Cover Page for Protocol

Sponsor name:	Forma Therapeutics, a Novo Nordisk Company
NCT number	NCT05568225
Sponsor trial ID:	4202-ONC-203
Official title of study:	A Phase 2 Open-Label Study to Evaluate Etavopivat for the Treatment of Anemia in Patients with Myelodysplastic Syndromes (MDS)
Document date*:	31-Jul-2023

*Document date refers to the date on which the document was most recently updated.

CLINICAL TRIAL PROTOCOL

Protocol No.	4202-ONC-203		
Title:	A Phase 2 Open-Label Study to Evaluate Etavopivat for the Treatment of Anemia in Patients with Myelodysplastic Syndromes (MDS)		
IND No.:	160509		
Version:	3.0	**Date:**	31 July 2023
Prior Version(s):	2.0	**Prior Date(s)**	15 June 2022
	1.0		11 April 2022 (Not Implemented)

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INVESTIGATOR AGREEMENT PAGE

Forma Therapeutics, Inc.

Protocol 4202-ONC-203, Version 3.0
31 July 2023

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Forma Therapeutics to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Forma Therapeutics and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Forma Therapeutics, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, Declaration of Helsinki and International Council for Harmonisation Guidelines for Good Clinical Practices, along with any applicable state and local regulations and any other institutional requirements.

Principal Investigator	**Date**

Institution:

Address

SERIOUS ADVERSE EVENT REPORTING

COMPLETE THE NOVO NORDISK SERIOUS ADVERSE EVENT (SAE) REPORT FORM AND SUBMIT TO NOVO NORDISK GLOBAL SAFETY WITHIN 24 HOURS OF KNOWLEDGE OF ANY SAE. IF THE SAE IS FATAL OR LIFE THREATENING, NOVO NORDISK MUST BE INFORMED IMMEDIATELY.

EMAIL (encrypted), FAX, or upload to the CLINICAL WEBFORM the SAE REPORT FORM TO:	GLOBAL MEDICAL MONITOR
Fax: + 45 44427787 Email: SOCLIN@NOVONORDISK.COM Webform: https://www.novonordisk.com/contact-us/partners-safety-information-reporting-hq.html	Email: Fortitude_medicalmonitor@novonordisk.com

For reporting of all SAEs, Investigators must email (encrypted), fax, or upload to the clinical webform all completed pages of the SAE report form within 24 hours of knowledge of the event to the following:

Novo Nordisk Global Safety

FAX: + 45 44427787

EMAIL: SOCLIN@NOVONORDISK.COM

CLINICAL WEBFORM: https://www.novonordisk.com/contact-us/partners-safety-information-reporting-hq.html

FOLLOW-UP INFORMATION TO SAEs MUST BE PROVIDED TO NOVO NORDISK GLOBAL SAFETY WITHIN 24 HOURS OF INVESTIGATOR KNOWLEDGE OF THE EVENT.

ALL FORMS MUST BE DATED AND SIGNED

In case of any questions, please reach out to:
Fortitude_medicalmonitor@novonordisk.com

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

2,3-DPG	2,3-diphosphoglycerate
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ATC	Anatomical Therapeutic Chemical
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BMI	body mass index
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicities
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ESA	erythropoiesis-stimulating agents
FDA	Food and Drug Administration
FIH	First-in-Human
GCP	Good Clinical Practice
HepBsAg	hepatitis B surface antigen
HepBcAb	hepatitis B core antibody
Hb	Hemoglobin
HCV	hepatitis C virus
HI-E	Hematologic improvement–erythroid
HIV	human immunodeficiency virus
HTB	High transfusion burden
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPSS-R	International Prognostic Scoring System-Revised
IRB	Institutional Review Board
IUD	intrauterine device
IWG	International Working Group
LDH	lactate dehydrogenase
MAD	multiple ascending dose
LTB	low transfusion burden
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndromes
NCI	National Cancer Institute
NTD	non-transfusion dependent
O_2	Oxygen
P_{50}	partial pressure of O_2 at which Hb O_2 saturation of 50% is achieved
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKR	pyruvate kinase-red blood cell
PROMIS	Patient-Reported Outcomes Measurement Information System

PT	preferred term
QD	once daily
QoL	Quality of Life
QTcF	QT interval corrected using Fridericia's correction formula
QUALMS	The Quality of Life in Myelodysplasia Scale
RBC	red blood cells
RBC-TI	RBC transfusion independence
ROS	reactive oxygen species
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SOC	system organ class
SOP	standard operating procedure
SRC	Safety Review Committee
TD	transfusion dependent
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse events
TIBC	Total Iron Binding Capacity
t-MDS	therapy-associated MDS
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Title: A Phase 2 Open-Label Study to Evaluate Etavopivat for the Treatment of Anemia in Patients with Myelodysplastic Syndromes (MDS)

Rationale:

Etavopivat (FT-4202) is a potent, selective, orally bioavailable, small-molecule activator of pyruvate kinase -red blood cell (PKR) being developed by Forma Therapeutics, Inc and is intended for use as a treatment for the anemia of MDS, inherited hemolytic anemias, and other refractory anemias.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess hematologic improvement based on an erythroid response (HI-E) for ≥ 8 weeks duration in patients with MDS within 24 weeks of etavopivat treatment	The HI-E for ≥ 8 weeks within 24 weeks of etavopivat. This endpoint will be based on the combined incidence of: o Non-transfusion dependent (NTD) patients: ≥ 1.5 g/dL increase in hemoglobin (Hb) from baseline maintained ≥ 8 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period o Low transfusion burden (LTB) patients: absence of any transfusion for ≥ 8 consecutive weeks o High transfusion burden (HTB) patients: reduction by ≥ 50% of red blood cell (RBC) units for ≥ 8 consecutive weeks
Secondary	
• To assess HI-E for ≥ 8 weeks duration in this population of patients within 16 and 48 weeks of etavopivat treatment	• The HI-E for ≥ 8 weeks within 16 and 48 weeks of etavopivat This endpoint will be based on the combined incidence of: o NTD patients: ≥ 1.5 g/dL increase in Hb from baseline maintained ≥ 8 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period o LTB patients: absence of any transfusion for ≥ 8 consecutive weeks o HTB patients: reduction by ≥ 50% of RBC units for ≥ 8 consecutive weeks
• To assess HI-E for ≥ 16 weeks duration in this population of patients within 24 and 48 weeks of etavopivat treatment	• The HI-E for ≥ 16 weeks within 24 and 48 weeks of etavopivat This endpoint will be based on the combined incidence of: o NTD patients: ≥ 1.5 g/dL increase in Hb from baseline maintained ≥ 16 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period o LTB patients: absence of any transfusion for ≥ 16 consecutive weeks o HTB patients: reduction by ≥ 50% of RBC units for ≥ 16 consecutive weeks

Secondary, continued	
• To assess the safety and tolerability of etavopivat in patients with MDS	• Incidence of adverse events (AEs), serious adverse events (SAEs), and AEs related to etavopivat • Number of premature discontinuations, dose interruptions, and dose reductions
• To assess additional measures demonstrating potential clinical benefit	• Overall response rate (2006 International Working Group [IWG] Criteria) (see Appendix A) • Duration of response (2006 IWG Criteria) • Reduction in RBC transfusions and rate of RBC transfusion independence ≥ 8 weeks in patients with LTB or HTB at study entry. • Increase in neutrophils and/or platelets counts • Decrease in ferritin and transferrin saturation (TSAT) • Decrease in iron chelation therapy • Overall survival
Pharmacokinetic / Pharmacodynamic	
• To assess the pharmacokinetic (PK) and pharmacodynamic (PD) properties of etavopivat in patients with MDS	• Etavopivat plasma PK parameters (including but not limited to): maximum observed plasma concentration, time to maximum observed plasma concentration, area under the plasma concentration-time curve from time zero until the last quantifiable time point ($AUC_{0\text{-}last}$), from time zero to infinity ($AUC_{0\text{-}inf}$), for a dosing interval ($AUC_{tau}/AUC_{0\text{-}24}$). • RBC 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) levels over time
Exploratory	
• To examine safety trends in patients with MDS receiving etavopivat	• Assessment of vital signs, clinical laboratory findings, and physical examination findings
• To assess changes in quality-of-life in patients with MDS taking etavopivat	• Change from baseline in Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Scale at Weeks 16, 24, and 48 • Change from baseline in The Quality of Life in Myelodysplasia Scale (QUALMS) patient-reported outcome assessment at Weeks 16, 24, and 48
• To characterize the biological effects of etavopivat treatment in patients with MDS	• Cell colony analysis of bone marrow progenitors • Cytomorphology (blast, M/E, and ringed sideroblast determination) and cytogenetics of bone marrow • Markers of ineffective erythropoiesis and iron metabolism • Cancer-associated mutations and/or genetic alterations in responding and non-responding patients • Flow cytometry analysis of terminal erythroid differentiation (EU Only)

Overall Design:

This study is a multicenter, open-label, Phase 2 study in adult patients with very low, low risk, or intermediate risk MDS per the International Prognostic Scoring System-Revised (IPSS-R) classification (see Appendix B).

The study will enroll up to 45 patients with MDS who will be evaluated for HI-E response composite derived from the MDS IWG 2018 criteria (modified by Platzbecker et al. 2019)

(see Appendix A). HI-E response assessment will be based on the individual patient's transfusion history in the 16 weeks prior to enrollment:

- NTD patients (received ≤ 2 RBC units for anemia within the prior 16 weeks): Hb increase of ≥ 1.5 g/dL over a continuous 8-week treatment period and no transfusion of RBC units for anemia over a continuous 8-week treatment period
    - Approximately 15 patients meeting the criteria for NTD may be enrolled in this study
- LTB patients (received 3 to 7 RBC units within the prior 16 weeks): No transfusion of RBC units for anemia over a continuous 8-week treatment period
    - Approximately 15 patients meeting the criteria for LTB may be enrolled in this study
- HTB patients (received ≥ 8 RBC units in the prior 16 weeks): ≥ 50% reduction in RBC units transfused over a continuous 8-week period.
    - Approximately 15 patients meeting the criteria for HTB may be enrolled in this study

Patients will be enrolled into a 48-week treatment period, including a 24-week Primary Treatment period and a 24-week Extension Treatment period. Patients demonstrating clinical benefit at the end of the 48-week treatment period may continue treatment. The dose of etavopivat is 400 mg once daily (QD) administered continuously; the selection of the starting dose is based on results from a Phase 1 study in patients with sickle cell disease (SCD) who were not receiving chronic RBC transfusions.

After the 6th patient completes a minimum of 4-weeks of daily etavopivat treatment, a safety review meeting will be held to confirm that the safety, exposure, and pharmacological response (PK/PD profile) are consistent with prior experience of etavopivat dosing in healthy volunteers and patients with sickle cell disease or thalassemia.

A futility assessment will be triggered when 15 patients across all strata or 8 patients in a single stratum reach 24 weeks of treatment, whichever occurs first. If both criteria are met at the same time, the overall futility assessment will be performed.

The futility criterion is defined as follows:

- All strata (n=15): ≤ 3 responses meeting HI-E criteria, sustained from Week 16 to Week 24.
- Single stratum (n=8): 0 (zero) responses.

If either the overall, or single stratum, futility criterion is met, enrollment may discontinue due to futility. Further enrollment may be considered if it is restricted to specific subsets of patients based on prior transfusion history. If neither criterion is met, enrollment will continue until a total of 45 response-evaluable patients are available at Week 24.

Enrollment will not pause during assessment periods unless futility analysis suggests clinical need to pause.

At final analysis, the study will evaluate the rate of MDS IWG 2018 criteria responses in the pooled, open-label etavopivat-treated patients versus a null-assumed rate of 20%.

Treatment Duration: Duration of study treatment will be up to 48 weeks, including 24 weeks in the Primary Treatment period and 24 weeks in the Extension Treatment period. Patients who demonstrate clinical benefit at 48 weeks of treatment, based on their MDS response assessment, may continue treatment until the patient experiences unacceptable

toxicities, disease progression, withdraws consent, or meets any other discontinuation criteria (Section 7.2.1).

Study Duration: Duration of study for an individual patient is approximately 58 weeks and includes a Screening Period (up to 6 weeks before study treatment), the 24-week Primary Treatment period, the 24-week Extension Treatment period, and Safety Follow-up visit occurring 28 days (+ 7 days) after last dose of study drug. The study duration will be greater than 58 weeks in patients who continue study treatment beyond the planned 48-week treatment period due to clinical benefit.

Number of Participants

Approximately 45 patients will be enrolled.

Key Inclusion Criteria

Type of Participant and Disease Characteristics

1. Documented diagnosis of idiopathic/*de novo* MDS according to World Health Organization (WHO) classification (see Appendix C) that meets the IPSS-R classification (see Appendix B) of very low, low, or intermediate risk disease, and:
   - < 5% blasts and no Auer rods in bone marrow based on local pathology review
   - < Intermediate risk cytogenetic abnormalities per IPSS-R (see Appendix B)
2. Anemia defined as:
   - NTD: Subjects with mean Hb concentration < 10.0 g/dL of 2 measurements (1 performed within 3 days prior to W1D1 and the other performed 7 to 28 days prior to W1D1, not influenced by RBC transfusion within 7 days of measurement) and < 3 RBC transfusions for anemia in the prior 16 weeks before W1D1 of etavopivat dosing

   OR

   - Transfusion Dependent: Subjects having received ≥ 3 units of RBCs for the treatment of anemia within 16 weeks prior to W1D1
3. Serum erythropoietin level > 200 U/L, OR, if ≤ 200 U/L, subject is non-responsive, refractory, or intolerant to erythropoiesis-stimulating agents, or erythropoiesis-stimulating agents are contraindicated or unavailable.
4. Eastern Cooperative Oncology Group performance status of ≤ 2 (see Appendix D)
5. Subject is non-responsive, refractory, or intolerant to luspatercept, or luspatercept is contraindicated or not indicated.
6. No alternative treatment options are available and/or appropriate for the subject, at the discretion of the investigator.
7. Patient is willing and able to adhere to the study visit schedule and other protocol requirements

Key Exclusion Criteria

MDS History

1. MDS associated with del 5q cytogenetic abnormality and known TP53 abnormality

2. Therapy-associated MDS (eg. t-MDS) that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases
3. Known history of acute myeloid leukemia (AML)
4. Any diagnosis of myelodysplastic/myeloproliferative neoplasms

Medical Conditions

5. Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding
6. Absolute neutrophil count < 500/µL (0.5×10^9/L)
7. Platelet count < 50,000/µL (50×10^9/L) without transfusion within 14 days
8. Hepatic dysfunction characterized by any one of the following:
    - Alanine aminotransferase (ALT) > 3.0 × upper limit of normal (ULN)
    - Total bilirubin > 2.0 × ULN (in the absence of cholestasis)
    - History and/or evidence of cirrhosis

Novo Nordisk Safety Committee

Novo Nordisk will perform ongoing safety surveillance. Safety surveillance activities encompass the regular periodic safety data review from clinical trials, literature surveillance and safety information derived from other sources.

