Cover Page for Statistical Analysis Plan

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*:	23-Aug-2024

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

STATISTICAL ANALYSIS PLAN

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

Protocol 4202-ONC-203

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

Protocol Number: **Protocol Version and Date:**	4202-ONC-203 Version 3.0: 31 July 2023 Version 2.0: 15 June 2022 Original: 11 April 2022
Name of Test Drug:	Etavopivat (FT-4202)
Phase:	Phase 2
Methodology:	Multicenter, Open-Label Study
Sponsor:	Forma Therapeutics, a Novo Nordisk Company 75 Hayden Ave 4th Floor Lexington, MA 02421
Sponsor Representative:	[redacted], Biostatistics
Analysis Plan Date:	23 AUG 2024
Analysis Plan Version:	Version 1.0

[redacted]

SIGNATURE PAGE

Protocol No. 4202-ONC-203

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

Prepared by: [redacted]

[redacted] Date

[redacted], Biostatistics

Novo Nordisk

Approved by: [redacted]

[redacted] Date

[redacted]

Novo Nordisk

TABLE OF CONTENTS

Section **Page**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
2,3-DPG	2,3-diphosphoglycerate
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARC	Absolute reticulocyte count
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
CNS	Central nervous system
CRF	Case report form
CS	Clinically Significant
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
EES	Efficacy Evaluable Set
EOET	End of Extended Treatment
EOPT	End of Primary Treatment
EOS	End of Study
FAS	Full Analysis Set
FCR	Fraction of cells remaining
FDA	Food and Drug Administration
Hb	Hemoglobin
HI-E	Hematologic Improvement - Erythroid
HTB	High transfusion burden
ICH	International Conference on Harmonization
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
IPSS-R	Revised International Prognostic Scoring System
ITT	Intent-to-treat
IWG	International Working Group
LDH	Lactate dehydrogenase
LIC	Liver Iron Concentration
LS	Least squares

Abbreviation	Definition
LTB	Low transfusion burden
m^2	Square meter
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndrome
MMRM	Mixed model repeated measures
Msec	Millisecond
NCS	Not clinically significant
NTD	Non-transfusion dependent
PD	Pharmacodynamic
PDGP	Protocol Deviation Guidance Plan
%	Percent
pH	Hydrogen ion concentration
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
PTT	Partial thromboplastin time
QD	Once daily
QoL	Quality of life
QT	Interval between Q and T waves
QTcF	Corrected interval between Q and T waves using Fridericia's correction formula
QUALMS	Quality of Life in Myelodysplasia Scale
RBC	Red blood cell
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sickle cell disease
SD	Standard deviation
SE	Standard error
SI	Système International
SOC	System organ class
SOE	Schedule of events
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
ULN	Upper limit of normal
WBC	White blood cell (count)

Abbreviation	Definition
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES

1.1. Introduction

Due to the early termination of the current study, this statistical analysis plan (SAP) is created to support an abbreviated clinical study report (CSR), focusing on the primary and secondary endpoints, and the final safety update. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided.

This SAP will also outline any differences between the current plan and the study protocol. Any revisions, updates, or differences will be documented and version controlled in the SAP and CSR.

1.1.1. Study Objectives and Endpoints

1.1.1.1. Primary

The primary objective of this study is to assess hematologic improvement based on an erythroid response (HI-E) for ≥ 8 weeks duration in patients with MDS within 24 weeks of etavopivat (FT-4202) treatment.

HI-E is defined based on transfusion history status at baseline, as defined in Section 1.2:

- Non-transfusion dependent (NTD): ≥ 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.
- Low transfusion burden (LTB): absence of any transfusion for ≥ 8 consecutive weeks.
- High transfusion burden (HTB): reduction by ≥ 50% of red blood cell (RBC) units for ≥ 8 consecutive weeks.

