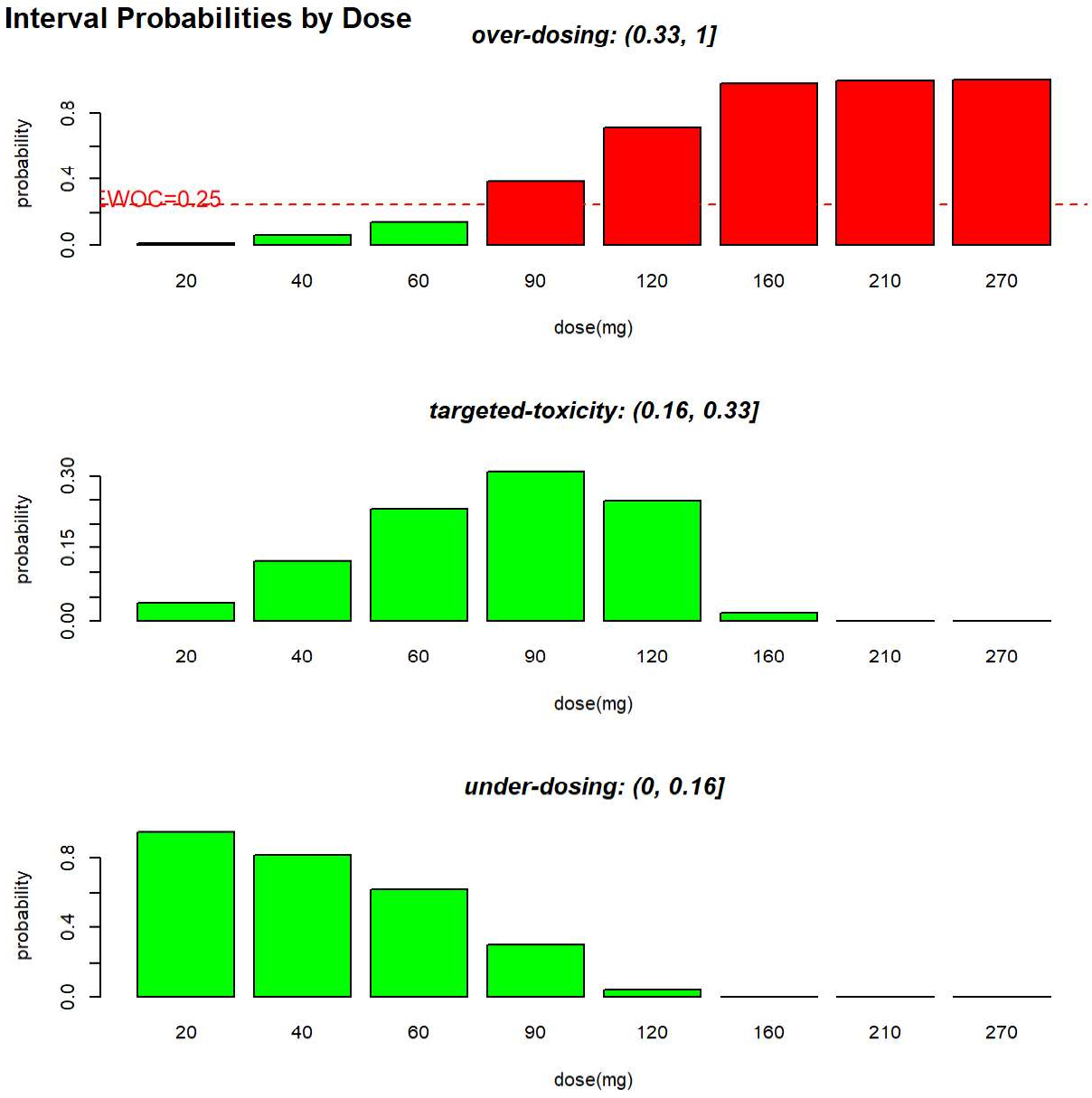
Table 15: Hypothetical Dose Allocation Scenarios in Early Cohorts

Scenario	Dose (mg)	Npat	Ntox	NDL	P(target) at NDL	P(overtox) at NDL	DLT Rate median at NDL
1	20	3	0	60	0.2314	0.1462	0.102
2	20, 40	3, 3	0, 0	90	0.3905	0.2312	0.205
3	20, 40, 60	3, 3, 3	0, 0, 0	90	0.3571	0.1501	0.162
4	20, 40, 60, 90	3, 3, 3, 4	0, 0, 0, 1	90	0.5059	0.1293	0.193
5	20, 40, 60, 90, 120	3, 3, 3, 3, 4	0, 0, 0, 0, 1	90	0.2547	0.0269	0.109
6	20, 40, 60, 90, 120	3, 3, 3, 4, 4	0, 0, 0, 0, 1	90	0.2426	0.0194	0.106
7	20, 40, 60, 90, 120, 160	3, 3, 3, 3, 3, 4	0, 0, 0, 0, 0, 1	120	0.6128	0.1222	0.207
8	20, 40, 60, 90, 120, 160	3, 3, 3, 3, 4, 6	0, 0, 0, 0, 0, 1	120	0.5706	0.0503	0.178
9	20, 40, 60, 90, 120, 160	3, 3, 3, 3, 4, 6	0, 0, 0, 0, 0, 1	120	0.5706	0.0503	0.178