If new safety signals are identified, these will be evaluated by the etavopivat internal safety committee.

The safety committee is cross-functional and the only Novo Nordisk body responsible for providing integrated assessments of safety data and endorsing appropriate actions in case of a safety signal.

Subsequently, safety information is communicated and reported to health authorities, ethics committees and investigators, as relevant and in accordance with regulatory requirements.

1.1.1 Study Safety Review Committee

A safety review via Study SRC, consisting of, at a minimum, members of the clinical study team (including Medical Lead), pharmacovigilance, and Principal Investigators participating from at least 2 study sites, will occur within 4 weeks of the following:

After the 6th patient completes a minimum of 4-weeks of daily etavopivat treatment, to confirm that the safety and PK/PD profile of 400 mg QD etavopivat continues to support enrollment and dosing of etavopivat. (See Section 4.4)

1.1.2 Dose-limiting Toxicities Evaluation Period/Definition

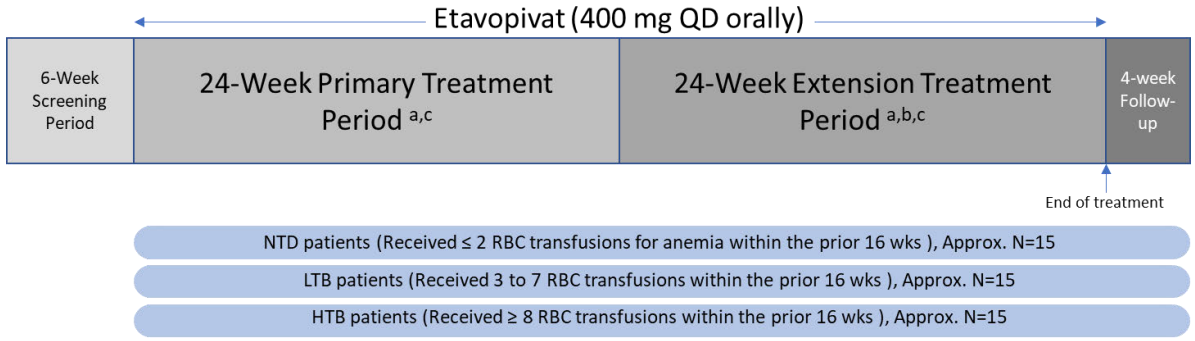
Dose-limiting toxicities (DLTs) will be evaluated during the first 28 days of treatment using NCI-CTCAE v5.0.

DLTs are determined by the Investigator and include any of the following AEs that are considered related to etavopivat (ie, all AEs of the specified grades except those that are

clearly and incontrovertibly due to underlying malignancy or extraneous causes, eg, intercurrent illness or concomitant medication):

- **Non-Hematologic Toxicity**
  - ≥ Grade 3 toxicity with the following exceptions: (1) nausea, vomiting, diarrhea lasting < 72 hours (with optimal medical management and other supportive care); (2) fatigue lasting < 1 week
  - Clinically relevant (requiring treatment or with potential clinical sequelae) ≥ Grade 3 non-hematologic laboratory finding. This includes:
    - ≥ Grade 3 electrolyte abnormality that lasts > 72 hours despite adequate management, unless the patient has clinical symptoms, in which case all Grade ≥ 3 electrolyte abnormality regardless of duration should count as a DLT.
    - Note: Grade ≥ 3 amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT
  - Hy's law as defined by aspartate aminotransferase or alanine aminotransferase (ALT) > 3 × ULN and total bilirubin > 2 × ULN with alkaline phosphatase < 2 × ULN in the absence of a clear alternative explanation
  - Inability to tolerate/receive a minimum of 75% of etavopivat scheduled doses during first 28 days of treatment due to an AE of any grade that is considered related to etavopivat, unrelated to underlying malignancy or intercurrent illness, and unrelated to a concomitant medication
- **Any death not clearly due to the underlying disease or extraneous causes**
- **Hematologic Toxicity**
  - Grade 4 thrombocytopenia for > 7 days
  - Grade 3 thrombocytopenia with bleeding
  - Grade 4 neutropenia lasting for > 7 days
  - Febrile neutropenia / neutropenic fever

1.2 Schema



NTD – Not transfusion dependent; LTB – Low transfusion burden; HTB – High transfusion burden

a. Patients who permanently discontinue treatment during the 48-weeks of treatment should complete both the End of Treatment visit (W48) and the Safety Follow-up visit (W52)
b. Patients who demonstrate clinical benefit at 48 weeks of treatment, based on their MDS response assessment, may continue treatment in an optional Prolonged Treatment Period until the patient experiences unacceptable toxicities, disease progreassion, withdraws consent or meets any of the discontinuation criteria.
c. After permanent discontinuation of treatment, study site may contact the patient approximately every 3 months for survival data.

Table 1-1: Schedule of Events, Primary and Extension Treatment Periods

Assessments	Screen	Primary treatment period												Extension treatment period											Safety follow-up visit
Study Day/Week(s):	D-42 to -1	W1D1 [b]	W2 D1 (±3 D)	W4 D1 (±3 D)	W6 D1 (±3 D)	W8 D1 (±3 D)	W10 D1 (±3 D)	W12 D1 (±3 D)	W14 D1 (±3 D)	W16 D1 (±3 D)	W20 D1 (±3 D)	W22 D1 (±3 D)	W24 D1 (±3 D)	W26 D1 (±3 D)	W28 D1 (±3 D)	W30 D1 (±3 D)	W32 D1 (±3 D)	W34 D1 (±3 D)	W36 D1 (±3 D)	W38 D1 (±3 D)	W40 D1 (±3 D)	W42 D1 (±3 D)	W44 D1 (±3 D)	W46 D1 (±3 D)	W48 D1 (±3 D)	W52 D1 (±3 D)
Informed Consent (a)	X																								
Inclusion/Exclusion	X																								
Medical History	X																								
Prior ESA/Luspatercept Therapies	X																								
Prior RBC and Platelet Transfusions	X																								
Demographics	X																								
Physical Examination	X	X																						X	
Physical Examination (symptom directed)			X	X		X		X		X	X		X				X				X				X
Height	X																								
Weight and BMI	X	X	X	X		X		X		X	X		X				X				X			X	X
Vital Signs (including temp) [d]	X	X	X	X		X		X		X	X		X				X				X			X	X
ECOG PS	X	X		X		X		X		X	X		X				X				X			X	X
ECG [e]	X	X	X	X		X				X			X				X				X			X	X
Adverse Events [f]	X	Recorded Throughout																							
Concomitant Medications	X	Recorded Throughout																							
Hematology [g]	X	X	X	X	X [h]	X	X [h]	X	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hb Electrophoresis	X																								
Serum Chemistry [g]	X	X	X	X		X		X		X	X		X				X				X			X	X
Serum Iron Profile [g]	X	X		X		X				X			X											X	X
Iron/TIBC (TSAT)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis [i]	X			X		X				X			X											X	X
Coagulation parameters [g]	X			X						X			X											X	X
Serum Pregnancy Test [j]	X																								
Serum Erythropoietin	X																								
Serum Virology [g]	X																								

Assessments	Screen	Primary treatment period												Extension treatment period											Safety follow-up visit
Study Day/Week(s):	D-42 to -1	W1D1 [b]	W2 D1 (±3 D)	W4 D1 (±3 D)	W6 D1 (±3 D)	W8 D1 (±3 D)	W10 D1 (±3 D)	W12 D1 (±3 D)	W14 D1 (±3 D)	W16 D1 (±3 D)	W20 D1 (±3 D)	W22 D1 (±3 D)	W24 D1 (±3 D)	W26 D1 (±3 D)	W28 D1 (±3 D)	W30 D1 (±3 D)	W32 D1 (±3 D)	W34 D1 (±3 D)	W36 D1 (±3 D)	W38 D1 (±3 D)	W40 D1 (±3 D)	W42 D1 (±3 D)	W44 D1 (±3 D)	W46 D1 (±3 D)	W48 D1 (±3 D)	W52 D1 (±3 D)
Transfusion Data Collection and Assessment		Assess and record on ongoing basis until end of treatment visit or 8 weeks after last dose of etavopivat, whichever comes first. Clinical staff should confirm if any transfusions were received by the patient (including any at outside local institutions in between study visits).																							
PROMIS Fatigue Scale	X	X		X		X		X		X	X		X				X				X				X	X
The QUALMS	X	X		X		X		X		X	X		X				X				X				X	X
MDS Baseline Assessment (IPSS-R) [k]	X																									
MDS Response Assessment [l]										X			X m												X	X
Exploratory Studies [n]	X	X		X						X	X		X				X				X				X	
PD Sampling [o]		X	X	X																					X	X
PK Sampling [p]		X	X	X									X												X	
Study Drug Administration		X	Daily throughout treatment period																							
Survival [q]			Q 3 months after End of Trial visit																							

Abbreviations: BMI = body mass index; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; ECG = electrocardiogram; ESA = Erythropoiesis-stimulating agent; Hb = hemoglobin; ICF = informed consent form; IPSS-R = International Prognostic Scoring System-Revised; MDS = myelodysplastic syndromes; PK/PD = pharmacokinetics/pharmacodynamics; PROMIS = Patient-Reported Outcomes Measurement Information System; RBC = red blood cell; The QUALMS = The Quality of Life in Myelodysplasia Scale; W = week.

Note: Study visits after W1D1 must be conducted within ± 3 days of the scheduled visit. For the purposes of assessments and analyses in this study, 4 weeks = 1 month.

a. Informed consent must be obtained before any study-specific procedures are performed. The date of informed consent and W1D1 of study treatment may be a maximum of 56 days apart. The screening period (up to 42 days prior to W1D1 of treatment) starts only after informed consent is obtained AND a study-specific procedure is performed.
b. W1D1 assessments should be performed prior to study drug administration and may be performed up to 3 days prior (Day -3 to Day -1).
c. Patients who prematurely discontinue the study during the Primary or Extension Treatment Periods should complete the End of Treatment visit (W48D1) and a Safety Follow-up visit approximately 28 days after last dose of etavopivat (see Table 1-2).
d. Recommend vital signs (blood pressure [BP] and heart rate [HR]) to be measured after a patient has rested for at least 5 minutes in the supine or recumbent position. A repeated measurement of HR and BP can be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.
e. Electrocardiograms (ECGs) (12-lead) should be recorded in triplicate. See Section 8.3.8 for detailed instructions on performing the ECGs.
f. Adverse events are reported as described in Section 8.7.5.
g. Assessments of iron profile (ferritin, transferrin (TIBC) and iron level) will be performed locally and will include the tests listed in Appendix E (as applicable).

h. Hematology assessments listed in Appendix E, may be performed as outpatient/non-study center.
i. Urinalysis will be performed locally and will include assessment for color and appearance and dipstick analysis for the tests listed in Appendix E.
j. Serum pregnancy test will be performed locally at Screening, and a urine pregnancy test may be performed if there is any suspicion of pregnancy during the study, for all female patients of child-bearing potential (see Section 6.8.1). If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test.
k. MDS baseline assessment during Screening to confirm IPSS-R category and study entry criteria requires bone marrow aspirate (BMA) samples for cytomorphology and cytogenetics and peripheral blood analysis. If a screening BMA cannot be obtained, bone marrow biopsy (BMB) may need to be performed. Local analysis will be used for study entry criteria review and treatment initiation. BMA screening samples (and where indicated, with results from local analysis) will be sent to central laboratories for confirmation of study entry criteria (see Section 8.1.6).
l. MDS response assessment includes BMA for cytomorphology and cytogenetics, and assessment of hematologic improvement.
m. Hematologic improvement assessment only to be performed at the W24D1 visit as no BMA samples for cytomorphology or cytogenetics at W24D1 are required (unless clinically indicated).
n. Serum for exploratory studies will be collected during Screening, pre-dose at W1D1, W4D1, W16D1, W20D1, W24D1, W32D1, W40D1, and W48D1. Fresh BMA samples, BMA smears, and peripheral blood smears for exploratory studies will be collected at Screening, W16D1, and W48D1.
o. PD samples will be collected pre-dose on W1D1, W2D1, W4D1, W48D1 and W52D1.
p. PK samples will be collected as follows:
    1. W1D1 and W4D1: Pre-dose (within 1 hour prior to dose), 1 hour (±5 minutes), 2 hours (±15 minutes), 4 hours (±30 minutes), and 6 hours (±30 minutes) post-dose
    2. W2D1 and W48D1: Pre-dose (within 1 hour prior to dose), 1 hour (±5 minutes), and 2 hours (±15 minutes) post-dose
    Note: If the scheduled time for a PK/PD sample coincides with a safety ECG, the safety ECG should be performed prior to the PK/PD sample collection.
q. After a patient discontinues study treatment and has completed their last study treatment visit, the study site may contact the patient approximately every 3 months to collect survival data.

