STATISTICAL ANALYSIS PLAN

PHASE I/II

Date of Plan: 15DEC2021

Based on Protocol Version: BBI-TP-0184-102 Version: 2

STUDY DRUG: TP-0184

STUDY NUMBER: BBI-TP-0184-102

STUDY TITLE:

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

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

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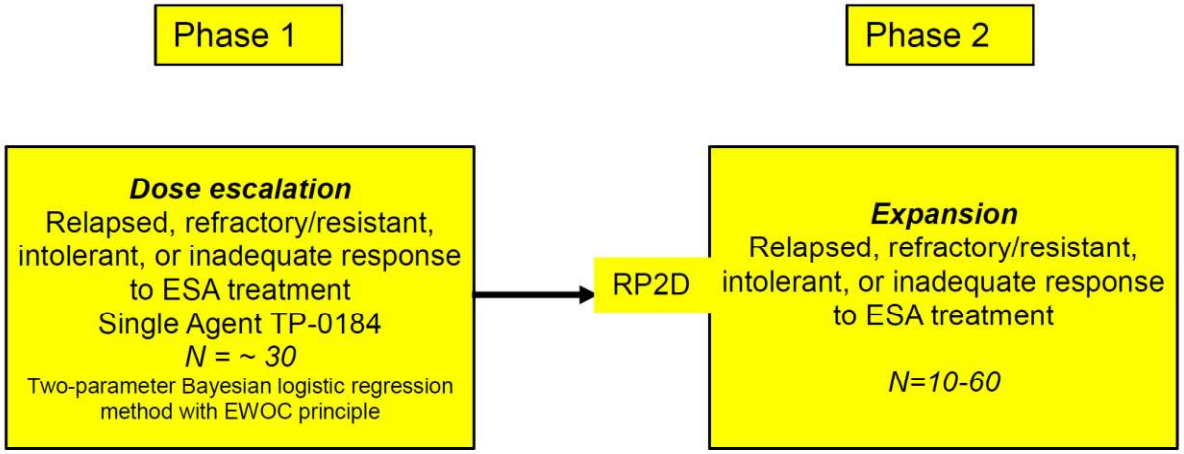
1. INTRODUCTION

1.1 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 Revised International Prognostic Scoring System (IPSS-R) low or intermediate risk Myelodysplastic Syndrome (MDS) who have received prior erythropoiesis stimulating agents (ESA)-containing regimen. 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.



Study schematic: from TP-0184-102 protocol

Phase 1

Dose-escalation for TP-0184 will be performed using a Bayesian logistic regression model (BLRM) at a starting dose of 20 mg/day every day, administered in the fasting state (6 hours before the dose and 1 hour after the dose).

The BLRM method will be applied along with escalation with overdose control (EWOC) principle to control the risk of exposing patients to toxic doses. Based on this principle, a dose level will be considered safe if the probability of excessive toxicity, ie, the probability of a dose limiting toxicities (DLT) rate greater than 33%, with EWOC is less than or equal to 25%. After completion of a given dose cohort, a decision will be made to either adjust the dose (de-escalate the dose, escalate the dose) or further enroll patients at the same cohort to be tested based on a risk assessment using the BLRM method. The dose recommended using the BLRM method will be treated as a guide and will be integrated with a clinical assessment of the toxicity information and review of other available data.
The phase 1 portion, will be conducted in approximately 30 patients due to the dynamic feature of BLRM.

Phase 2

Phase 2 will determine the preliminary efficacy of TP-0184 in an expansion phase of up to 60 patients. Preliminary efficacy as assessed by the response rate will be monitored using the Bayesian posterior probability to optimize the enrollment with Bayesian stopping rules.

1.2 Study Objectives and Endpoints

Phase 1

Primary

Objectives	Endpoints
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 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

Secondary

Objectives	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 (Appendix 1: Consideration of Response for Composite Endpoint)	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

Objectives	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 ≥ 12 weeks (Appendix 1 in Protocol: Consideration of Response for Composite Endpoint)	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
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
Median duration of hemoglobin response	Duration of hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions.
Median duration of reduction in RBC transfusions (4 units / 8 weeks)	Duration of reduction in units of ≥ 4 RBC transfusions / 8 weeks (consecutive)
Median duration of RBC-transfusion-free period ≥ 8 weeks	Duration of RBC transfusion-free period
To determine the cardiac safety of TP-0184	Assessment of the presence of symptoms of CHF (based on New York Heart Association (NYHA) criteria) and 12-Lead ECGs abnormalities, intensive ECG recordings taken at time of PK draws, cardiac Magnetic resonance imaging (MRI), echocardiogram (ECHO) or multigated acquisition (MUGA) scans, and peripheral blood cardiac markers
Progression to Acute myeloid leukemia (AML)	Proportion of patients progressing to AML, time to AML progression
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