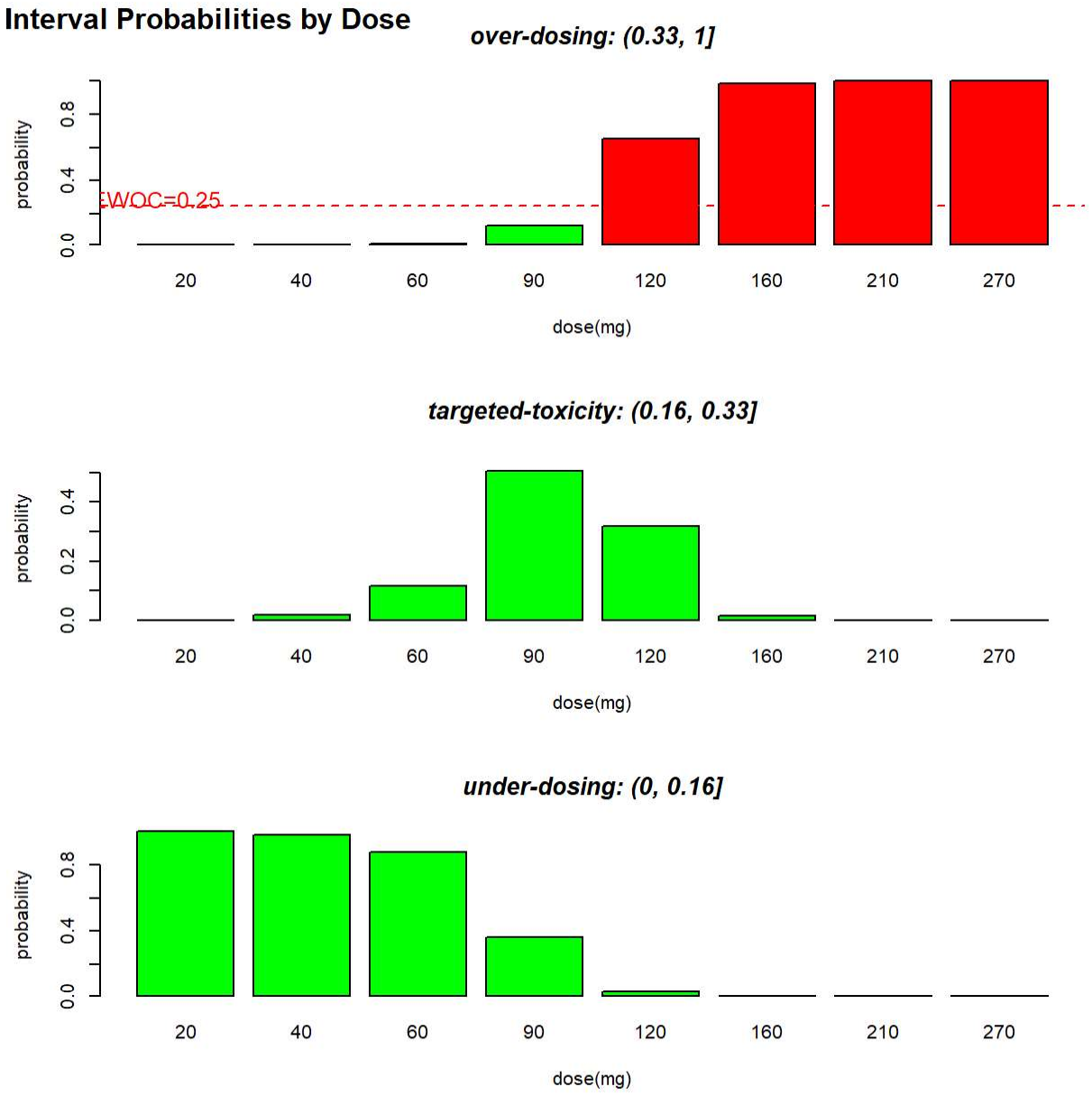
Abbreviations: DLT = Dose-limiting toxicity; EWOC = Escalation with overdose control; NDL = Next dose level; Npat = Number of patients; Ntox = Number of toxicities.
P(target) at NDL: posterior probability that the true DLT rate for the next recommended dose lies in the targeted interval (16%, 33%].
P(overtox) at NDL: posterior probability that the true DLT rate for the next recommended dose lies in the excessive toxicity interval (33%, 100%].