Table 1-2 Schedule of Events – Optional Prolonged Treatment Period

Optional Prolonged treatment period[a]	
Assessments	**Timeframe**
Physical Examination (symptom directed)	Q 2 Months (±2 weeks)
Weight and BMI	Q 2 Months (±2 weeks)
ECOG PS	Q 2 Months (±2 weeks)
Vital Signs (including temp) [b]	Q 2 Months (±2 weeks)
ECG [c]	Q 2 Months (±2 weeks)
Adverse Events [d]	Recorded Throughout
Concomitant Medications	Recorded Throughout
Hematology [e]	Q 1 Month (±1 week)
Serum Chemistry [e]	Q 2 Months (±2 weeks)
Serum Iron Profile [e]	Q 6 Months (±4 weeks)
Urinalysis [f]	Q 6 Months (±4 weeks)
Coagulation parameters [e]	Q 6 Months (±4 weeks)
Urine Pregnancy Test [g]	Q 2 Months (±2 weeks)
Transfusion Data Collection and Assessment [h]	Ongoing
PROMIS Fatigue Scale	Q 6 Months (±4 weeks)
The QUALMS	Q 6 Months (±4 weeks)
BMA	Q 12 Months (±4 weeks), and or earlier if clinically indicated
Hematologic Improvement	Q 6 Months (±4 weeks)
Exploratory studies	Q 6 Months (±4 weeks)
Study Drug Administration	Daily during treatment period
Survival [j]	Q 3 months (±4 weeks)

Abbreviations: BMI = body mass index; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; ECG = electrocardiogram; Hb = hemoglobin; HR = heart rate; MDS = myelodysplastic syndromes; PD = pharmacodynamics; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; Q = every; RBC = red blood cell; The QUALMS = The Quality of Life in Myelodysplasia Scale; Wks = weeks.

Note: Study visits must be conducted within ± 2 weeks for Q 2 months assessments and ±1 month for the yearly BMA assessment. For the purposes of assessments and analyses in this study, 4 weeks = 1 month.

a. Patients who demonstrate clinical benefit at 48 weeks of treatment, based on their MDS Response Assessment, may continue treatment until the patient experiences unacceptable toxicities, disease progression, withdraws consent, or meets any other discontinuation criteria (Section 7.2.1).

b. Vital signs should be measured after a patient has rested for at least 5 minutes in the supine or recumbent position. A repeated measurement of HR and BP should be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.
c. ECG (12-lead) should be recorded in triplicate after a patient has rested for at least 5 minutes in the supine position, with the three ECGs collected within about a five-minute window. If the scheduled time for a safety ECG coincides with a blood collection, the safety ECG should be performed prior to the blood collection. The same timing for obtaining safety ECGs (ie, prior to blood collection) should be used for all safety ECG measurements. If the ECG cannot be performed prior to blood collection, the ECG should be done after a sufficient rest period of at least 15 minutes to minimize interference with ECG measurements.
d. Adverse events are reported as described in Section 8.7.5.
e. Assessments will be performed locally and will include the tests listed in Appendix E (as applicable).
f. Urinalysis will be performed locally and will include assessment for color and appearance and dipstick analysis for the tests listed in Appendix E. Microscopic analysis performed as clinically indicated.
g. Serum pregnancy test will be performed locally during Screening, and a urine pregnancy test may be performed if there is any suspicion of pregnancy during the study, for all female patients of childbearing potential.
h. Assess and record on ongoing basis until the end of treatment visit or 8 weeks after last dose of etavopivat, whichever comes first. Clinical staff should confirm if any transfusions were received by the patient (including any at outside local institutions in between study visits).
i. PD samples will be collected at the end of treatment visit.
Note: If the scheduled time for a PK sample coincides with a safety ECG, the safety ECG should be performed prior to the PK sample collection.
j. After a patient discontinues study treatment and has completed their last study treatment visit, the study site will contact the patient approximately every 3 months to collect survival data.

2.0 INTRODUCTION

2.1 Study Rationale

Etavopivat (FT-4202) is a potent, selective, orally bioavailable, small-molecule activator of pyruvate kinase-red blood cell (PKR) being developed by Forma Therapeutics, Inc. and is intended for use as a treatment for the anemia of myelodysplastic syndromes (MDS), inherited hemolytic anemias, and other refractory anemias.

In patients with very low risk, low risk, or intermediate risk MDS, the clinical hypothesis is that PKR activation will increase hemoglobin levels and/or reduce transfusion burden.

2.2 Background

Myelodysplastic syndromes are a heterogeneous group of clonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis that manifests as anemia, neutropenia and/or thrombocytopenia of variable severity. These often result in red blood cell (RBC)-transfusion dependent anemia, increased risk of infection, and/or hemorrhage, as well as the potential to progress to acute myeloid leukemia (AML) (Fenaux et al. 2013; Ades et al. 2014). Patients with MDS can be categorized into 1 of 5 risk groups according to the International Prognostic Scoring System-Revised (IPSS-R) (ie, very low, low, intermediate, high, and very high) based on bone marrow cytogenetics, bone marrow blast percentage and peripheral blood cytopenias (Greenberg et al. 2012). From this risk classification, a population of patients with anemia as the predominant cytopenia can be identified with a lower rate of AML progression and longer survival. Anemia within this population can range in severity from mild (asymptomatic) to severe, requiring regular RBC transfusion support. Of the approximately 80-90% of patients with MDS who develop anemia, 40% become transfusion dependent (Zeidan et al. 2013).

Lower hemoglobin (Hb) levels and RBC transfusion dependence are associated with poor cardiovascular outcomes and increased mortality in patients with MDS (Platzbecker et al. 2019; Zeidan et al. 2013). Long-term RBC transfusion dependence also has significant clinical impact including iron overload and its associated complications and potentially negative impact on health-related quality of life (Fenaux et al. 2019). A therapeutic option that would raise hemoglobin levels and/or achieve transfusion independence or reduced transfusion burden in patients with MDS for a sustained period of time is an important unmet medical need.

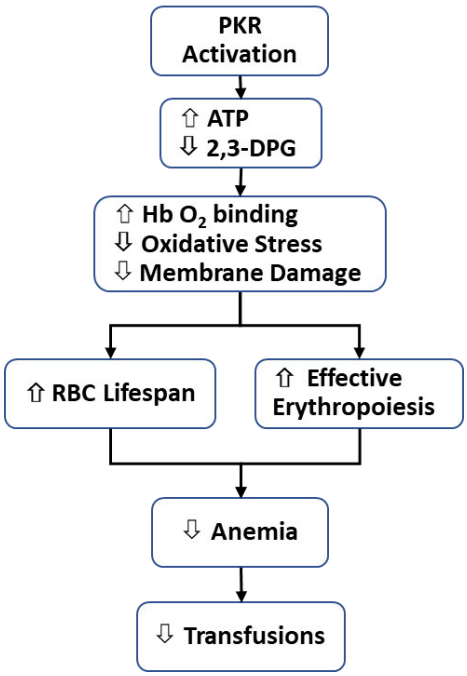
Pyruvate kinase-red blood cell is a key enzyme in glycolysis and production of adenosine triphosphate (ATP) (Zanella et al. 2005). Adenosine triphosphate has been shown to support overall RBC membrane integrity and stress resilience (Betz et al. 2009). Increased ATP may thus decrease hemolysis and extend RBC lifespan. ATP also supports elimination of reactive oxygen species (ROS) which damage RBCs and impairs their functionality, and reduces vascular adhesion associated with membrane injuries (Banerjee et al. 2004). This increase in ATP based on direct effects of PKR activation is accompanied by a decrease in 2,3-diphosphoglycerate (2,3-DPG), a metabolic intermediate that regulates the affinity of hemoglobin for oxygen. Decreased 2,3-DPG results in increased affinity of hemoglobin for oxygen (Macdonald 1977; Kalfa et al. 2019; Estepp et al. 2020). Increased oxygen affinity may reduce the premature release of oxygen reducing the generation of ROS within the RBC.

PKR is expressed early in the hematopoietic stem cell differentiation into the erythroid progenitor lineage, leading to the observation that metabolic abnormalities or stress early in erythroid progenitor development may alter the differentiation of erythroid progenitors into mature RBCs

(Kim et al. 2005). Studies in murine models of PKR deficiency and β-thalassemia have linked the role of glucose metabolism to apoptosis (Mathias et al. 2000; Lang et al. 2002; Aizawa et al. 2005). The addition of a PKR-activator improves the anemia and the ineffective erythropoiesis observed in the bone marrow of β-thalassemic mice, suggesting the pathogenesis of the anemia of β-thalassemia is not only due to hemolysis but also ineffective erythropoiesis (Matte et al. 2021). These observations have been demonstrated clinically where a PKR activator has improved the anemia of patients with pyruvate-kinase deficiency and thalassemia (Grace et al. 2019; Kuo et al. 2021).

In patients with MDS, the clinical hypothesis is that the ineffective erythropoiesis associated with MDS may be in part due to insufficient glycolysis/glucose metabolism leading to increased erythroid lineage apoptosis. The addition of etavopivat may improve the energy status (ATP) and decrease apoptotic signaling, leading to improved RBC differentiation/development and decreased anemia (increased Hb). Moreover, increased ATP levels in the mature RBC may improve the health of the RBC, prolonging survival of both the autologous RBC and the donor RBC in MDS patients receiving RBC transfusions for anemia resulting in a decrease in the transfusion requirements (Figure 1).

Figure 1: PKR Activation as a Strategy to Reduce the Anemia Associated with Myelodysplastic Syndrome



2,3-DPG = 2,3-diphosphoglycerate; ATP = adenosine triphosphate; Hb = hemoglobin; PKR = pyruvate kinase-red blood cell; RBC = red blood cell.

2.3 Risk/Benefit Assessment

Etavopivat is a potent, selective, orally bioavailable PKR activator with a wide therapeutic margin relative to preclinical toxicity. Clinical studies in healthy volunteers and patients with SCD continues to support an acceptable safety profile for continuous dosing in patients with hemolytic anemias. Exposures that are well tolerated, result in maximum pharmacodynamic (PD) effects of increased ATP with a concomitant reduction in 2,3-DPG that have translated into improved RBC in RBC health and function in healthy and SCD RBCs (Forsyth et al. 2022; Schroeder et al. 2022).

Ongoing studies in patients with SCD continue to support these initial findings and are supportive for expanding these studies into MDS. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of etavopivat may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

A First-in-Human (FIH) clinical study (Protocol 4202-HVS-101) entitled "*A Randomized, Placebo-controlled, Double Blind, Single Ascending and Multiple Ascending Dose Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of FT-4202 in Adult Healthy Volunteers and Sickle Cell Disease Patients*" is currently on-going. As of 22-November-2021, a total of 90 healthy subjects had been enrolled in the study, including 32 subjects in the single ascending dose (SAD) cohorts, 48 subjects in the multiple ascending dose (MAD) cohorts, and 10 subjects in the food effect cohort. In addition, 42 patients with SCD had been enrolled into the SCD cohorts, including 7 patients in the SAD cohort, 10 patients in the SCD MAD-1 cohort (etavopivat [300 mg] or placebo once daily [QD] × 14 days), 10 patients in the SCD MAD-2 cohort (etavopivat [600 mg] or placebo QD × 14 days), and 15 patients in the 12-week open-label cohort (etavopivat [400 mg]).

For the healthy subject cohorts, the most common treatment-emergent adverse event (TEAE) was headache, which was reported in 10 (27.8%) subjects receiving 2-weeks of etavopivat and 2 (16.7%) subjects receiving 2-weeks of placebo. For headache TEAEs, there was no apparent relationship between daily etavopivat exposure and incidence. No treatment-emergent serious adverse events (TESAEs) were reported and there were no TEAEs that led to dose reduction/interruption or discontinuation of study drug.

For the SCD cohorts, as of 22-November-2021, 3 TEAEs (arthralgia, headache, and palpitations) were reported in 2 (40%) patients who received a single dose (700 mg) of etavopivat and 3 TEAEs (back pain, myalgia, and pruritus) were reported in 2 (100%) patients receiving placebo. For patients with SCD receiving 2-weeks of etavopivat, the TEAEs reported in > 1 patient were sickle cell anemia with crisis (n=6 [37.5%]), headache (n=4 [25.0%]), nausea (n=3 [18.8%]), and vomiting (n=2 [12.5%]). No TESAEs were reported for the SCD SAD cohort; 1 (12.5%) patient in the MAD-2 cohort was reported with a TESAE of unrelated Grade 3 sickle cell anemia with crisis. There were no TEAEs that led to dose reduction/interruption or discontinuation of study drug for the SCD SAD or MAD cohorts.

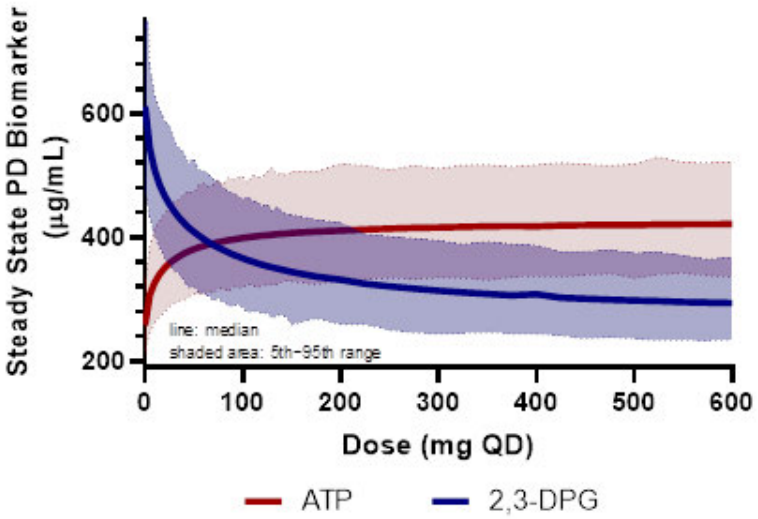
In adult and adolescent patients with SCD (n=15) receiving 400 mg etavopivat QD for 12 weeks in the open-label portion of Study 4202-HVS-101, etavopivat was well tolerated (Brown et al. 2021b). In the 12-week cohort, the TEAEs reported in > 1 patient were sickle cell anemia with crisis (n=7 [46.7%]), headache (n=4 [26.7%]), and dizziness, nausea, and upper respiratory tract infection (n=2 [13.3%] for each). TESAEs were reported in 5 (33.3%) patients in the 12-week open-label cohort (2 patients with events of unrelated Grade 3 sickle cell anemia with crisis and single-patient events of acute chest syndrome [unrelated Grade 3], corona virus infection [unrelated Grade 3], deep vein thrombosis [DVT; possibly related Grade 3], non-cardiac chest pain [unrelated Grade 3], and syncope [unrelated Grade 3]). The DVT event led to discontinuation of study drug.

These preliminary human data are supported by nonclinical toxicity studies in rats and monkeys with up to 9 months of etavopivat dosing (see the Investigator's Brochure for additional details).