1.1.1.2. Secondary

The secondary objectives are:

1) To assess the safety and tolerability of etavopivat in patients with MDS.
2) To assess additional measures demonstrating potential clinical benefit.

The secondary efficacy and safety endpoints are defined as the following:

- The incidence of adverse events (AEs), serious adverse events (SAEs), and AEs related to etavopivat.
- Number of premature discontinuations, dose interruptions, and dose reductions.
- Reduction in RBC transfusions and rate of RBC transfusion independence ≥ 8 weeks in patients with LTB or HTB at study entry.

1.1.1.3. Pharmacokinetics

The study will assess the Pharmacokinetics (PK) of etavopivat in patients with MDS. The PK endpoint is observed plasma concentration.

1.2. Study Design

1.2.1. Synopsis of Study Design

4202-ONC-203 is a multicenter, open-label Phase 2 study in adult patients with very low, low risk, or intermediate risk MDS per the Revised International Prognostic Scoring System (IPSS-R) classification. The study will enroll approximately 45 patients.

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 protocol 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).

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.

1.2.2. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1 for the Primary and Extension Treatment Periods.

Table 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	X
Hb Electrophoresis [g]	X	X								X			X												X	
Serum Chemistry [g]	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	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																									
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 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 Protocol Section 8.3.8 for detailed instructions on performing the ECGs.

f. Adverse events are reported as described in Protocol 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 Protocol Appendix E (as applicable).

h. Hematology assessments listed in Protocol 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 Protocol 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 Protocol 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 Protocol 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.

2. PATIENT POPULATION

2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- All Enrolled Patients: This is defined as all patients who signed the informed consent form.
- Full Analysis Set (FAS): All patients who signed the informed consent and received at least 1 dose of etavopivat.
- Safety Set: All patients who receive at least one dose of etavopivat (including partial dosing).
- Efficacy Evaluable Set (EES): All patients in the FAS who have completed the Week 24 Response visit and who have a baseline record of the primary endpoint.
- 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 and documented as part of the DBL minutes.

The Efficacy Evaluable Set is the primary population for the analysis of efficacy parameters. The PK Set is the primary population for the analysis of PK parameters. The Safety Set is the primary population for the analysis of safety endpoints. The FAS is used for demography tables.

2.2. Protocol Deviations

Protocol deviations will be assessed and documented according to the Protocol Deviation Guidance Plan (PDGP).

Protocol deviations will be classified as major and minor no later than the final data review meeting, prior to database lock. All protocol deviations will be finalized prior to the database lock and reported for all enrolled patients.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

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.

3.2. General Methods

In general, tables will summarize data by transfusion history stratum at Day 1. All statistical analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. For categorical variables, descriptive statistics will include frequency count and percentage. If missing is observed, a "Missing" category will be added without percentage. For shift tables, total rows and columns will not include patients from the "Missing" category except the "Missing" column and row and percentage will be calculated based on evaluable patients. For continuous variables, descriptive statistics are number of patients, mean, median, standard deviation (SD), 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

For parameters assessed across multiple visits, by-visit summaries will be presented for planned visits from Table 1 and Table 2.

Minimum and maximum values will be presented to the same decimal precision as the raw values, mean, median, Q1, and Q3 values to one more decimal than the raw values, and the SD to two more decimals than the raw values. All percentages will be presented to one decimal place. All p-values will be presented with 4 decimal places and will be shown as '<0.0001' if the value is smaller than 0.0001.

Relative study day will be provided in data listings. Day 1 is defined as the date of first treatment. Other study days are defined relative to Study Day 1. Relative day is calculated as (date of interest - date of the first treatment + 1) for study days on or after the date of the treatment start, and as (date of interest - date of the first treatment) for study days prior to the date of the treatment start.

Figures will be created to plot the data where it is deemed necessary. All data collected on study in the eCRF will be included in data listings.

3.3. Baseline Definitions

Baseline values for Hb will be defined as the mean of the screening and Day 1 pre-treatment values. If one of the two assessments is missing, then a single assessment prior to the start of study treatment will be defined as baseline.