Exploratory

Objectives	Endpoints
To determine whether TP-0184 treatment modulates hepcidin and iron metabolism profiling results in peripheral blood	Evaluation of iron metabolism including hepcidin and other markers of iron regulation[1] with response to treatment with TP-0184 [1]iron panel (serum iron, ferritin, transferrin, soluble transferrin receptor (STR), and total iron binding capacity (TIBC))
Correlative biomarkers of therapy	Evaluation of potential biomarkers in plasma and bone marrow samples
Metabolites of TP-0184 in patients via Phase 1 data.	Profile of potential metabolites of TP-0184 inpatients in Phase 1
Pharmacodynamic effects of TP-0184 therapy	Determination of in vivo markers of ALK-2 /ALK-5 inhibition, not limited to SMAD/phospho-SMAD signaling
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
Changes in platelet levels	Proportion of patients achieving hematologic improvement in platelets (HI-P) over any consecutive 8-week (56-day) period and / or decrease in platelet levels
Change from baseline in the Brief Fatigue Inventory (BFI) in RP2D and one dose level below RP2D subgroup	The Brief Fatigue Inventory (BFI) that measures the severity of fatigue based on the worst fatigue experienced during the past 24-hours

Phase 2

Primary

Objectives	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 • (TP-0184-102 Protocol Appendix 1: Consideration of Response for Composite Endpoint)	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

Secondary

Objectives	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≥ 12 weeks. • (TP-0184-102 Protocol Appendix 1: Consideration of Response for Composite Endpoint)	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
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
Median duration of hemoglobin response	Duration of hemoglobin increase ≥ 1.5 g/dL maintained for a consecutive period of > 8 weeks with no transfusions
Median duration of reduction in RBC transfusions (4 units / 8 weeks)	Duration of reduction in units of ≥ 4 RBC transfusions / 8 weeks. (consecutive)
Median duration of RBC-transfusion-free period ≥8 weeks	Duration of RBC transfusion-free period

Objectives	Endpoints
Changes in neutrophils	Proportion of patients achieving HI-N over any consecutive 8-week (56-day) period and / or decrease in neutrophil levels
Changes in platelet counts	Proportion of patients achieving hematologic improvement in platelets (HI-P) over any consecutive 8-week (56-day) period and / or decrease in platelet levels
To assess the safety and tolerability of TP-0184	Assessment of 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
To determine the cardiac safety of TP-0184 administered as single agent.	Assessment of the presence of symptoms of CHF (based on NYHA criteria) and 12-Lead ECG abnormalities, cardiac MRI, ECHO or MUGA scans, and peripheral blood cardiac markers
Steady-state trough PK characterization	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
Progression to AML	Proportion of patients progressing to AML, time to AML progression
Overall Survival	Time from first dose of TP-0184 to death due to any cause
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
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

Exploratory

Objectives	Endpoints
Correlative biomarkers of therapy	Evaluation of potential biomarkers in plasma and bone marrow samples

Objectives	Endpoints
To determine whether TP-0184 treatment modulates hepcidin and iron metabolism profiling results in peripheral blood	Evaluation of iron metabolism including hepcidin and other markers of iron regulation[1] with response to treatment with TP-0184 [1]iron panel (serum iron, ferritin, transferrin, soluble transferrin receptor (STR), and total iron binding capacity (TIBC))
Pharmacodynamic effects of TP-0184 therapy	Determination of in vivo markers of ALK-2/ALK-5 inhibition, not limited to SMAD/phospho-SMAD signaling

2. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

Per decision of Sumitomo Dainippon Pharma Oncology, Inc., TP-0184-102 is terminated.

Two patients have been enrolled, dosed, and discontinued in this study. TEAEs will be coded preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The following data of both patients will be presented in by patient listings:

- Adverse Events
- Concomitant Medication
- Death Listing
- Demographic and disease characteristics
- Dosing
- End of Treatment/Study
- Laboratory

3. STATISTICAL SOFTWARE

SAS version 9.4 (or higher) will be used for providing statistical outputs.
R was used for BLRM monitoring and other modeling work.