17.2.5 Hypothetical Dose Allocation Scenarios in Early Cohorts: Visualize Interval Probabilities by Dose

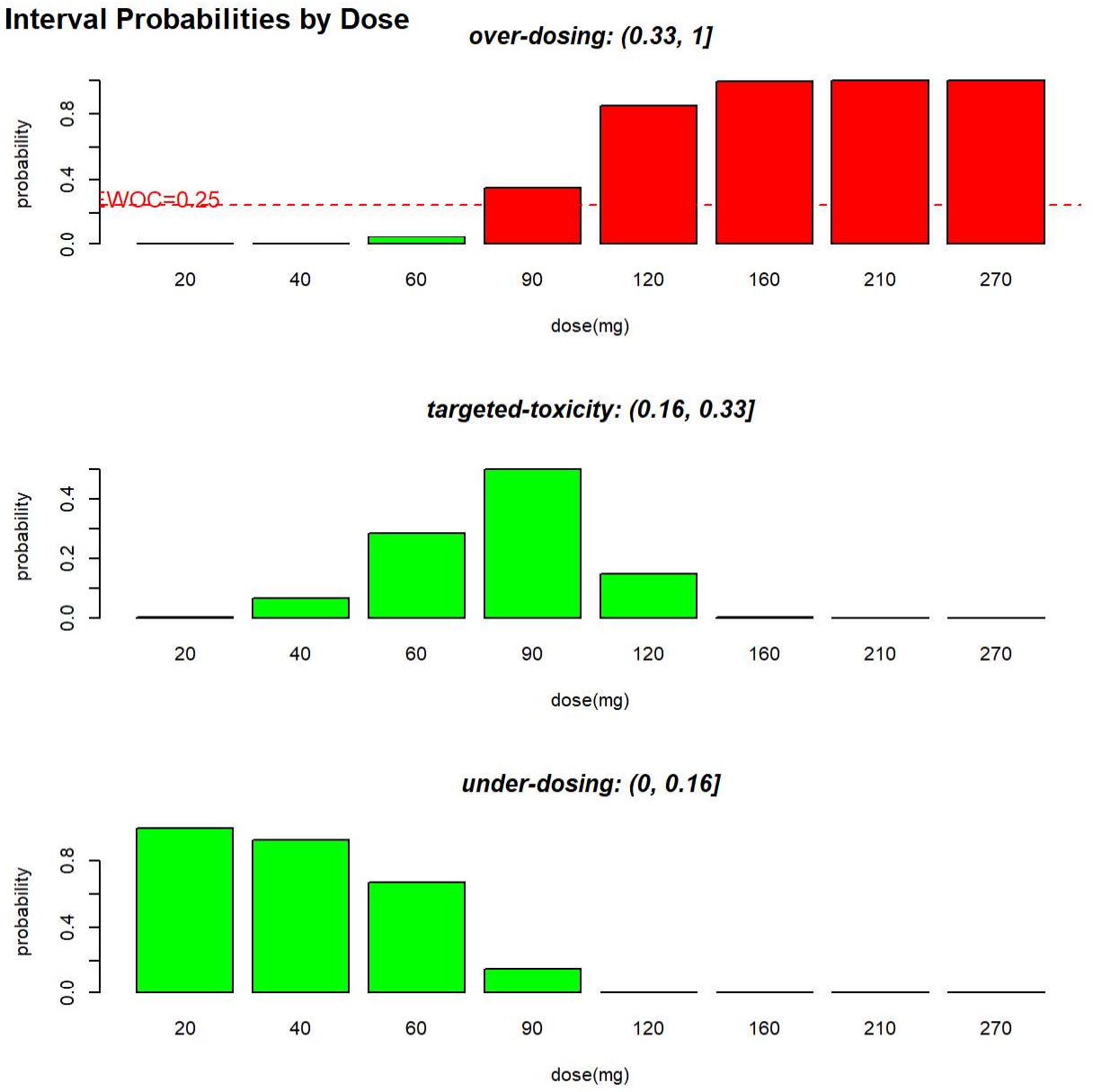
Scenario 1: 0/3 pts at 20 mg



Scenario 2: 1/4 pts at 90 mg



Scenario 3: 2/4 pts at 90 mg



In general, when no DLTs are observed in 3 patients at a dose level, the decision is to increase the dose. When 1 DLT is observed in 3 patients, the decision is to stay at the current dose level or to escalate to the higher provisional dose level. When more than 1 DLT is observed in a 3-patient cohort, the decision is to decrease the dose level or to stay at the current level.

APPENDIX 3. REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R)

IPSS-R Cytogenetic Risk Groups*,**

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

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good	-	Good	-	Intermediate	Poor	Very Poor
BM Blasts (%)	≤2	-	>2 - <5	-	5 - 10	>10	-
Hemoglobin (g/dL)	≥10	-	8 - <10	<8	-	-	-
Platelets (x10^9/L)	≥100	50 - <100	<50	-	-	-	-
ANC (x10^9/L)	≥0.8	<0.8	-	-	-	-	-

IPSS-R Prognostic Risk Categories/Scores*

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

IPSS-R: Prognostic Risk Category Clinical Outcomes*

	No. pts	Very Low	Low	Intermediate	High	Very High
Subjects (%)	7012	19%	38%	20%	13%	10%
Survival***	-	8.8	5.3	3.0	1.6	0.8
AML/25%***,^	-	NR	10.8	3.2	1.4	0.7

*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.

***Medians, years.

^ Median time to 25% AML evolution.

Schanz J, Tüchler H, Solé F, Mallo M, Luño E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 2012;30(8):820-9.

APPENDIX 4. GUIDELINES RELATED TO MDS CLASSIFICATION

Myelodysplastic Syndromes World Health Organization Classification System

Myelodysplastic Syndromes World Health Organization Classification System		
Category	Definition	
	Peripheral Blood Smear Evaluation	Bone Marrow Evaluation
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia[a] No or rare blasts (< 1%)[b]	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ringed sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with Multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)[b] No Auer rods < $1x10^9$/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/orerythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts[b] No Auer rods < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts[b] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts[c] Auer rods[c] < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts[c] Auer rods ±[c]
Myelodysplastic syndrome - unclassified (MDS-U)	Cytopenias < 1% blasts[b]	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages whenaccompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS[d] < 5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

[b] If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

[c] Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rods + and/or 5% to 19% blasts in the blood.

[d] Includes unbalanced abnormalities -7 or del(7q), -5 or del(5q), i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13), balanced abnormalities t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.1), T2;11)(p21;q23),

inv(3)(q21q26.2), and t(6;9)(p23;q34), and complex karyotype (3 or more chromosomal abnormalities) involving one of more of the listed abnormalities.