History of RBC transfusions will be gathered for each patient for up to 16 weeks before start of study treatment. Baseline RBC transfusion burden units per 8 weeks will be defined as the summed units transfused in the 8 weeks up to pre-dose Day 1 (Rel Day -55 to 1).

For all other analyses, baseline will be defined as the most recent non-missing measurement prior to the first administration of study drug.

3.4. Methods of Pooling Data

No data pooling will be performed in this study.

3.5. Adjustments for Covariates

No statistical modeling will be applied in this study, therefore adjustment for covariates would not be applicable.

3.6. Multiplicity

There are no planned multiplicity corrections for this study.

3.7. Subgroup Analysis

No analyses of patient subgroups are planned. However, summary tables will include separate displays for each transfusion history stratum.

3.8. Withdrawals and Dropouts

Patients who are withdrawn or discontinue from the study may be replaced to achieve the threshold of 45 evaluable patients at Week 24. If enrollment is discontinued in one or more transfusion history groups after the interim assessment, enrollment in the remaining transfusion history group(s) may be increased to allow for 45 total evaluable patients at study completion.

3.9. Missing Data

Unless otherwise specified, there will be no substitutions made to accommodate missing data. All data recorded on the case report form (CRF) will be included in data listings that will accompany the CSR.

RBC transfusion history dates may be imputed for the purposes of calculating baseline RBC transfusions. If the day or month are missing, the first day of the month or month of the year will be assumed. If the year is missing or the full date is missing, the RBC transfusion will be assumed to have occurred more than 8 weeks prior to study entry (to be excluded from the baseline calculation).

When tabulating adverse event data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as the first dose. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment initiation. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the date of first dose in order to conservatively report the event as treatment-emergent. A completely missing AE onset date will be coded as the day of first treatment

unless the end date is prior to study start. In this case, no imputation will be done and the AE will be considered as not treatment-emergent.

Partial start dates for concomitant medications will be handled in the same manner as partial adverse event onset dates. For concomitant medication end dates, where the day of the month is missing, it will be imputed to the last day of the month. If both day and month are missing, the day and month will be assumed to be December 31st.

3.10. Visit Windows

Efficacy analysis will be analyzed based on nominal visit. If no nominal assessment exists, but an unscheduled assessment falls into the analysis visit window as defined in Table 3 and the preceding instructions, this assessment will be used. If more than one unscheduled assessment exists in the window, the visit closest to the target date will be used. If there is a tie, the latest value will be used.

Safety analyses will be based on nominal visits, where applicable. Unscheduled safety assessments will not have visit windows applied.

Table 3 Evaluation Intervals for Efficacy Analysis

Nominal Visit	Target Study Day	Protocol-Specified Study Day Window (inclusive)	Interval for Analysis
Screening	NA	-56 to -1	-56 to -1
Week 1 Day 1	1	1 to 1	1 to 1
Week 2 Day 1	8	5 to 11	2 to 15
Week 4 Day 1	22	19 to 25	16 to 29
Week 6 Day 1	36	33 to 39	30 to 43
Week 8 Day 1	50	47 to 53	44 to 57
Week 10 Day 1	64	61 to 67	58 to 71
Week 12 Day 1	78	75 to 81	72 to 85
Week 14 Day 1	92	89 to 95	86 to 99
Week 16 Day 1	106	103 to 109	100 to 120
Week 20 Day 1	134	131 to 137	121 to 141
Week 22 Day 1	148	145 to 151	142 to 155
Week 24 Day 1	162	159 to 165	156 to 169
Week 26 Day 1	176	173 to 179	170 to 183
Week 28 Day 1	190	187 to 193	184 to 197
Week 30 Day 1	204	201 to 207	198 to 211
Week 32 Day 1	218	215 to 218	212 to 225
Week 34 Day 1	232	229 to 235	226 to 239
Week 36 Day 1	246	243 to 249	240 to 253
Week 38 Day 1	260	257 to 263	254 to 267
Week 40 Day 1	274	271 to 277	268 to 281
Week 42 Day 1	288	285 to 291	282 to 295
Week 44 Day 1	302	299 to 305	296 to 309