2.3.2 Benefit Assessment

In the FIH clinical study 4202-HVS-101, etavopivat exposure resulted in sustained reductions in 2,3-DPG levels and sustained increases in ATP levels in the RBCs of healthy subjects. Additionally, increased Hb oxygen affinity (decreased P_{50} [partial pressure of oxygen (O_2) at which Hb O_2 saturation of 50% is achieved]) was observed at all doses, correlating with the observed reductions in 2,3-DPG (Kalfa et al. 2019). Based on a dose-exposure-response analysis performed utilizing the pharmacokinetic (PK)/ PD results from the healthy volunteer studies, maximal PKR activation is anticipated at a dose ≥ 400 mg QD (maximum and sustained ATP and 2,3-DPG effects are predicted at dose levels ≥ 150 mg daily and ≥ 400 mg daily, respectively, Figure 2).

Figure 2: Healthy Volunteers PK/PD Simulations Identifies Potential Phase 2 Dose Selections



ATP = adenosine triphosphate; 2,3-DPG = 2,3-diphosphoglycerate; PD = pharmacodynamic; PK = pharmacokinetic QD = once daily.

In the FIH clinical study 4202-HVS-101, a single dose of 700 mg of etavopivat has been evaluated in patients with SCD (n=7 [Estepp et al. 2020]). Etavopivat demonstrated similar PK in both healthy volunteers and patients with SCD. In the sickle RBC's, 24 hours after 700 mg of etavopivat, ATP blood concentrations increased by 30% and 2,3-DPG blood concentrations decreased by 26%. Increased O_2 affinity (decreased P_{50}) with a decreased point of sickling and an improved sickle RBC deformability were observed in all etavopivat-treated patients. Improved sickle RBC membrane function, as demonstrated by Lorrca® Osmoscan was also noted. Improved hematologic parameters (~0.9 mg/dL Hb increase compared to placebo controls) were also observed.

Doses of 300 mg and 600 mg etavopivat QD for 14 days were evaluated in patients with SCD, with overlapping PD activity and biologic effects observed across doses (Brown et al. 2020; Brown et al. 2021a; Brown et al. 2021b). Notably, despite the increased exposure observed with etavopivat 600 mg QD vs. 300 mg QD, PD responses (decreased 2,3-DPG and increased ATP) were comparable across the two 14-day SCD cohorts confirming prior studies in healthy RBCs predicting that etavopivat doses ≥ 400 mg QD would provide maximum PD activity (Brown et al. 2021a; Brown et al. 2021b).

In adult and adolescent patients with SCD receiving 400 mg etavopivat QD for 12 weeks in the open-label portion of Study 4202-HVS-101, Hb increases > 1 g/dL were observed in 11/15 (73%)

patients with a mean (range) response of 1.5 (0.75-2.35) g/dL (Brown et al. 2021b). Notably, these Hb responses were sustained throughout the 12-week treatment period. Similar to results for the 2-week cohorts, significant and sustained decreases in absolute reticulocytes, indirect bilirubin, and lactate dehydrogenase (LDH) were noted by 2 weeks, with sustained responses throughout the 12-week treatment period. Importantly, improved sickle RBC functions associated with metabolic health, adhesion, and vaso-occlusion were observed after 2 weeks of etavopivat treatment, with evidence that these improvements in RBC functional health may persist for several weeks after treatment discontinuation.

Based on these initial findings, the dose level of 400 mg QD selected for evaluation in patients with very low, low, or intermediate-risk-MDS.

2.3.3 Overall Benefit: Risk Conclusion

In Study 4202-HVS-101, reductions in 2,3-DPG and increases in ATP levels in RBCs of healthy volunteers and patients with SCD confirm PKR activation by etavopivat. Increased Hb O_2 affinity in RBCs from healthy volunteers and patients with SCD demonstrates proof of mechanism consistent with observations from preclinical studies. Additionally, increased Hb levels along with marked reduction of absolute reticulocytes, indirect bilirubin and LDH in SCD patients receiving 400 mg etavopivat daily provide proof of concept that a PKR activator can improve the anemia associated with SCD. These data, together with the available safety data from Study 4202-HVS-101 (see the Investigator's Brochure for additional details), support further clinical development of etavopivat and suggest that patients with MDS enrolled in this study have the potential to benefit from treatment with etavopivat.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoints

Objective	Endpoints
• To assess hematologic improvement based on an erythroid response (HI-E) for ≥ 8 weeks duration in patients with MDS within 24 weeks of etavopivat treatment	• The HI-E for ≥ 8 weeks within 24 weeks of etavopivat This endpoint will be based on the combined incidence of: ○ Non-transfusion dependent (NTD) patients: ≥ 1.5 g/dL increase in Hb from baseline maintained ≥ 8 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period ○ Low transfusion burden (LTB) patients: absence of any transfusion for ≥ 8 consecutive weeks ○ High transfusion burden (HTB) patients: reduction by ≥ 50% of red blood cell (RBC) units for ≥ 8 consecutive weeks

3.2 Secondary Objectives and Endpoints

Objectives	Endpoints
• To assess for HI-E for ≥ 8 weeks duration in this population of patients within 16 and 48 weeks of etavopivat treatment	• The HI-E for ≥ 8 weeks within 16 and 48 weeks of etavopivat This endpoint will be based on the combined incidence of: ○ NTD patients: ≥ 1.5 g/dL increase in Hb from baseline maintained ≥ 8 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period ○ LTB patients: absence of any transfusion for ≥ 8 consecutive weeks ○ HTB patients: reduction by ≥ 50% of RBC units for ≥ 8 consecutive weeks
• To assess HI-E for ≥ 16 weeks duration in this population of patients within 24 and 48 weeks of etavopivat treatment	• The HI-E for ≥ 16 weeks within 24 and 48 weeks of etavopivat This endpoint will be based on the combined incidence of: ○ NTD patients: ≥ 1.5 g/dL increase in Hb from baseline maintained ≥ 16 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period ○ LTB patients: absence of any transfusion for ≥ 16 consecutive weeks ○ HTB patients: reduction by ≥ 50% of RBC units for ≥ 16 consecutive weeks
• To assess the safety and tolerability of etavopivat in patients with MDS	• Incidence of AEs, serious adverse events (SAEs), and AEs related to etavopivat • Number of premature discontinuations, dose interruptions, and dose reductions
• To assess additional measures demonstrating potential clinical benefit	• Overall response rate (2006 International Working Group [IWG] Criteria) (see Appendix A) • Duration of response (2006 IWG Criteria) • Reduction in RBC transfusions and rate of RBC transfusion independence ≥ 8 weeks in patients with LTB or HTB at study entry • Increase in neutrophils and/or platelets counts • Decrease in ferritin and transferrin saturation (TSAT) • Decrease in iron chelation therapy • Overall survival

3.3 Pharmacokinetic / Pharmacodynamic Objective and Endpoints

Objective	Endpoints
• To assess the PK and PD properties of etavopivat in patients with MDS	• Etavopivat plasma PK parameters (including but not limited to): maximum observed plasma concentration, time to maximum observed plasma concentration, area under the plasma concentration-time curve from time zero until the last quantifiable time point ($AUC_{0\text{-last}}$), from time zero to infinity ($AUC_{0\text{-inf}}$), for a dosing interval (AUC_{tau}/$AUC_{0\text{-24}}$). • RBC 2,3-DPG and ATP levels over time

3.4 Exploratory Objectives and Endpoints

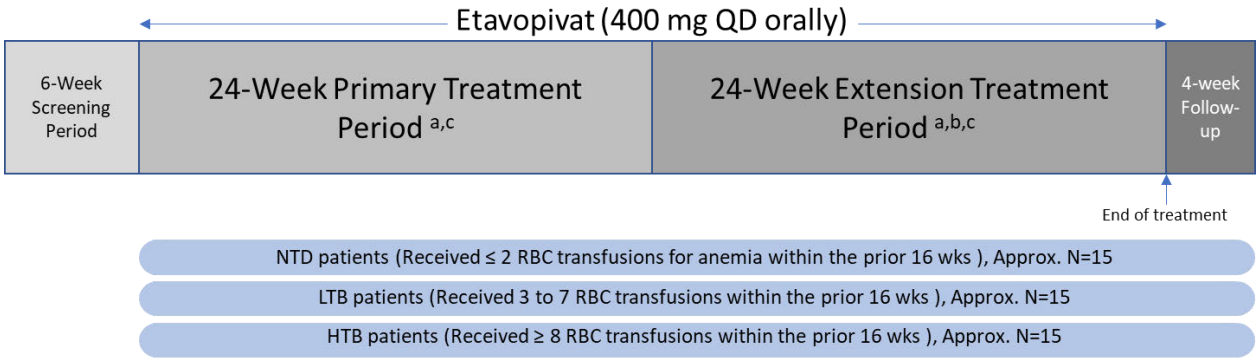
Objectives	Endpoints
• To examine safety trends in patients with MDS receiving etavopivat	• Assessment of vital signs, clinical laboratory findings, and physical examination findings
• To assess changes in quality-of-life in patients with MDS taking etavopivat	• Change from baseline in Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Scale at Weeks 16, 24, and 48 • Change from baseline in The Quality of Life in Myelodysplasia Scale (QUALMS) patient-reported outcome assessment at Weeks 16, 24, and 48
• To characterize the biological effects of etavopivat treatment in patients with MDS	• Cell colony analysis of bone marrow progenitors • Cytomorphology (blast, M/E, and ringed sideroblast determination) and cytogenetics of bone marrow • Markers of ineffective erythropoiesis and iron metabolism • Cancer-associated mutations and/or genetic alterations in responding and non-responding patients • Flow cytometry analysis of terminal erythroid differentiation (EU Only)

4.0 STUDY DESIGN

4.1 Overall Design

This study is a multicenter, open-label Phase 2 study in adult patients with very low, low risk or intermediate risk MDS per the IPSS-R classification (see Appendix B). The study will enroll approximately 45 patients (see Figure 3).

Figure 3: Schema



NTD – Not transfusion dependent; LTB – Low transfusion burden; HTB – High transfusion burden

a. Patients who permanently discontinue treatment during the 48-weeks of treatment should complete both the End of Treatment visit (W48) and the Safety Follow-up visit (W52)
b. Patients who demonstrate clinical benefit at 48 weeks of treatment, based on their MDS response assessment, may continue treatment in an optional Prolonged Treatment Period until the patient experiences unacceptable toxicities, disease progreassion, withdraws consent or meets any of the discontinuation criteria.
c. After permanent discontinuation of treatment, study site may contact the patient approximately every 3 months for survival data.

Initially, 6 patients will be enrolled and dosed a minimum of 4-weeks with etavopivat 400 mg daily to confirm if safety, exposure, and pharmacological response (PK/PD profile) are consistent with prior experience of etavopivat dosing in healthy volunteers and patients with SCD or thalassemia.

Approximately 45 MDS patients (inclusive of the initial 6 patients enrolled for safety/PK/PD confirmation) will be enrolled and evaluated for an erythroid response based on the revised MDS IWG 2018 criteria (see Appendix A). Response assessment will be based on the individual patient's transfusion history in the 16 weeks prior to enrollment:

- NTD patients (received ≤ 2 RBC units for anemia within the prior 16 weeks): Hb increase of ≥ 1.5 g/dL over a continuous 8-week treatment period and no transfusion of RBC units for anemia over a continuous 8-week treatment period
    - Approximately 15 NTD patients may be enrolled in this study
- LTB patients (received 3 to 7 RBC units within the prior 16 weeks): No transfusion of RBC units for anemia over a continuous 8-week treatment period
    - Approximately 15 LTB patients may be enrolled in this study
- HTB patients (received ≥ 8 RBC units in the prior 16 weeks): ≥ 50% reduction in RBC units transfused over a continuous 8-week period.
    - Approximately 15 HTB patients may be enrolled in this study

A futility assessment will be triggered when 15 patients across all strata or 8 patients in a single stratum reach 24 weeks of treatment, whichever occurs first. If both criteria are met at the same time, the overall futility assessment will be performed.

The futility criterion is defined as follows:

- All strata (n=15): ≤ 3 responses meeting HI-E criteria, sustained from Week 16 to Week 24
- Single stratum (n=8): 0 (zero) responses

If either the overall or single stratum futility criterion is met, enrollment may discontinue for futility or further enrollment restricted to specific subsets of patients based on prior transfusion history may be considered. If neither criterion is met, enrollment will continue until a total of 45 response-evaluable patients are available at Week 24.

Enrollment will not pause during assessment periods unless futility analysis suggests clinical need to pause.

Patients will be enrolled into a 48-week treatment period, followed by a 28-day off-drug period. A safety follow-up visit occurs at the End of the Study (W52D1).

Patients demonstrating clinical benefit at the end of the planned 48-week treatment period may be offered the opportunity to remain on treatment and enter the Optional Prolonged treatment period. Patients who enter the Optional Prolonged treatment period will follow the Schedule of Events outlined in Table 1-2. Patients who permanently discontinue treatment during the Optional Prolonged treatment period should attend a safety follow-up visit no sooner than 28 days after their last dose of etavopivat.

Novo Nordisk will perform ongoing safety surveillance. Safety surveillance activities encompass the regular periodic safety data review from clinical trials, literature surveillance and safety information derived from other sources.

If new safety signals are identified, these will be evaluated by the etavopivat internal safety committee.

4.2 Justification for Dose

Dose selection for this study was based on an integrated evaluation of available etavopivat safety, PK, and PD data in healthy subjects and patients diagnosed with SCD following QD dosing for up to 84 consecutive days (see also Section 2.3.1 and Section 2.3.2).

Evidence of pharmacological activity, consistent with the expected PD effects of PKR activation, was demonstrated following a single dose and repeated dosing of etavopivat in healthy subjects and patients with SCD. Based on a dose-exposure-response analysis, maximal PKR activation is anticipated at a dose ≥ 400 mg QD. Overlapping PD activity and biologic effects were observed at doses of 300 mg and 600 mg QD for 14 days in patients with SCD and no dose-limiting toxicities (DLTs) were reported. Taken together, dose selection of 400 mg QD enables further evaluation of the dose that is expected to safely offer benefit (see also Section 2.3.2).

4.3 Treatment and Study Duration

4.3.1 Treatment Duration

Duration of study treatment will be 48 weeks, including 24 weeks in the Primary Treatment period, and 24 weeks in the Extension Treatment period.