Sources:

Brunning RD, Bennett JM, Flandrin G, Matutes E, Head D, Vardiman JW, et al. Pathology and genetics of tumors of hematopoietic and lymphoid tissues. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumors. Lyon (France). IARC Press 2001:63-73.

Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute myeloid leukemia: rationale and important changes. Blood 2009;114(5):937-51.

APPENDIX 5. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), 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.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone 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 one follicle stimulating hormone 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.

Contraception Guidance:

Female patients of childbearing potential (defined as first menarche through post-menopause or permanent sterilization) must agree to continued abstinence from heterosexual intercourse or 2 acceptable methods of birth control, including one highly effective method and one additional barrier method at the same time, during the study and for 7 months following the last dose of study drug.

Highly effective contraceptive methods are as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral

  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

Additional barrier methods of contraception are as follows:

- Barrier methods of contraception (diaphragm, cervical cap, contraceptive sponge, male condom)

  Note: Barrier methods have a higher failure rate than the highly effective methods listed above. To be considered acceptable, use two barrier methods (each partner must use one method) with a spermicide.
- Males must use the male condom (latex or other synthetic material) with spermicide
- Females must choose either a diaphragm with spermicide, or cervical cap with spermicide, or contraceptive sponge (spermicide is already in the contraceptive sponge)

Male patients (post-pubertal unless permanently sterilized by bilateral orchidectomy) must agree to use male contraception (condom) during the study and for 4 months following the last dose of study drug. Male patients must also not donate sperm during the Screening and treatment periods and for at least 4 months after the last dose of TP-0184.

Collection and Reporting Pregnancy Information

Any female patient who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study (see Section 12.1.6.4.4).

APPENDIX 6. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROMES, 2006

Altering Natural History of MDS According to IWG Criteria for MDS (Cheson, 2006)	
Category	**Response Criteria (responses must last at least 4 weeks)**
Complete Remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] – Hgb ≥ 11 g/dL – Platelets ≥ 100 X 109/L – Neutrophils ≥ 1.0 X 109/Lb Blasts 0%
Partial Remission (PR)	All CR criteria if abnormal before treatment except: – Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5% – Cellularity and morphology not relevant
Marrow CR[b]	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment[a] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b].
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pre-treatment.
Relapse After CR or PR	At least 1 of the following: – Return to pre-treatment bone marrow blast percentage – Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets – Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic Response	Complete: – Disappearance of the chromosomal abnormality without appearance of new ones Partial: – At least 50% reduction of the chromosomal abnormality
Disease Progression	For subjects with: – Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts – 5%-10% blasts: ≥ 50% increase to > 10% blasts – 10%-20% blasts: ≥ 50% increase to > 20% blasts – 20%-30% blasts[d]: ≥ 50% increase to > 30% blasts Any of the following: – ≥ 50% decrease from maximum remission/response in granulocytes or platelets – Reduction in Hgb by ≥ 2 g/dL – Transfusion dependence
Survival	Endpoints: – Overall: death from any cause – Event free: failure or death from any cause – PFS: disease progression or death from MDS – DFS: time to relapse – Cause-specific death: death related to MDS

KEY: CR = complete remission; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; PR = partial remission; PFS= progression-free survival; DFS= disease-free survival.

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[b] Modification to IWG (2000) response criteria.

Hematologic Improvement According to IWG Criteria (Cheson, 2006)	
Hematologic Improvement[a]	**Response criteria (responses must last at least 8 week)[b]**
Erythroid Response (HI-E) (pre-treatment, <11 g/dL)	– Hemoglobin increase by ≥ 1.5 g/dL – Relevant Reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk
Platelet Response (HI-P) (pre-treatment, <100 X 109/L)	– Absolute increase of ≥ 30 X 10^9/L for subjects starting with > 20 X 10^9/L platelets – Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%[b]
Neutrophil Response (HI-N) (pre-treatment, <1.0 X 109/L)	– At least 100% increase and an absolute increase > 0.5 X 10^9/L[b]
Progression or Relapse After HIc	At least 1 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

KEY: HI-E = hematologic improvement erythroid response; HI-N = hematologic improvement neutrophil response; HI-P = hematologic improvement platelet response; IWG = International Working Group; RBC = red blood cell.

[a] Pretreatment counts averages of at least 2 measurements (not influenced by transfusions, ie, no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) ≥ 1 week apart (modification).

[b] Modification to IWG (2000) response criteria.

[c] In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Note: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: 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):419-25.

APPENDIX 7. ECOG PERFORMANCE STATUS

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	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	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair.

Source: Oken MM, et al.., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol (1982) 5:649-655.