Week 46 Day 1	316	313 to 319	310 to 323
Week 48 Day 1	330	327 to 333	324 to 333

3.11. Futility Assessment

A futility assessment will occur once 15 patients overall or 8 patients in a single transfusion stratum have evaluable responses on the HI-E criteria at W24D1, 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 W24D1. A patient with confirmed HI-E response at W16D1 but progression/relapse at W24D1 will be considered a responder for the purposes of the futility assessment.

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.

An informal futility assessment will occur after 15 patients have completed the W24D1 visit or dropped out. The proportion of patients with confirmed HI-E response at any timepoint up to W24D1 will be summarized. Patients discontinuing prior to completing HI-E assessment will be considered non-responders. Additional efficacy and safety data will be summarized for these patients as deemed appropriate.

3.11.1. Statistical Justification

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.

4. STUDY ANALYSES

4.1. Study Population Analyses

4.1.1. Patient Disposition

The number of screened patients, proportion of screened patients enrolled, and reasons for screen failure will be summarized by transfusion history group at screening. Proportions will be out of the total number of patients screened.

Patient disposition will be tabulated by stratum and overall for all enrolled patients. Summaries will include:

- Patients enrolled
- Patients dosed
- Patients in each analysis population
- Patients who completed the primary treatment period (through Week 24 study visit)
- Patients who completed the extension treatment period (through Week 48 study visit)
- Patient's treatment discontinuations and primary reasons(based on End of Treatment form) by treatment period
- Patient's study discontinuations and primary reasons(based on End of Study form) by treatment period

Patients who discontinued treatment/study due to the current early study termination will have the corresponding primary reason reported as "Study termination by sponsor".

A by-patient data listing will be included.

4.1.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by transfusion history stratum and overall in FAS. Age, age group (<64, 65-74, ≥75), gender, ethnicity, race, height, weight, and body mass index (BMI) at the screening visit will be summarized using descriptive statistics by transfusion history stratum and overall.

Demographic and baseline data for each patient will be provided in data listings.

4.1.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the March 2022 version of the World Health Organization (WHO) Drug Global dictionary (B3 format). Prior medications and non-medication therapies will be reported only in data listings.

Concomitant medications are defined as medications started prior to or after the start of study treatment and continued during the study or until the completion of the End of Study (EOS) visit. Prior medications are defined as those that both start and end before dosing.

Concomitant medications will be summarized descriptively for each stratum and overall by therapeutic subgroup (Anatomical Therapeutic Chemical [ATC] 2nd level), chemical subgroup (ATC 4th level) and preferred name for the FAS and displayed in data listings. Patients taking the same medication multiple times will be counted once per medication.

Concomitant procedures (non-medical therapies) will be coded using version 26.1 of the Medical Dictionary of Regulatory Activities (MedDRA). Concomitant procedures will be reported only in data listings.

4.1.4. Protocol Deviations

Major protocol deviations will be summarized in FAS with descriptive statistics for each transfusion history stratum and overall by type (as applicable). All protocol deviations will be presented in a data listing.

4.1.5. Medical and Disease Histories

4.1.5.1. MDS Disease History

Patient MDS disease history will be summarized in FAS by transfusion history stratum and overall with descriptive statistics for years since diagnosis, ECOG performance status at W1D1 (0, 1, 2), and IPSS-R classification at Screening (Very Low, Low, Intermediate).

4.1.6. Prior and Concomitant MDS Treatment

Prior and concomitant treatment for the following supportive therapies will be presented in a data listing: any iron chelation therapy, any erythropoiesis-stimulating agent, G-CSF, luspatercept, lenalidomide.