Duration of study for an individual patient may last up to 58 weeks and includes a Screening Period (up to 6 weeks before study treatment), the treatment period of the study for up to 48 weeks, and a Safety Follow-up visit at 28 days (+ 7 days) after last dose of study drug. Study duration in patients who continue etavopivat treatment due to clinical benefit will be > 58 weeks.

4.3.2 End of Study Definition

The study will end when the last patient's last visit of the extension treatment period occurs, approximately 52 weeks after the last patient is enrolled in the efficacy portion of the study. The study will stop when all patients who enter the optional prolonged treatment period complete a safety follow-up visit or discontinue study participation.

For the purposes of the primary analysis, a patient is considered to have completed the study if he/she has completed 48 weeks of treatment, and either attended the safety follow-up visit at W52 or entered the optional prolonged treatment period.

4.4 Safety Committees Structure

4.4.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. Safety surveillance activities encompass the regular periodic safety data review from clinical trials, literature surveillance and safety information derived from other sources.

If new safety signals are identified, these will be evaluated by the etavopivat internal safety committee.

The safety committee is cross-functional and the only Novo Nordisk body responsible for providing integrated assessments of safety data and endorsing appropriate actions in case of a safety signal.

Subsequently, safety information is communicated and reported to health authorities, ethics committees and investigators, as relevant and in accordance with regulatory requirements.

4.4.2 Study Safety Review Committee

A safety review via Study SRC, consisting of, at a minimum, members of the clinical study team (including Medical Lead), pharmacovigilance, and Principal Investigators participating from at least 2 study sites, will occur within 4 weeks of the following:

- After the 6th patient completes a minimum of 4-weeks of daily etavopivat treatment, to confirm that the safety and PK/PD profile of 400 mg QD etavopivat continues to support enrollment and dosing of etavopivat.

4.5 Dose-Limiting Toxicities Evaluation Period/Definition

Dose-limiting toxicities (DLTs) will be evaluated during the first 28 days of treatment using NCI-CTCAE v5.0.

DLTs are determined by the Investigator and include any of the following AEs that are considered related to etavopivat (ie, all AEs of the specified grades except those that are clearly and incontrovertibly due to underlying malignancy or extraneous causes, eg, intercurrent illness or concomitant medication):

- **Non-Hematologic Toxicity**
  - ≥ Grade 3 toxicity with the following exceptions: (1) nausea, vomiting, diarrhea lasting < 72 hours (with optimal medical management and other supportive care); (2) fatigue lasting < 1 week
  - Clinically relevant (requiring treatment or with potential clinical sequelae) ≥ Grade 3 non-hematologic laboratory finding. This includes:
    - ≥ Grade 3 electrolyte abnormality that lasts > 72 hours despite adequate management, unless the patient has clinical symptoms, in which case all Grade ≥ 3 electrolyte abnormality regardless of duration should count as a DLT.
    - Note: Grade ≥ 3 amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT
  - Hy's law as defined by aspartate aminotransferase or alanine aminotransferase (ALT) > 3 × ULN and total bilirubin > 2 × ULN with alkaline phosphatase < 2 × ULN in the absence of a clear alternative explanation
  - Inability to tolerate/receive a minimum of 75% of etavopivat scheduled doses during first 28 days of treatment due to an AE of any grade that is considered related to etavopivat, unrelated to underlying malignancy or intercurrent illness, and unrelated to a concomitant medication
- **Any death not clearly due to the underlying disease or extraneous causes**
- **Hematologic Toxicity**
  - Grade 4 thrombocytopenia for > 7 days
  - Grade 3 thrombocytopenia with bleeding
  - Grade 4 neutropenia lasting for > 7 days
  - Febrile neutropenia / neutropenic fever

5.0 STUDY POPULATION

This study will enroll approximately 45 total adult patients with MDS.

The inclusion and exclusion criteria are detailed below; the Sponsor of this clinical investigation, Forma Therapeutics, Inc., does not grant waivers of inclusion or exclusion criteria.

5.1 Inclusion Criteria

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

Informed Consent

1. Patient has provided documented informed consent; the informed consent form (ICF) must be reviewed and signed by each patient prior to any study-related assessments/procedures being conducted.

Age

2. Age ≥ 18 years at time of first dose

Sex and Contraceptive/Barrier Requirements

3. Patients, if female and of childbearing potential, must agree to use acceptable methods of contraception and agree not to donate ova from study start to 90 days after the last dose of study drug, and who if male are willing to use acceptable methods of contraception and agree not to donate sperm, from study start to 90 days after the last dose of study drug.

Disease Specific Requirements

4. Documented diagnosis of idiopathic/*de novo* MDS according to 2016 WHO classification (see Appendix C) that meets IPSS-R classification (see Appendix B) of very low, low, or intermediate risk disease, and:
   - < 5% blasts and no Auer rods in bone marrow based on local pathology review
   - < Intermediate risk cytogenetic abnormalities per IPSS-R
5. Anemia defined as:
   - NTD: Subjects with mean Hb concentration < 10.0 g/dL on 2 measurements (1 performed within 3 days prior to W1D1 and the other performed 7 to 28 days prior to W1D1, not influenced by RBC transfusion within 7 days of measurement) and < 3 RBC transfusions for anemia in the prior 16 weeks before W1D1 of etavopivat dosing

   OR

   - Transfusion Dependent: Subjects having received ≥ 3 units of RBCs for the treatment of anemia within 16 weeks prior to W1D1
6. Serum erythropoietin level > 200 U/L, OR, if ≤ 200 U/L, subject is non-responsive, refractory, or intolerant to erythropoiesis-stimulating agents, or erythropoiesis-stimulating agents are contraindicated or unavailable.
7. Eastern Cooperative Oncology Group performance status of ≤ 2 (see Appendix D)

8. Subject is non-responsive, refractory, or intolerant to luspatercept, or luspatercept is contraindicated or not indicated.
9. No alternative treatment options are available and/or appropriate for the subject, at the discretion of the investigator.
10. Patient is willing and able to adhere to the study visit schedule and other protocol requirements

5.2 Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria

MDS History

1. MDS associated with del 5q cytogenetic abnormality and known TP53 abnormality
2. Therapy-associated MDS (eg. t-MDS) that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases
3. Known history of AML
4. Any diagnosis of myelodysplastic/myeloproliferative neoplasms

Medical Conditions

5. Female who is breast feeding or pregnant
6. Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding
7. Absolute neutrophil count < 500/μL (0.5×10^9/L)
8. Platelet count < 50,000/μL (50×10^9/L) without transfusion within 14 days
9. Hepatic dysfunction characterized by:
    - ALT > 3.0 × ULN
    - Total bilirubin > 2.0 × ULN (in the absence of cholestasis, and > 3.0 ULN in patients with a diagnosis of Gilbert syndrome)
    - History and/or evidence of cirrhosis
10. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the local laboratory < 30 mL/min/1.73 m^2) or on chronic dialysis.
11. Patients with clinically significant and active bacterial, fungal, parasitic, or viral infection.
    - Patients with acute bacterial, fungal, parasitic, or viral infection requiring systemic therapy should delay Screening and enrollment until active therapy has been completed and the infection resolved
    - Patients with acute viral infections without available therapies (e.g., coronavirus disease 2019 [COVID-19]) should delay Screening and enrollment until the acute infection has resolved.

    Note: Infection prophylaxis is allowed (see concomitant medication restrictions).
12. Known human immunodeficiency virus (HIV) infection
13. Active infection with hepatitis B virus (hepatitis B surface antigen [HepBsAg] and hepatitis B core antibody [HepBcAb] positive)

14. Active hepatitis C infection
15. History of malignancy, other than MDS, requiring systemic chemotherapy and/or radiation beyond low-dose radiation of skin non-melanoma skin cancer.
    - Patients with malignancy considered surgically cured are eligible (eg, non-melanoma skin cancer, carcinoma in situ of the cervix, or carcinoma in situ of the breast)
    - Patients with incidental histologic findings of prostate cancer (T1a or T1b) are eligible
16. History of unstable or deteriorating cardiac or pulmonary disease within 180 days prior to consent including but not limited to the following:
    - Unstable angina pectoris or myocardial infarction or elective coronary intervention
    - Heart disease, heart failure as classified by the New York Heart Association classification 3 or higher, or significant arrhythmia requiring treatment,
    - Pulmonary fibrosis or pulmonary hypertension which are clinically significant ie, ≥ Grade 3 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (or higher)
17. Uncontrolled hypertension, defined as repeated elevation of diastolic blood pressure ≥ 100 mmHg despite adequate treatment
18. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).

Prior/Concomitant Therapy

19. Prior treatment with azacitidine (injectable or oral) or decitabine (injectable or oral)
20. Use of erythropoietin (ESA), other hematopoietic growth factor treatment or lenalidomide within 30 days of starting study treatment or anticipated need for such agents during the study. If patient has stage 3 or 4 chronic kidney disease (CKD) defined by 30 mL/min/1.73 m^2 ≤ eGFR <60 mL/min/1.73 m^2 and has been on a stable ESA dose for ≥6 months and plans to continue on ESA at the same dose throughout the duration of the study, patient is eligible.
21. Prior use of luspatercept:
    - NTD patients must not have received luspatercept within 30 days prior to W1D1 treatment
    - Transfusion-dependent (TD) patients must not have received luspatercept within 80 days prior to W1D1 treatment
22. Receiving or use of concomitant medications that are strong inducers of cytochrome P450 (CYP)3A4/5 (see Appendix F) within 14 days of starting study treatment or anticipated need for such agents during the study.
23. Prior allogeneic or autologous stem cell transplant or any organ transplant
24. Initiation of a new chelation therapy within 90 days before the first dose of study treatment

Prior/Concurrent Clinical Study Experience

25. Participated in another clinical trial of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another trial of an investigational agent (or medical device).

Other Exclusions

26. Medical, psychological, or behavioral conditions, which, in the opinion of the Investigator, may preclude safe participation, confound study interpretation, interfere with compliance, or preclude informed consent.

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

If the patient has failed the inclusion criteria or fulfilled one of the exclusion criteria related to lab values or pathology analysis, only one re-sampling of the relevant parameter within 2 weeks is allowed if the result is expected to fall within the timeframe limit. However, in case of technical issues (e.g. haemolysed or lost samples), resampling is allowed for the affected parameters or pathology samples. If a timeframe longer than 2 weeks is required for analysis, the patient must be re-screened; all screening assessments must be repeated (including laboratory parameters) and the patient must be reconsented. Screening bone marrow results may be used if the subject is reconsented within 90 days of the latest bone marrow procedure.

If the patient has failed any other inclusion criterion, or fulfilled any other exclusion criterion, resampling/rescreening is not allowed.

6.0 STUDY INTERVENTION, CONCOMITANT THERAPY, AND PRECAUTIONS

6.1 Clinical Trial Material

Intervention Name	Etavopivat
Type	drug
Dose Formulation	tablet
Unit Dose Strength	200 mg
Dosage Level	two tablets daily
Route of Administration	oral
Use	experimental
Sourcing	Sponsor
Appearance	film coated, oval-shaped tablets
Packaging and Labeling	blister pack

See the Study Pharmacy Manual for additional detail.

6.2 Preparation/ Handling/ Storage/ Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the research site and its designated pharmacy, the site's standard operating procedures (SOPs), and applicable regulations. Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug.

Upon receipt by the study site, the study drug will be promptly transferred to the appropriate environmentally controlled storage area. The research pharmacy staff will examine the shipment and temperature monitoring devices, if applicable, to verify that the study drugs were received in acceptable condition. Once inspected, the study drug will be stored in a secure area with access restricted to authorized research pharmacy staff, under physical conditions consistent with the investigational product's specific requirements.

The research site's pharmacist or delegate is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study, according to applicable regulations and the site's SOPs. All original containers, whether empty or containing study drug will be returned to the pharmacy. Study drug returned by study patients will be stored and disposed of according to the Sponsor's instructions. Contents of the study drug containers will not be combined. Unused study drug and study drug returned by the patients will be available for verification by the Sponsor's site monitor. See the Study Pharmacy Manual for additional detail, including reporting of Product Complaints.

6.3 Study Drug Administration

Etavopivat may be taken with or without food. Each dose should be taken with a glass of water. Subjects should be instructed to take their daily dose at approximately the same time each day except for dosing on in-clinic visiting days.

6.4 Study Intervention Compliance

Patients will be asked to return their unused study drug as well as their empty drug packets at each clinic visit. The study site will record the number of pills dispensed and the number returned at each visit, thereby assessing compliance.

6.5 Treatment of Overdose

For this study, any dose of etavopivat greater than the intended dose will be considered an overdose (see also Section 8.7.11). There is no known antidote for etavopivat. Should an overdose occur, the patient should be treated with appropriate supportive care based on medical judgment.

As described in Section 8.7.11, in the event of an overdose, the Investigator should:

- Monitor the patient for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose
- Complete the Special Situations Report form and fax/email to Novo Nordisk Global Safety within 24 hours of knowledge of the event (as outlined in Section 8.7.11)

6.6 Missed Dose

Subjects will be instructed that if they miss a dose by 12 or more hours after the scheduled dosing time, they should skip the dose and take the next dose of study drug as scheduled.

6.7 Concomitant Therapy

6.7.1 Concomitant Medications

All medications taken by patients from Screening until the completion of the Safety Follow-up visit will be documented as concomitant medications. The reported medications will be reviewed and evaluated by the Investigator to determine if they affect a patient's eligibility or continued participation in the study.

Patients are required to avoid starting new non-prescription medicine within 14 days to first study dose and throughoput the study, unless discussed with the investigator. The use of St John's wort should be avoided in this period.

Strong inducers of CYP3A4/5 (see Appendix F) are prohibited during the study.

With the exception of strong inducers of CYP3A4/5, concomitant prescribed medications are allowed for patients if prescribed by the Investigator to treat clinical events or exempted by the Medical Lead on a case-by-case basis because they would be unlikely to affect the study results or patient safety.

Use of erythropoietin or thrombopoietin mimetics are prohibited during the study and within 30 days prior to starting study treatment, with the exception of erythropoietin (ESA) in patients with diagnosed stage 3 or 4 CKD and who had been on a stable ESA dose for ≥6 months and plans to continue ESA at the same dose throughout the duration of the study. Hematopoietic growth factors for the treatment of transient neutropenia may be used when clinically indicated.