APPENDIX 8. DRUG INTERACTIONS – CYP3A4 INHIBITORS AND INDUCERS

Please check the following website for the most up-to-date information: University Of Washington, DIDB – The Drug Interaction Database
https://www.druginteractionsolutions.org/solutions/drug-interaction-database/

January 2021

Inhibitor	Therapeutic Class
Strong CYP3A Inhibitors (AUCR ≥ 5 or CL Ratio ≤ 0.20)	
VIEKIRA PAK	Antivirals
indinavir / ritonavir	Protease Inhibitors
tipranavir / ritonavir	Protease Inhibitors
ritonavir	Protease Inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
troleandomycin	Antibiotics
telaprevir	Antivirals
danoprevir / ritonavir	Antivirals
elvitegravir / ritonavir	Treatments of AIDS
saquinavir / ritonavir	Protease Inhibitors
lopinavir / ritonavir	Protease Inhibitors
itraconazole	Antifungals
indinavir	Protease Inhibitors
voriconazole	Antifungals
mifepristone	Antiprogestins
mibefradil	Calcium Channel Blockers
LCL161	Cancer Treatments
clarithromycin	Antibiotics
josamycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice DS	Food Products
ceritinib	Kinase Inhibitors
conivaptan	Diuretics
tucatinib	Kinase Inhibitors
nefazodone	Antidepressants
nelfinavir	Protease Inhibitors
saquinavir	Protease Inhibitors
ribociclib	Kinase Inhibitors
idelalisib	Kinase Inhibitors

boceprevir	Antivirals
Moderate CYP3A Inhibitors (2 ≤ AUCR < 5 or 0.20 < CL Ratio ≤ 0.50)	
erythromycin	Antibiotics
fluconazole	Antifungals
atazanavir / ritonavir	Protease Inhibitors
darunavir	Protease Inhibitors
ACT-539313	Hypnotics - Sedatives
duvelisib	Kinase Inhibitors
diltiazem	Calcium Channel Blockers
darunavir / ritonavir	Protease Inhibitors
dronedarone	Antiarrhythmics
crizotinib	Kinase Inhibitors
atazanavir	Protease Inhibitors
fedratinib	Kinase Inhibitors
letermovir	Antivirals
GSK2647544	Alzheimer's Disease & Dementia Treatments
aprepitant	Antiemetics
lefamulin	Antibiotics
casopitant	Antiemetics
amprenavir	Protease Inhibitors
faldaprevir	Antivirals
imatinib	Antineoplastic Agents
verapamil	Calcium Channel Blockers
ravuconazole	Antifungals
netupitant	Antiemetics
nilotinib	Kinase Inhibitors
istradefylline	Other Antiparkinsonians
grapefruit juice	Food Products
tofisopam	Benzodiazepines
ACT-178882	Renin Inhibitors
ciprofloxacin	Antibiotics
voxelotor	Hemoglobin S Polymerization Inhibitors
Schisandra sphenanthera	Herbal Medications
isavuconazole	Antifungals
cimetidine	H-2 Receptor Antagonists
FK1706	Central Nervous System Agents

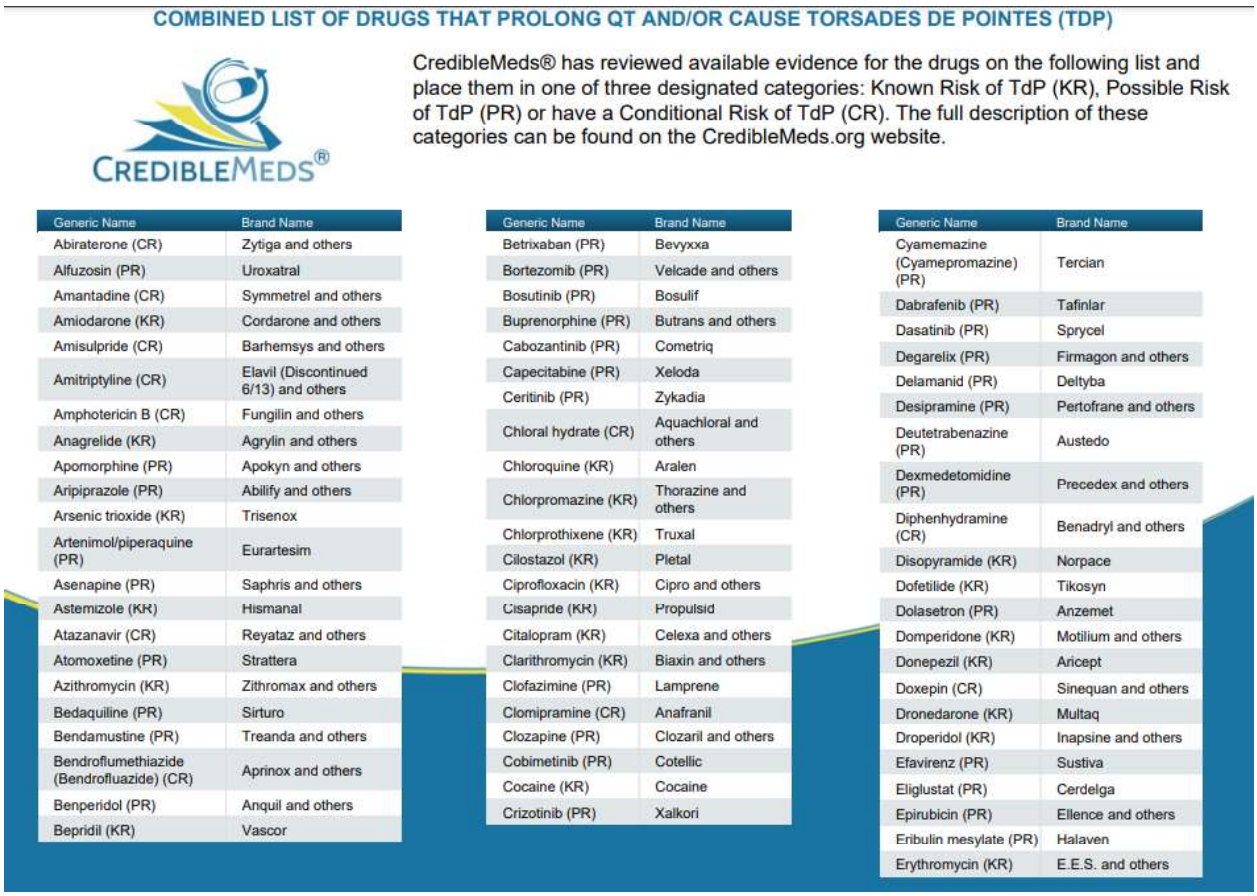
January 2021

Inducers	Therapeutic class
Strong Inducers (AUCR ≤ 0.2 or CL Ratio ≥ 5)	
rifampin	Antibiotics
mitotane	Other Antineoplastics
avasimibe	Other Antilipemics
rifapentine	Antibiotics
apalutamide	Antiandrogens
ivosidenib	Cancer Treatments
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
st John's wort extract	Herbal Medications
lumacaftor	Cystic Fibrosis Treatments
phenobarbital	Anticonvulsants
Moderate Inducers (0.20 < AUCR ≤ 0.50 or 2 ≤ CL Ratio < 5)	
semagacestat	Alzheimer's Treatments
efavirenz	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)
tipranavir / ritonavir	Protease Inhibitors
dabrafenib	Kinase Inhibitors
cenobamate	Anticonvulsants
lesinurad	Antigout and Uricosuric Agents
bosentan	Endothelin Receptor Antagonists
thioridazine	Antipsychotics
rifabutin	Antibiotics
lorlatinib	Kinase Inhibitors
nafcillin	Antibiotics
talviraline	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)
lopinavir	Protease Inhibitors
asunaprevir / beclabuvir / daclatasvir	Antivirals
modafinil	Psychostimulants
PF-06282999	Myeloperoxidase Inactivators
etravirine	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)
elagolix	Other
lersivirine	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)
telotristat ethyl	Antidiarrheals

APPENDIX 9. MEDICATIONS WITH KNOWN OR POSSIBLE RISK OF PROLONGING QT OR INDUCING TORSADES DE POINTES

Please check the following website for the most up-to-date information:

https://crediblemeds.org/new-drug-list/



COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CredibleMeds®

CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR). The full description of these categories can be found on the CredibleMeds.org website.

Generic Name	Brand Name
Abiraterone (CR)	Zytiga and others
Alfuzosin (PR)	Uroxatral
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Barhemsys and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others
Amphotericin B (CR)	Fungilin and others
Anagrelide (KR)	Agrylin and others
Apomorphine (PR)	Apokyn and others
Aripiprazole (PR)	Abilify and others
Arsenic trioxide (KR)	Trisenox
Artenimol/piperaquine (PR)	Eurartesim
Asenapine (PR)	Saphris and others
Astemizole (KR)	Hismanal
Atazanavir (CR)	Reyataz and others
Atomoxetine (PR)	Strattera
Azithromycin (KR)	Zithromax and others
Bedaquiline (PR)	Sirturo
Bendamustine (PR)	Treanda and others
Bendroflumethiazide (Bendrofluazide) (CR)	Aprinox and others
Benperidol (PR)	Anquil and others
Bepridil (KR)	Vascor

Generic Name	Brand Name
Betrixaban (PR)	Bevyxxa
Bortezomib (PR)	Velcade and others
Bosutinib (PR)	Bosulif
Buprenorphine (PR)	Butrans and others
Cabozantinib (PR)	Cometriq
Capecitabine (PR)	Xeloda
Ceritinib (PR)	Zykadia
Chloral hydrate (CR)	Aquachloral and others
Chloroquine (KR)	Aralen
Chlorpromazine (KR)	Thorazine and others
Chlorprothixene (KR)	Truxal
Cilostazol (KR)	Pletal
Ciprofloxacin (KR)	Cipro and others
Cisapride (KR)	Propulsid
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others
Clofazimine (PR)	Lamprene
Clomipramine (CR)	Anafranil
Clozapine (PR)	Clozaril and others
Cobimetinib (PR)	Cotellic
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori

Generic Name	Brand Name
Cyamemazine (Cyamepromazine) (PR)	Tercian
Dabrafenib (PR)	Tafinlar
Dasatinib (PR)	Sprycel
Degarelix (PR)	Firmagon and others
Delamanid (PR)	Deltyba
Desipramine (PR)	Pertofrane and others
Deutetrabenazine (PR)	Austedo
Dexmedetomidine (PR)	Precedex and others
Diphenhydramine (CR)	Benadryl and others
Disopyramide (KR)	Norpace
Dofetilide (KR)	Tikosyn
Dolasetron (PR)	Anzemet
Domperidone (KR)	Motilium and others
Donepezil (KR)	Aricept
Doxepin (CR)	Sinequan and others
Dronedarone (KR)	Multaq
Droperidol (KR)	Inapsine and others
Efavirenz (PR)	Sustiva
Eliglustat (PR)	Cerdelga
Epirubicin (PR)	Ellence and others
Eribulin mesylate (PR)	Halaven
Erythromycin (KR)	E.E.S. and others