Current use of luspatercept is prohibited during the study and within 30 to 80 days before starting study treatment (based on transfusion history).

6.8 Precautions

Because etavopivat is an investigational agent in development, all possible side effects are not yet known. Please refer to the etavopivat Investigator's Brochure for additional Warnings and Precautions.

6.8.1 Childbearing Potential

Female patients of child-bearing potential must have a negative serum pregnancy test during the Screening period. Urine pregnancy testing may be performed locally if indicated during the study. If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test.

Female patients may not be pregnant, lactating, or breast-feeding or plan to become pregnant (including ova donation) within 90 days of last study drug administration.

Female patients will be considered of childbearing potential after the onset of their first menstrual period. For all patients of childbearing potential, acceptable methods of contraception including abstinence, must be in use from the time of consent through the final study visit, and for 90 days after the last dose of study drug. Patients who are not sexually active during the Screening Period must agree to the contraceptive requirements if they become sexually active with a partner of the opposite sex during the study and for 90 days after the last dose of study drug.

Adult female patients are deemed of non-childbearing potential if they are either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks (182 days) before the Screening visit) or are post-menopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone in the post-menopausal range at the Screening visit.

It should be noted, that based on nonclinical toxicity studies no effect on fertility and embryofetal development have been observed. Based on the non-clinical data, the safety committee endorsed the category for the Embryo-fetal risk assessment: Unlikely risk of human teratogenicity/fetotoxicity.

6.8.1.1 Contraception Guidelines

Sexually active female patients of childbearing potential and sexually active male patients must use an acceptable method of contraception, as a minimum, during their participation in the study from the time of consent until 90 days after the last administration of study drug. If a patient prefers to use more highly effective forms of birth control, that is allowed.

Acceptable methods of contraception under this protocol are listed below. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

Male patients

Male patients who can father a child and are sexually active must agree to use at least an acceptable effective method of contraception, which includes:

- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the patient.
- Male condom

- If a male patient confirms that his female partner(s) is not of childbearing potential (ie, post-surgical sterilization, as defined above) or is using an acceptable method of contraception, this is acceptable as the only means of contraception.

Examples of acceptable methods of contraception for male patients' female partner(s) are listed in Table 6-1.

Male patients with documented infertility or surgical sterilization (performed at least six months before the first dose of study drug) are exempt from the contraception requirement. Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens on ultrasound before the first dose of study drug (W1D1).

Female patients

Female patients of childbearing potential must agree to use an acceptable method of contraception, as a minimum, consistently and correctly, as described in Table 6-1.

As a minimum, contraception should be maintained until 90 days after treatment discontinuation.

Table 6-1 Acceptable contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
ACCEPTABLE METHODS[b]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[c] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods).
NOTES a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Considered effective, but not highly effective – failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. c. Male condom and female condom should not be used together (due to risk of failure with friction).

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

A patient may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. If a patient is prematurely discontinued from participation in the study prior to Week 48, the Investigator or designee must make every effort to perform the assessments scheduled for the EOT visit (W48D1) and schedule a Safety Follow-up visit 28 days after last study treatment. (see Table 1.2).

The Investigator will document the reason(s) for study drug discontinuation on the electronic case report form (eCRF) and the patient's source medical record. Patients who permanently discontinue the study treatment should be encouraged to continue participating in safety follow-up. Only patients who withdraw consent will be considered as withdrawn from the trial. Once a patient permanently discontinues study treatment, they may not be retreated.

7.1 Dose Modification / Discontinuation of Study Intervention

7.1.1 Adverse Event Interruption/Stopping Criteria

Criteria for treatment interruption, dose reduction, and treatment discontinuation due to AEs will be assessed at the investigator's discretion (see Section 8.7.6 and Section 8.7.7). Specific reporting criteria for liver enzyme abnormalities are provided in Section 8.7.2

Table 7-1 Suggested Dose Modifications for Treatment Related AEs

Severity	Non-Hematologic	Hematologic
Grade 3	Hold treatment until recovery to ≤ G1 or baseline, whichever is worse[b], then resume at the next lower dose level (50% reduction). Contact Medical Monitoring if resumption of etavopivat at full dose is clinically indicated.	Continue treatment at the same dose. If dose interruption is clinically indicated, resume dosing at same dose level after recovery to ≤ G2 or baseline, whichever is worse.
Grade 4	Permanently discontinue treatment[c]	Hold treatment until recovery to ≤ G2 or baseline, whichever is worse, then resume at the next lower dose level. Contact Medical Monitoring if resumption of etavopivat at full dose is clinically indicated.

a. In the event of Grade 3 nausea, vomiting, diarrhea, or rash, the patient can continue at the same dose if the patient is responsive to treatment measures within 72 hr.
b. A patient with a Grade 4 AE may resume treatment at the next lower dose level if the AE recovers to Grade 0-1 or baseline and if in the opinion of the Investigator and Sponsor, the patient can be monitored for recurrence of AE.

7.1.2 Study Intervention Restart or Rechallenge after Stopping Criteria Met

Patients who require treatment interruption > 28 days for a related AE will be withdrawn from the study.

Patients who require a dose reduction after recovery from the AE causing a treatment interruption should be seen in clinic. At the Investigator's discretion, restarting a patient's study treatment at the modified dose prior to a clinic visit using the patient's previous study treatment supply is allowed. However, the rationale and instructions for how the patient should modify their daily dose of study treatment should be documented.

After a dose reduction, if treatment is tolerated at the reduced dose for ≥ 14 days, a dose increase to the original dose is allowed (i.e., rechallenge). Patients should be seen in clinic and receive a new supply of study treatment reflecting the modified dose. Rechallenge without a clinic visit is not allowed, unless discussed with the Medical Monitor. Recurrence of the same AE after a rechallenge should follow the dose interruption/modification steps outlined above. However, in these cases if the AE recurred within 4 weeks of the rechallenge, a subsequent dose increase is not allowed.

A new Grade 3 or higher AE occurring while the patient is receiving a reduced dose should require treatment discontinuation. Discussion with the Global Medical Monitor is required before restarting treatment.

Treatment discontinuation may be required if the AE causing the dose interruption and dose reduction re-occurs at Grade 2 or higher while the patient is receiving the reduced dose. Discussion with the Global Medical Monitor is required before restarting treatment.

7.2 Treatment Discontinuation/ Withdrawal from the Study

7.2.1 Treatment Discontinuation

Treatment discontinuation is defined as any patient who permanently stops receiving study drug. A patient should be discontinued from study treatment if, in the opinion of the Investigator or Sponsor, it is medically necessary, or if it is the wish of the patient.

Patients who prematurely discontinue study drug prior to 48 weeks of treatment will have an EOT (W48D1) visit performed at the time of discontinuation followed by the Safety Follow-up visit within 28 days.

Patients must be discontinued from treatment for any of the following reasons:

- An AE that requires permanent discontinuation of study treatment
- Withdrawal of consent by the patient
- Treatment interruption for > 28 days due to a related AE
- Lack of efficacy
- Disease progression
- Pregnancy
- Patient lost to follow-up
- Investigator decision
- Noncompliance to protocol
- Termination of the study by the Sponsor

AEs leading to the discontinuation of study drug will be followed for 28 days after administration of last dose of study drug or until resolution, resolution to baseline, or until the event is considered stable or chronic.

7.2.2 Study Withdrawal

Patients may voluntarily withdraw from the study at any time for any reason without prejudice.

Patients may withdraw or be withdrawn from the study for any of the following reasons:

- Death
- Lost to follow-up
- Termination of study by Sponsor
- Withdrawal of consent

7.3 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 study site.

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the participant 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 reasonable effort to regain contact with the patient with a minimum of 3 telephone contact attempts and if these fail, follow-up with a certified letter to the patient's last known mailing address These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

All study assessments will be performed at the visits and time points outlined in the Schedule of Events (Table 1-1, and Table 1-2).

8.1 Baseline Characteristics

8.1.1 Medical History

Medical histories will be obtained and will include demographic data; histories of acute, chronic, and infectious disease; surgical histories; and any reported conditions affecting major body systems. Any history of earlier chemotherapy or radiation therapy must be recorded.

All findings on medical history will be evaluated by the Investigator for clinical significance and patient's eligibility for trial participation.

8.1.2 MDS Disease History

Diagnosis of MDS with prior diagnostic cytogenetic and cytomorphologic evaluations, prior IPSS-R scores, and any prior therapies will be obtained.

8.1.3 Transfusion History

RBC transfusion history will be collected during Screening and will include up to a minimum of 16 weeks prior to initiation of study treatment on W1D1 (e.g., an RBC transfusion occurring prior to etavopivat dosing on W1D1 should be collected as part of the patient's transfusion history).

All transfusions, RBC and platelet transfusions received by the patients will be recorded in the source documentation and eCRF in a dedicated page, and not as medication history.

Sites who prescribe transfusions and have the transfusion records only in volumes should use for conversion of volume to units based on the following criteria, in order to obtain number of units within the last 16 weeks to assess the eligibility: one unit in this protocol refers to a quantity of packed RBCs approximately 200-350 mL. (i) Sites who use transfusion bags within this range, or ≥ 350 mL, the conversion in units should be done by dividing the volume transfused to the patient by 350 mL, (ii) sites who use transfusion bags < 200 mL, the conversion in units should be done by dividing the volume transfused to the patient by 200 mL.

8.1.4 Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, cannabinoids, and investigational drugs) taken by the patients during the 30 days prior to Screening will be recorded in the source documentation and eCRF as medication history. Additionally, non-prescription medications should be avoided for 7 days prior to W1D1, and 14 days for St. John's wort as outlined in Section 6.7.1.

8.1.5 Viral Serology / Antigen Testing

Viral serology / antigen testing will be performed during Screening and will include: HIV, HepBsAg, HepBcAb, and Hepatitis C virus (HCV) by polymerase chain reaction.

8.1.6 Bone Marrow Aspirate

A bone marrow aspirate (BMA) will be performed during the Screening period to confirm eligibility and IPSS-R score, including cytogenetics, and cytomorphology. Local analysis will be used for study entry criteria and treatment initiation, and redacted result reports shared with sponsor for eligibility confirmation. BMA screening samples (and where indicated, with results from local analysis) will be sent to central laboratories for confirmation of study entry criteria and for exploratory studies. If the IPSS-R score cannot be verified, or it is determined the patient had ≥ 5% blasts at study entry, the patient may be taken off treatment.

8.2 Efficacy Assessments

8.2.1 MDS Disease Assessment

The MDS Disease Assessment will be performed as described in Table 1-1 and Table 1-2. The disease assessment will use response criteria per Cheson et al. 2006 (Appendix A) and will include assessment of hematologic improvement (HI-E criteria, modified based on Platzbecker et al. 2019).

An assessment of hematologic improvement response only may be made when a bone marrow aspirate is not performed (for example Week 24 Day 1 of treatment).

8.2.2 Assessment of Transfusions

RBC, and platelet, transfusions will be recorded on an ongoing basis throughout the study as indicated in Table 1-1 and Table 1-2. For any RBC, and platelet, transfusions received during the study, collect Hb and platelet values prior to transfusion, the number of units transfused, and the dates of transfusion. If available, the Hb/hematocrit of the transfused unit should also be collected.

8.2.2.1 LTB/HTB Patient Transfusion Treatment Plan:

Each patient will have an individualized transfusion treatment plan in place prior to study treatment (see Appendix G). This treatment plan assumes a pre-transfusion Hb value is collected within 7 days of a scheduled transfusion. The decision on the RBC transfusion schedule and amount of RBC units to transfuse will be based on the following parameters:

1) A baseline pre-transfusion Hb threshold determined by the mean of all documented pre-transfusion Hb values during the 16 weeks prior to start of study treatment.
2) During treatment, if the pre-transfusion Hb level is increased by ≥ 1 g/dL compared to the pre-transfusion Hb threshold for that patient, transfusion may be delayed by a minimum of 7 days and/or the number of units transfused may be reduced by 1 or more RBC units.

8.2.3 Hemoglobin Response and Clinical Measures of Hemolysis

Hemoglobin response and measures of hemolysis (reticulocytes, unconjugated bilirubin, and LDH) will be assessed.

8.2.4 Iron Chelation Therapy and Iron Profile

Iron chelation therapy will be recorded at Screening and on an ongoing basis throughout the study.

Iron profile, consisting of ferritin, iron and transferrin levels, will be measured during Screening, on W1D1 and throughout the study.

8.2.5 Patient-Reported Outcomes

Patient-reported outcomes (PROs) will be evaluated using the PROMIS fatigue scale and the QUALMS assessment.

The PROMIS is a patient-reported health outcome measurement system which can be used to evaluate quality of life in both children and adults. The PROMIS Fatigue 7a short form will be administered during scheduled clinic visits. The QUALMS is a validated MDS specific scale developed through input from MDS patients, their caregivers and providers.

The PROMIS and The QUALMS assessments will be performed throughout the study, as indicated in Table 1-1 and Table 1-2.

8.2.6 Bone Marrow Aspirate

A BMA, for response assessments and research, will be obtained as indicated in Table 1-1 and Table 1-2.

8.3 Safety Assessments

8.3.1 Clinical Laboratory Assessments

A list of testing to be performed on the blood and urine samples is provided in (Appendix E). All laboratory safety data will be reviewed by the Investigator or designee for clinical significance as defined by an applicable list of normal values on file (i.e., local or central, as applicable).

Additional laboratory samples may be taken at the discretion of the Investigator or designee (e.g., if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure patient safety).

8.3.2 Physical Examination

Full and symptom-directed physical examinations will be performed according to the schedule in Table 1-1, and Table 1-2. Full physical examinations, assessing the patient's overall health and physical condition, will consist of the following body systems: eyes, ears, nose, throat, lymph nodes, dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and nervous systems.

8.3.3 Hematology

Hematology assessments will be performed according to the schedule in Table 1-1 and Table 1-2. A list of hematology tests to be performed is provided (Appendix E).

8.3.4 Hemoglobin Electrophoresis

A hemoglobin electrophoresis will be performed locally according to the schedule in Table 1-1.

8.3.5 Coagulation Parameters

Coagulation parameters assessments will be performed according to the schedule in Table 1-1 and Table 1-2. A list of coagulation parameters tests to be performed is provided (Appendix E).