Generic Name	Brand Name
Escitalopram (KR)	Cipralex and others
Esomeprazole (CR)	Nexium and others
Ezogabine (Retigabine) (PR)	Potiga and others
Famotidine (CR)	Pepcid and others
Felbamate (PR)	Felbatol
Fingolimod (PR)	Gilenya
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluorouracil (5-FU) (PR)	Adrucil and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Furosemide (frusemide) (CR)	Lasix and others
Galantamine (CR)	Reminyl and others
Garenoxacin (CR)	Geninax
Gatifloxacin (KR)	Tequin
Gemifloxacin (PR)	Factive
Granisetron (PR)	Kytril and others
Grepafloxacin (KR)	Raxar
Halofantrine (KR)	Halfan
Haloperidol (KR)	Haldol and others
Hydrochlorothiazide (CR)	Apo-Hydro and others
Hydrocodone - ER (PR)	Hysingla™ ER and others
Hydroxychloroquine (KR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others

Generic Name	Brand Name
Imipramine (Melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lansoprazole (CR)	Prevacid and others
Lapatinib (PR)	Tykerb and others
Lenvatinib (PR)	Lenvima
Leuprolide (Leuprorelin) (PR)	Lupron and others
Levetiracetam (PR)	Keppra
Levofloxacin (KR)	Levaquin and others
Levomepromazine (Methotrimeprazine) (KR)	Nosinan and others
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Lesuride and others
Lithium (PR)	Eskalith and others
Lofexidine (PR)	Lucemyra
Loperamide (CR)	Imodium
Lopinavir/Ritonavir (PR)	Kaletra and others
Lurasidone (PR)	Latuda
Maprotiline (PR)	Ludiomil
Melperone (PR)	Bunil and others
Memantine (PR)	Namenda XR
Mesoridazine (KR)	Serentil
Methadone (KR)	Dolophine and others
Metoclopramide (CR)	Reglan and others

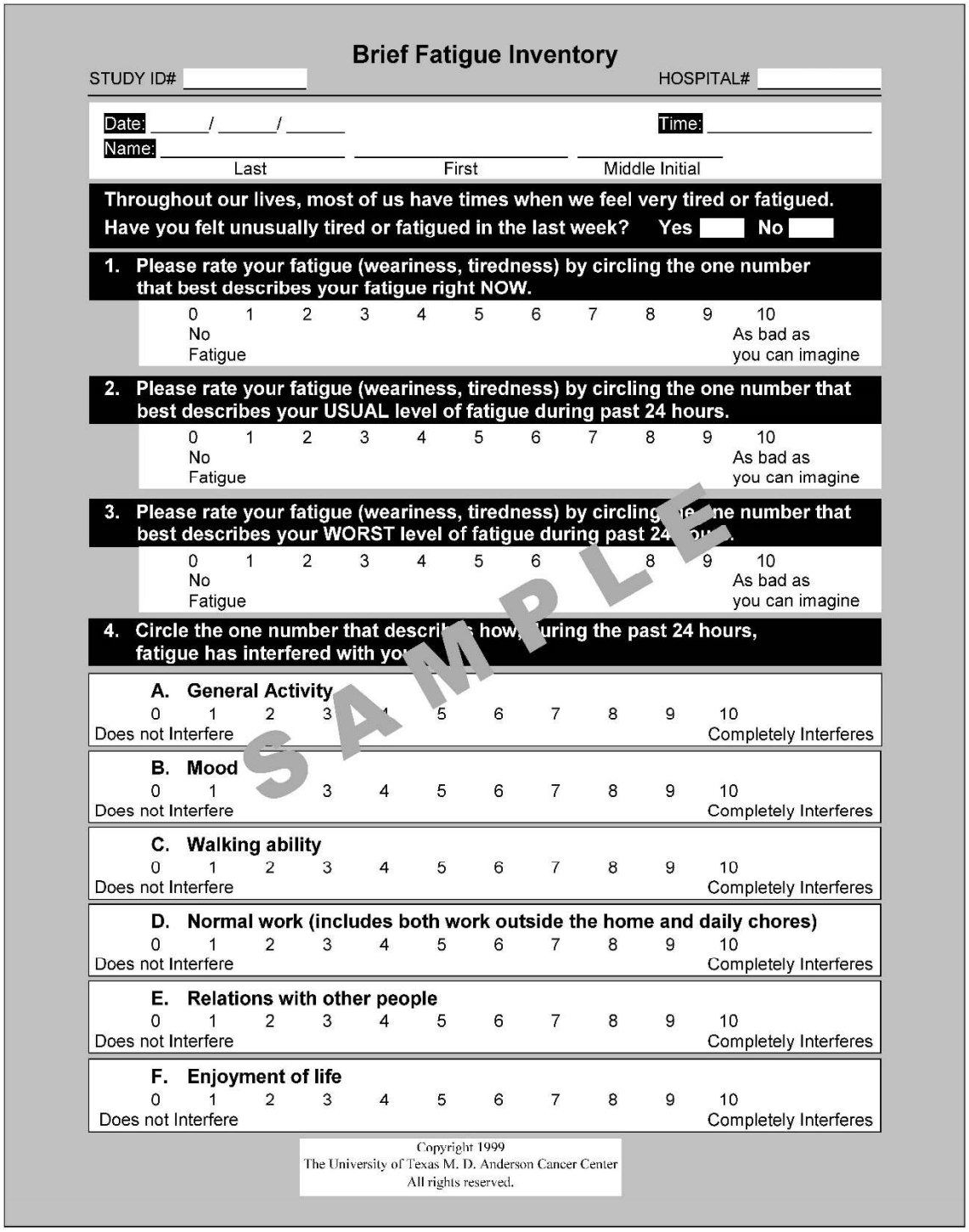
Generic Name	Brand Name
Metolazone (CR)	Zytanix and others
Metronidazole (CR)	Flagyl and others
Mianserin (PR)	Tolvon
Midostaurin (PR)	Rydapt
Mifepristone (PR)	Korlym and others
Mirabegron (PR)	Myrbetriq
Mirtazapine (PR)	Remeron
Moexipril/Hydrochlorothiazide (PR)	Uniretic and others
Moxifloxacin (KR)	Avelox and others
Necitumumab (PR)	Portrazza
Nelfinavir (CR)	Viracept
Nicardipine (PR)	Cardene
Nilotinib (PR)	Tasigna
Norfloxacin (PR)	Noroxin and others
Nortriptyline (PR)	Pamelor and others
Nusinersen (PR)	Spinraza
Ofloxacin (PR)	Floxin
Olanzapine (CR)	Zyprexa and others
Omeprazole (CR)	Losec and others
Ondansetron (KR)	Zofran and others
Osimertinib (PR)	Tagrisso
Oxaliplatin (KR)	Eloxatin
Oxytocin (PR)	Pitocin and others
Paliperidone (PR)	Invega and others
Palonosetron (PR)	Aloxi
Panobinostat (PR)	Farydak
Pantoprazole (CR)	Protonix and others
Papaverine HCl (Intra-coronary) (KR)	

Generic Name	Brand Name
Paroxetine (CR)	Paxil and others
Pasireotide (PR)	Signifor
Pazopanib (PR)	Votrient
Pentamidine (KR)	Pentam
Perflutren lipid microspheres (PR)	Definity and others
Perphenazine (PR)	Trilafon and others
Pilsicainide (PR)	Sunrythm
Pimavanserin (PR)	Nuplazid
Pimozide (KR)	Orap
Pipamperone (PR)	Dipiperon and others
Piperacillin/Tazobactam (CR)	Tazosyn and others
Posaconazole (CR)	Noxafil and others
Primaquine phosphate (PR)	
Probucol (KR)	Lorelco
Procainamide (KR)	Pronestyl and others
Promethazine (PR)	Phenergan
Propafenone (CR)	Rythmol SR and others
Propofol (KR)	Diprivan and others
Prothipendyl (PR)	Dominal and others
Quetiapine (CR)	Seroquel
Quinidine (KR)	Quinaglute and others
Quinine sulfate (CR)	Qualaquin and others
Ranolazine (CR)	Ranexa and others

Generic Name	Brand Name
Ribociclib (PR)	Kisqali
Rilpivirine (PR)	Edurant and others
Risperidone (CR)	Risperdal
Romidepsin (PR)	Istodax
Roxithromycin (KR)	Rulide and others
Saquinavir (PR)	Invirase(combo)
Sertindole (KR)	Serdolect and others
Sertraline (CR)	Zoloft and others
Sevoflurane (KR)	Ultane and others
Solifenacin (CR)	Vesicare
Sorafenib (PR)	Nexavar
Sotalol (KR)	Betapace and others
Sparfloxacin (KR)	Zagam
Sulpiride (KR)	Dogmatil and others
Sultopride (KR)	Barnetil and others
Sunitinib (PR)	Sutent
Tacrolimus (PR)	Prograf and others
Tamoxifen (PR)	Nolvadex and others
Telaprevir (CR)	Incivo and others
Telavancin (PR)	Vibativ
Telithromycin (PR)	Ketek
Terfenadine (KR)	Seldane
Terlipressin (KR)	Terlipress and others

Generic Name	Brand Name
Terodiline (KR)	Micturin and others
Tetrabenazine (PR)	Nitoman and others
Thioridazine (KR)	Mellaril and others
Tiapride (PR)	Tiapridal and others
Tipiracil/Trifluridine (PR)	Lonsurf
Tizanidine (PR)	Zanaflex and others
Tolterodine (PR)	Detrol and others
Toremifene (PR)	Fareston
Torsemide (Torasemide) (CR)	Demadex and others
Tramadol (PR)	Crispin and others
Trazodone (CR)	Desyrel and others
Trimipramine (PR)	Surmontil and others
Tropisetron (PR)	Navoban and others
Valbenazine (PR)	Ingrezza
Vandetanib (KR)	Caprelsa
Vardenafil (PR)	Levitra
Vemurafenib (PR)	Zelboraf
Venlafaxine (PR)	Effexor and others
Voriconazole (CR)	VFend
Vorinostat (PR)	Zolinza
Ziprasidone (CR)	Geodon and others
Zotepine (PR)	Losizopilon and others
Zuclopenthixol (Zuclopentixol) (PR)	Cisordinol and others

APPENDIX 10. BRIEF FATIGUE INVENTORY



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL# _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how during the past 24 hours, fatigue has interfered with you

A. General Activity
0 1 2 3 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood
0 1 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

APPENDIX 11. NEW YORK HEART ASSOCIATION CLASSIFICATION SCALE

NYHA Classification - The Stages of Heart Failure

Class	Functional Capacity	Objective Assessment
I	No symptoms and no limitation in ordinary physical activity, eg, shortness of breath when walking, climbing stairs etc.	A. No objective evidence of cardiovascular disease.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.	B. Objective evidence of minimal cardiovascular disease.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 m). Comfortable only at rest.	C. Objective evidence of moderately severe cardiovascular disease.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.	D. Objective evidence of severe cardiovascular disease.
V	No NYHA class listed or unable to determine	N/A

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.