8.3.6 Serum Chemistry

Chemistry assessments will be performed according to the schedule in Table 1-1 and Table 1-2. A list of serum chemistry tests to be performed is provided (Appendix E).

8.3.7 Urinalysis

Urinalysis will include assessment of color, appearance, and by urine dipstick according to the schedule in Table 1-1 and Table 1-2. Microscopic analysis (RBCs, white blood cells [WBCs], microalbumin, bacteria and casts) may be performed as clinically indicated. A list of the tests to be performed is provided (Appendix E).

8.3.8 12-Lead Electrocardiogram

12-Lead ECGs will be performed according to the schedule in Table 1-1 and Table 1-2. Electrocardiograms (ECGs) (12-lead) should be recorded in triplicate after a patient has rested for at least 5 minutes in the supine position. All Triplicate ECGs will be taken one minute apart or with the three ECGs collected within about a five-minute window.

If the scheduled time for a safety ECG coincides with a blood collection, the safety ECG should be performed prior to the blood collection. The same timing for obtaining safety ECGs (ie, prior to blood collection) should be used for all safety ECG measurements. If the ECG cannot be performed prior to blood collection, the ECG should be done after a sufficient rest period of at least 15 minutes to minimize interference with ECG measurements.

8.3.9 Pregnancy

A serum pregnancy test for the presence of β-human chorionic gonadotropin (β-HCG) will be performed during Screening for all female participants of childbearing potential.

During active study participation, pregnancy tests will be urine pregnancy tests and will be performed locally if indicated.

If a urine pregnancy test is positive, study treatment must be held until the results are confirmed with a serum pregnancy test, and permanently discontinued if confirmed positive. Results of all pregnancy tests will be reported and must be negative prior to study continuation and/or dosing (see also Section 8.7.4).

8.3.10 Concomitant Medications and Procedures

All medications received by the patient while in the study as described in Section 6.7.1, or any procedures that the patient has undergone will be recorded according the Schedule of Events (Table 1-1, Table 1-2).

8.4 Pharmacokinetic Sampling

Venous blood samples will be collected to characterize the PK of etavopivat. Samples will be collected, processed, and shipped according to a lab manual provided by the Sponsor and/or bioanalytical laboratory.

8.5 Pharmacodynamic Sampling

Pharmacodynamic analysis will include measurement of 2,3-DPG and ATP and will be conducted as indicated in Table 1-1 and Table 1-2.

8.6 Exploratory Laboratory Assessments

Exploratory laboratory samples will be collected according to the Schedule of Events (Table 1-1 and Table 1-2).

Samples obtained will include BMA to evaluate bone marrow progenitors by cell colony assays and terminal erythroid differentiation by flow cytometric analysis. BMA and peripheral blood will be obtained for cancer-associated mutations and/or genetic alterations.

Serum will be obtained to evaluate markers of ineffective erythropoiesis and iron metabolism, including but not limited to erythropoietin, soluble transferrin receptor, iron, total iron binding capacity (including transferrin saturation), erythroferrone, and hepcidin.

Refer to the study laboratory manual for additional details on processing, storage, and shipment of exploratory laboratory samples where indicated.

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

8.7.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not the AE is related to the investigational medicinal product.

This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments.

Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the Investigator to document all AEs that occur during the study (from time of the first dose of study drug through 28 days after the last dose of study drug). AEs should be elicited by asking the patient a non-leading question (eg, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE).

8.7.2 Serious Adverse Events

8.7.2.1 Definition

An SAE is any untoward medical occurrence that occurs at any dose that:

- Results in death. Any event resulting in death during the reporting period [from time of the first dose of study drug through 28 days after last dose of study drug] must be treated as an SAE and reported as such.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred) NOTE*: this is different than life-threatening severity criteria.*
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization. NOTE: visits to Emergency Rooms, Urgent Care, Accident/Emergency Units, or visits resulting in brief care under, 'Observation Status', do not meet the criteria of in-patient hospitalization.
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- Suspicion of transmission of infectious agents via IMP
- Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x ULN and total bilirubin > 2x ULN where no alternative aetiology exists (Hy's law)

8.7.2.2 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned procedures (planned prior to signing of ICF) or elective hospitalization such as social and/or convenience situations (e.g., hospitalization due to weather or travel issues)

Overdose of either study drug or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as described in Section 8.7.11.

8.7.3 Clinical Laboratory Assessments as Adverse Events

It is the responsibility of the Investigator to assess the clinical significance of all abnormal values as defined by the applicable list of reference ranges from the laboratory (i.e., local or central, as applicable). In some cases, significant changes in lab values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality
- Intervention for management of the abnormality is required
- At the discretion of the Investigator should the abnormality be deemed clinically significant

8.7.4 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study the Investigator is to stop dosing with study drug immediately. A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor using the Pregnancy Report Form within the same timelines as an SAE. This applies to a female patient or the female partner of a male patient. The pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Reporting Form should be completed and reported to the Sponsor. AEs or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms. Should the outcome of pregnancy meet SAE criteria (for example, spontaneous abortion, congenital anomaly, stillbirth, etc.), that should be reported as an SAE accordingly.

8.7.5 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

Any AE or SAE that occurs from time of the first dose of study drug through 28 days after the last dose of study drug should be recorded on the AE eCRF. Only SAEs that occur from the time of consent until first dose of study drug that are considered to be related to a protocol-mandated procedure need to be reported as an SAE. All other AEs and SAEs from time of consent until first dose of study drug should be reported as medical history.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the Investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is the final diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Serious Adverse Events: SAEs that occur during Screening and are related to a protocol-mandated procedure or SAEs that occur from first dose to within 28 days after last dose of study drug, whether or not related to study drug, must be reported to Novo Nordisk Global Safety within 24 hours of knowledge of the event (see Page 4). After the 28-day reporting window, only SAEs assessed as related to study drug need to be reported. All SAEs, regardless of relationship to study drug, must be reported using the Novo Nordisk SAE Report Form. It is important that the Investigator provides an assessment of relationship of the SAE to study treatment at the time of the initial report. The contact information for reporting of SAEs can be found on the Novo Nordisk SAE Report Form itself and is also provided on Page 4.

8.7.6 Grading the Severity of Adverse Events

The severity of the AE will be graded according to the CTCAE grading scale (Grades 1-5), per CTCAE v5. Should criteria not be available for a specific event term, the definitions noted below may be used:

- Grade 1 (Mild): event is usually transient and does not interfere with the patient's daily activities
- Grade 2 (Moderate): event introduces a low level of inconvenience or concern to the patient and may interfere with daily activities

- Grade 3 (Severe): event interrupts the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Grade 4 (Life-threatening): event requires urgent intervention to prevent death *NOTE: this is different than life-threatening serious criteria.*
- Grade 5 (Fatal): Event resulted in death

8.7.7 Causal Relationship of Adverse Events to Investigational Medicinal Products

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge. It should be evaluated as to whether or not there is a reasonable possibility that the study drug caused the event.

Not Related (includes events thought to be Unlikely Related)

- An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.)
- It does not follow a reasonable temporal sequence from administration of study drug
- It does not follow a known pattern of response to study drug
- It does not reappear or worsen when study drug is restarted
- An alternative explanation is likely even if not clearly identifiable

Related (includes events thought to be Probably or Possibly Related)

- An AE that is difficult to assign to alternative causes
- It follows a strong or reasonable temporal sequence from administration of study drug
- It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient
- It follows a known response pattern to study drug
- It is confirmed with a positive rechallenge or supporting laboratory data

8.7.8 Outcome and Action Taken

The Investigator will record the action taken and outcome for each AE according to the following criteria:

8.7.8.1 Action Taken with Study Drug

- None
- Dose reduced
- Study drug held/interrupted
- Study drug permanently discontinued
- Not applicable (patient not on study drug at the time of the event)

8.7.8.2 Outcome

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Not recovered/Not resolved
- Death
- Lost to follow-up/Unknown

8.7.9 Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs occurring during the study are to be followed up in accordance with good medical practice until resolution or stabilization, until the event returns to baseline status, is determined to be a chronic condition or until patient is lost to follow-up or dies.

8.7.10 Regulatory Aspects of Serious Adverse Event Reporting

8.7.10.1 Investigator and Sponsor Responsibilities

All SAEs, regardless of relationship to study drug, must be reported to the Sponsor within 24 hours of knowledge of the event, according to the procedures below. It is important that the Investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. The Novo Nordisk SAE Report Form must be used for reporting SAEs. The contact information for reporting of SAEs can be found on the Novo Nordisk SAE Report Form and Pregnancy Reporting Forms.

The Sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the United States Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations.

All Investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the Sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions as individual notifications or through periodic line listings.

8.7.10.2 Sponsor Reporting Timeline

The Sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements (ie, within 7 days for treatment related unexpected fatal or life-threatening events; within 15 days for all other treatment related unexpected serious events).

8.7.11 Special Situation Reports

Special situation reports include reports of overdose, medication error, abuse or misuse.

1. **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s), or the Investigator has reason to suspect that the patient has taken additional dose(s).
2. **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
3. **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
4. **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Novo Nordisk Global Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation events should be reported as AEs or SAEs (as applicable) as well as recorded on the AE eCRF and/or the Novo Nordisk SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Novo Nordisk Global Safety
Fax: + 45 44427787
e-mail: SOCLIN@NOVONORDISK.COM

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Methods

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP). This document will include details of analysis populations, summary strategies, analytic approaches, and any amendments to the proposed analyses listed here. Any changes in analyses from those planned in the SAP will be detailed in the final study report.

9.2 Patient Populations for Analysis

- Full Analysis Set (FAS): All patients who signed the informed consent and received at least 1 dose of etavopivat.
- Interim Assessment Set: The first 15 patients overall or first 8 patients per transfusion history stratum in the FAS who completed the Week 24 Response visit and have a baseline record of the primary endpoint.
- Efficacy Evaluable Set: All patients in the FAS who have completed the Week 24 Response visit and who have a baseline record of the primary endpoint.
- Per-Protocol Set (PPS): All patients in the Full Analysis Set who did not have any major protocol violations impacting the efficacy outcomes.
- Safety Set: All patients who received at least one dose of etavopivat.
- Pharmacokinetic Set: All Safety Set patients who have at least one evaluable concentration for etavopivat at a scheduled PK time point after the start of dosing. For patients with protocol violations or events with potential to affect the PK concentrations, a decision regarding inclusion in the analysis will be made on a case-by-case basis.

9.3 Sample Size Considerations

An overall sample size of N=45 will provide 87.3% power to detect an increase in the response rate for the HI-E criteria. Specifically, the assumed response rates are 40% for the etavopivat intervention and 20% otherwise (null-hypothesis comparator). One-sided testing, a significance level of 0.025, and the exact binomial distribution are used for the calculations.

9.4 General Statistical Considerations

Continuous variables will be summarized descriptively via number of patients, mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized as the number and percent of patients in each category. Data summaries will be performed using the nominal visit unless otherwise specified.

Unless otherwise specified, all testing will be 2-sided at the 0.05 level of significance.

All data collected on study in the eCRF will be included in data listings.

9.4.1 Multicenter Studies

Data collected will be analyzed as a whole. Exploratory analyses by individual study sites may be conducted as warranted.

9.4.2 Handling of Missing Data

For patient reported outcome data, missing data imputation will be based on published instrument specific methods.

Full details of how missing data will be handled will be described in the SAP.

9.5 Futility Assessment and Decision Rules

A futility assessment threshold has been selected for this study once 15 patients overall or 8 patients in a single transfusion stratum have evaluable responses on the HI-E criteria at Week 24, whichever occurs first. If the overall futility assessment is performed and ≤ 3 responses are observed, enrollment may discontinue for futility. If there are 4 or more responses at 24-weeks observed, enrollment will continue until a total of approximately 45 response evaluable patients are available at Week 24. If the stratum-specific futility assessment is performed and no responses are observed, further enrollment may be restricted to specific subsets of patients based on prior transfusion history.

Enrollment will not pause during assessment periods unless futility analysis suggests clinical need to pause.

Assuming the pooled response rate of 40% is met, the probability of incorrectly declaring futility with 15 evaluable patients is 0.0905. This is calculated using the binomial cumulative distribution function with parameters n=15, p=0.4, x=3.

The single stratum futility assessment allows for the possibility that response rates in a single stratum may be lower than 40%, but the pooled response rate after incorporating the other strata could still reach 40%. The per-stratum futility threshold is intended to terminate enrollment in a stratum where the true response rate can be expected to be <25%. Under a binomial distribution with parameters n=8 and p=0.25, the probability of observing x=0 successes is 0.10011.

9.6 Analysis of Efficacy

The primary analysis of Efficacy will be performed using the Efficacy Evaluable Set. Sensitivity will be performed using the PPS.

9.6.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the pooled incidence of the HI-E criteria of ≥ 8 weeks duration (across strata), and it will be summarized with frequencies and proportions. Specifically, the primary endpoint is assessed following 24 weeks of etavopivat treatment. During those 24 weeks, if there had been an 8-week interval (or longer) where one of the below 3 conditions was maintained/persistently held, then the incidence of the primary endpoint is fulfilled:

- NTD patients: ≥ 1.5 g/dL increase in Hb from baseline
- LTB patients: absence of any transfusion
- HTB patients: reduction by ≥ 50% of RBC units

Analysis of the pooled incidence will test the hypothesis:

H_0: $0.2 \leq P_1$

H_1: $0.2 > P_1$

Where $P_0 = 0.20$ is the assumed null proportion and P_1 is the observed proportion for etavopivat treated patients. This will be tested using a one-sided binomial exact test at the significance level of 0.025 for accuracy.

Tabular summaries will also include the exploratory incidence and test for each of the separate strata.

9.6.2 Analysis of Secondary Efficacy Endpoints

The analysis of all secondary endpoints will be based on the Efficacy Evaluable Set. Sensitivity of the primary analysis will be performed using the PPS.

9.6.2.1 HI-E Criteria ≥ 8 weeks

The HI-E criteria of ≥ 8 weeks will also be evaluated following 16 and 48 weeks of treatment. The summary and analysis at Weeks 16 and 48 will follow the same methodology as the primary endpoint.

9.6.2.2 HI-E criteria ≥ 16 weeks

The incidence of HI-E responses lasting 16 weeks or longer within 24 and 48 weeks of etavopivat treatment, will be evaluated using the following 3 conditions:

- NTD: ≥ 1.5 g/dL increase from baseline maintained for at least 16 consecutive weeks
- LTB: no transfusion for at least 16 weeks
- HTB: reduction by ≥ 50% in RBC units for at least 16 consecutive weeks.

Responses will be summarized and analyzed with the same methodology as the primary endpoint.

9.6.2.3 Additional Measures of Clinical Benefit

Additional measures of potential clinical benefit will be summarized with descriptive statistics. These consist of the following:

- Overall Response Rate (2006 IWG Criteria)
- Duration of response (2006 IWG Criteria)
- Increase in neutrophils and/or platelets
- Decrease in ferritin and decrease in iron chelation therapy
- Overall survival
- Reduction in RBC transfusions and rate of RBC transfusion independence (RBC-TI) in patients with LTB or HTB at study entry

The Overall Response Rate (ORR) and duration of response are based on the 2006 IWG Criteria (Cheson et al. 2006) as assessed at each scheduled assessment. ORR will be summarized with descriptive statistics by disease strata and overall. Duration of response will be summarized with quantiles based on product limit estimates (ie, Kaplan-Meier). Duration of response is defined as the time from date of first known incidence of a 2006 IWG criteria response to the most recent date that the 2006 IWG criteria is not met following the initial response. If the subject has met IWG criteria throughout the period following the initial response, the subject will be censored at the latest date of end of study, loss to follow-up, or death.

Overall survival is defined as the time from first dose to date of death. If the subject was alive at last contact, the end date will be censored at the latest of either end of study, loss to follow-up, or study discontinuation. Overall survival will be summarized with quantiles based on product limit estimates, in the same manner as the duration of response.

Laboratory results and change from baseline will be summarized with descriptive statistics for neutrophils and platelets. On-study use of iron chelation therapies will also be summarized with descriptive statistics. The study SAP will detail chelation therapy strata and summary methods as required.

For LTB and HTB patients, RBC transfusions will be summarized by both unit and volume with descriptive statistics by nominal visit. The incidence of 56-day transfusion independence by Week 16, Week 24, and Week 48 and duration of transfusion independence will be summarized with descriptive statistics.

9.6.3 PK/PD and Exploratory Efficacy Analyses

Etavopivat plasma concentrations will be summarized descriptively by time point, disease strata (NTD, LTB, and HTB), and overall.

Pharmacokinetic parameters will be based on the actual sample collection times and determined using standard noncompartmental methods. Pharmacokinetic analyses will be conducted on patients in the Pharmacokinetic Set and will be detailed in a separate PK plan.

Pharmacodynamic (PD) results will include RBC 2,3-DPG and ATP levels over time. All PD endpoints will be based on the efficacy evaluable set and will be summarized with descriptive statistics by time point, disease strata, and overall.

9.6.3.1 Pharmacokinetic and/or Pharmacodynamic Modelling

Data from the study may be used for exploratory pharmacokinetic and/or pharmacodynamic analysis as needed.

9.7 Analysis of Study Population Endpoints

All study population analyses will be conducted on the Full Analysis Set.

9.7.1 Disposition and Reasons for Discontinuation

The number of patients completing informed consent, dosed, completing the study, early discontinuation, and treatment discontinuation will be summarized with descriptive statistics for each disease strata (NTD, LTB, and HTB) and overall. The number of patients in each analysis population will also be summarized.

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment will be listed, as well as the major/minor status and the effect on the per-protocol set (PP).

9.7.2 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for each disease strata and overall using descriptive statistics.

9.7.3 Study Drug Compliance

Study drug compliance will be assessed by examination of the dispensed and returned pills. Percent compliance will be calculated based on comparing the returned pills to the expected number of pills to be taken between visits.

Study drug compliance will be summarized using descriptive statistics for each disease strata and overall.

9.8 Analysis of Safety Assessments

All Safety analyses will be performed on the Safety Set.

9.8.1 Adverse Events

Original verbatim terms used in the eCRFs by Investigators or designees to identify AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or higher.

Summaries of AEs will be based on TEAEs. A TEAE is an AE that begins or worsens following first dose of study drug and prior to 28 days after the last dose of study drug. The number and percentage of patients with TEAEs will be summarized for each disease strata, and overall, by MedDRA System Organ Class (SOC) and Preferred Term (PT) for the following categories:

- TEAEs
- Drug-Related TEAEs
- Grade 3 or Higher TEAEs
- Grade 3 or Higher Drug-Related TEAEs
- Serious TEAEs
- Serious Drug-related TEAEs
- TEAEs Leading to Dose Reduction
- TEAEs Leading to Dose Interruption
- TEAEs Leading to Dose Discontinuation

Maximum Severity of TEAEs will also be summarized by SOC and PT. Additional summary tabulations of TEAEs may also include: most commonly reported TEAEs, deaths, serious TEAEs, serious drug-related TEAEs, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to study drug discontinuation will be also provided, summarized by SOC and PT.

All adverse events will be presented in data listings with non-treatment-emergent events being included in a separate listing.

9.8.2 Other Safety Assessments

Vital signs may include blood pressure (systolic and diastolic), heart rate, respiratory rate, and oral temperature. Descriptive statistics of each collected vital sign will be summarized for each disease

strata and overall. Temporal assessments will include both raw and change from baseline summaries for each time point.

ECG result interpretations will be summarized with descriptive statistics for each disease strata and overall. Quantitative ECG results will be summarized in the same manner as vital signs for the PR, QT, QRS, HR, and QT interval corrected using Fridericia's correction formula (QTcF). Additionally, categories of quantitative results and shift tables may be included with details included in the SAP.

Laboratory test data will be summarized descriptively by the type of laboratory test and nominal visit (absolute value and change from baseline) and disease strata and overall. Shift tables may be produced for selected laboratory test results based on clinical interpretations and NCI-CTCAE severity level thresholds. Details of these analyses will be included in the SAP.

Concomitant medications and prior systemic therapies will be coded using the World Health Organization Drug Dictionary (WHODrug) into Anatomical Therapeutic Chemical (ATC) and PT. The number and percentage of subjects taking concomitant medications will be tabulated by ATC, PT, disease strata, and overall.

Physical examination results will be included in data listings.

10.0 DATA MANAGEMENT AND RECORD KEEPING

10.1.1 Data Handling

Data will be recorded on eCRFs and reviewed by the clinical research associate (CRA), data manager and/or Sponsor representative. The CRAs will verify data recorded in the relevant system(s) with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the relevant system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the relevant system while the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA for medical history and adverse events
- WHODrug for prior and concomitant medications and prior systemic therapies

10.1.5 Data Validation

Validation checks programmed within the relevant system, as well as supplemental validation performed via review of the data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.0 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/ Independent Ethics Committee

The IRB/ IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/ IEC approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/ IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/ IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/ IEC.

No drug will be released to the site for dosing until written IRB/ IEC authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/ IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study--specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/ IEC and/ or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the

Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/ her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Visits and Assessments in Emergency Situations

In the event of local or widespread emergencies (eg, COVID-19, weather-related emergencies), in-person clinic visits may present excessive risks or difficulties for study participants and site staff. In these situations, in-person visits may be replaced by alternate methods to assess patients. Arrangements should be made to ensure all samples are collected for laboratory analyses and that study patients have an adequate supply of study drug. Such changes to the research plan should be first discussed with the Medical Lead and must be documented in the study files.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.0 REFERENCES

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13.0 APPENDICES

APPENDIX A: RESPONSE CRITERIA FOR MDS

Adapted from IWG Response Criteria for MDS (Cheson et al. 2006)

Response Category	Response criteria (responses must last at least 4 wks)
Complete remission (CR)	• Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted* • Peripheral blood‡: o Hb ≥ 11 g/dL o Platelets ≥ 100 × 10^9/L o Neutrophils ≥ 1.0 × 10^9/L o Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% • Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hb concentration by ≥ 1.5 g/dL or transfusion dependence
Disease progression (PD)	For patients 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: ≥ 50% increase to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hb by ≥ 2 g/dL • Transfusion dependence

Hb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; wks = weeks.

*Dysplastic changes should consider the normal range of dysplastic changes.

‡ Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

RESPONSE CRITERIA FOR MDS (continued)

Modified International Working Group Response Criteria for Hematologic Improvement (Updated 2018)

Hematologic Improvement		Response Criteria
Erythroid Response (HI-E)	Non-transfused (NTD)*	At least 2 consecutive Hb measurements ≥1.5 g/dL for a period of minimum 8 wk in an observation period of 16 to 24 wk compared with the lowest mean of 2 Hb measurements (apart from any transfusion) within 16 wk before treatment onset
	Low transfusion burden (LTB)	Absence of any transfusions for at least 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment
	High transfusion burden (HTB)	Major response: Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment Minor response: Reduction by at least 50% of RBCs over a minimum of 16 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment
	On-treatment RBC transfusion policy	Transfusion policy for the individual patient prior to therapy should be maintained on treatment if not otherwise clinically indicated (documentation by the treating physician required); maximum variation between pre- and on-study practice of 1 g/dL (or 0.6 mmol/L) in terms of transfusion threshold
Platelet response (pretreatment, <100 × 109/L), HI-P		• Absolute increase of 30 × 10^9/L for patients starting with >20 × 10^9/L PLTs or • Increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100% In addition, • Evolution of bleeding symptoms is to be taken into account
Neutrophil response (pretreatment, all patients), HI-N		• At least 100% increase and an absolute increase >0.5 × 10^9/L (pretreatment, <1.0 × 10^9/L)
Progression or relapse after HI		For HI-N and HI-P: • At least 50% decrement from maximum response levels in neutrophils or platelets, and not meet response criteria when compared to baseline For HI-E: • Reduction in Hb by ≥ 1.5 g/dL, and not meet response criteria when compared to baseline • Transfusion dependence • HTB: increase in transfusion burden by at least 50%

Hb = hemoglobin; HI = hematologic improvement; PLTs = platelets; wk = week(s).

*If patients received 1 or 2 RBC concentrates during the 16-wk pre-treatment period, it is recommended that HI-E achievement requires not only transfusion independence but also an increase of Hb by at least 1.5 g/dL (= 0.9 mmol/L).

APPENDIX B: INTERNATIONAL PROGNOSTIC SCORING SYSTEM SCORE – REVISED

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 (x 10^9/L)	≥100	50 - <100	<50	-	-	-	-
ANC (x 10^9/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 et al. 2012.
** Schanz et al. 2012.

APPENDIX C: DIAGNOSIS OF IDIOPATHIC/DE NOVO MDS ACCORDING TO WORLD HEALTH ORGANIZATION

Name	Dysplastic Lineages	Cytopenias*	Ring Sideroblasts as % of Marrow Erythroid Elements	BM and PM Blasts	Cytogenetics by Conventional Karyotype Analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	< 15% / < 5%†	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	< 15% / < 5%†	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥ 15% / ≥ 5%†	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥ 15% / ≥ 5%†	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM < 5%, PB < 1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19%, no Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM < 5%, PB = 1%‡, no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM < 5%, PB < 1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	< 15% §	BM < 5%, PB < 1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM < 5%, PB < 2%	Any

* Cytopenias defined as: hemoglobin, < 10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be < 1 × 10^9/L.
† If *SF3B1* mutation is present.
‡ One percent PB blasts must be recorded on at least 2 separate occasions.
§ Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Abbreviations: BM = bone marrow; MDS = Myelodysplastic Syndrome; PB = peripheral blood.

Adapted from Arber et al. 2016.

APPENDIX D: ECOG PERFORMANCE STATUS

Grade	ECOG Performance Status
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, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al. 1982.

APPENDIX E: CLINICAL LABORATORY ANALYSES

Chemistry

Alanine aminotransferase	Ferritin, transferrin (TIBC) and iron level (timing per Table 1-1, and Table 1-2)
Albumin	Gamma-glutamyl transferase
Alkaline phosphatase	Glucose
Amylase	Lactate dehydrogenase
Aspartate aminotransferase	Lipase
Bicarbonate	Magnesium
Bilirubin – total, direct, indirect	Phosphorus
Blood urea nitrogen	Potassium
Calcium	Sodium
Chloride	Total protein
Creatinine	Uric acid
Erythropoietin (Screening only)	

Hematology

Hematocrit	White blood cell (WBC) count and differential:
Hemoglobin	• Basophils
Red blood cell (RBC) count	• Eosinophils
Reticulocyte count (% and absolute)	• Lymphocytes
Mean corpuscular hemoglobin concentration (MCHC)	• Monocytes
Mean corpuscular volume (MCV)	• Neutrophils
RBC distribution width (RDW)	• Blasts
Absolute neutrophil count (ANC)	
Platelets	

Hemoglobin Electrophoresis

Screening only

Coagulation

International normalized ratio (INR)	Partial thromboplastin time (PTT)
Prothrombin time (PT)	Fibrinogen

Serology

Hepatitis B surface antigen (HepBsAg)	Hepatitis C virus (HCV) by polymerase chain reaction (PCR)
Hepatitis B core antibody (HepBcAb)	Human immunodeficiency virus (HIV)

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	pH
Nitrite	Specific gravity
Protein	
Urobilinogen	

Microscopic analysis (RBCs, WBCs, microalbumin, bacteria, crystals, and casts) will be performed locally as clinically indicated.

Pregnancy Tests (Female patients)

Serum (Screening)	Urine (post-Screening)

APPENDIX F: EXAMPLES OF DRUGS THAT ARE STRONG INDUCERS OF CYP3A4/5

Strong Inducers:

Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Additional information can be found at:
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3

APPENDIX G: SAMPLE TRANSFUSION PLAN: LTB AND HTB PATIENTS

Patient:

Date of plan:

Planned frequency of transfusions:

Patient will receive transfusions approximately every _____ weeks

Baseline pre-transfusion Hb threshold _____

If Hb is below the level above, a transfusion is required. Threshold should be determined based on ≥ 16 weeks of pre-treatment mean of Hb.

During treatment, if the pre-transfusion Hb level is increased by ≥ 1 g/dL compared to the pre-transfusion Hb threshold for that patient, transfusion may be delayed by a minimum of 7 days and/or the number of units transfused may be reduced by 1 or more RBC units.

Pre-treatment Hb results from ≥ 16 weeks prior to start of study treatment:

Date	Hb Result