Prior and concomitant systemic therapy will be presented in a data listing by therapy type (systemic cytotoxic chemotherapy, systemic targeted therapy, hypomethylating agent, anti-cancer hormonal therapy, immuno-oncology agents, other systemic therapy).

4.1.6.1. Transfusion History

By-patient data listings for RBC and platelet transfusion prior to initiation of study treatment will be presented.

4.1.6.2. General Medical History

Medical history will be coded using version 26.1 of MedDRA. Number and percentage of patients who had medical history will be tabulated in FAS by transfusion history stratum and overall using system organ class (SOC) and preferred term (PT). Patients will be counted only once within each SOC and PT.

By-patient data listings will be presented.

4.2. Efficacy Evaluation

Efficacy analyses will be conducted using the EES.

4.2.1. Analysis of Primary Endpoints

4.2.1.1. HI-E Response and MDS assessments

The proportion of patients with HI-E response ≥ 8 weeks within 24 weeks of etavopivat treatment will be analyzed across the pooled strata and within each stratum. Patients will be considered responders if they satisfy HI-E criteria during any continuous ≥ 8-week treatment interval up to W24D1.

HI-E criteria are defined based on the patient's transfusion history stratum at D1:

NTD: A patient is considered a responder where at least one continuous interval >= 8 weeks occurs where all of the following criteria are met:

- Hb is increased by ≥ 1.5 g/dL relative to baseline at 2 or more consecutive visits
- Relapse date (date of first Hb measurement with < 1.5 g/dL change from baseline following the qualifying increase) occurs at least 8-weeks after the first incidence of qualifying Hb increase
- Patient is free of RBC transfusions

LTB: A patient is considered a responder if they are free of RBC transfusions over any continuous 8-week period.

HTB: A patient is considered a responder if they have a ≥ 50% reduction in RBC transfusion burden relative to baseline RBC transfusion burden per 8 weeks over any continuous 8-week period.

Percent reduction in RBC transfusion burden is calculated for all rolling 56-day intervals in the 24-week primary treatment period (i.e. Days 2-57, Days 3-58,…, Days 113-168) as

$$-100 \times \frac{RBC\ units\ transfused\ in\ 56\ day\ interval - Baseline\ RBC\ transfusion\ burden\ per\ 8\ weeks}{Baseline\ RBC\ transfusion\ burden\ per\ 8\ weeks}$$

The numerator for the response rate will be the total number of responders (summed across all baseline transfusion categories). The denominator will be the number of patients in the EES.

MDS baseline assessment including the score based on Revised International Prognostic Scoring System (IPSS-R) for MDS and MDS response assessment wll be presented in data listings.

4.2.2. Analysis of Secondary Endpoints

4.2.2.1. Transfusion Burden

For the LTB and HTB strata only, the total RBC units transfused and % reduction from baseline will be summarized for each of the following 8-week study intervals: Week 1 to 8 (Rel Day 2 to 57), Week 9 to 16 (Rel Day 58 to 113), Week 17 to 24 (Rel Day 114 to 169), Week 25 to 32 (Rel Day 170 to 225), Week 33 to 40 (Rel Day 226 to 281), Week 41 to 48 (Rel Day 282 to 337).

% reduction from baseline in RBC transfusion burden is defined as

$$-100 \times \frac{Total\ RBC\ Units\ Transfused\ During\ Interval}{Baseline\ RBC\ Units\ Transfused\ Per\ 8\ Weeks}$$

Patients who have discontinued treatment prior to completing the specified interval will be excluded from the analysis.

4.3. Pharmacokinetic Evaluations

Etavopivat plasma concentrations will be summarized for each transfusion history stratum and overall with descriptive statistics by study visit, and planned collection time (e.g., pre-dose, 1-hour post-dose, etc..) and included in data listings. A line plot of semi-intensive PK concentration data by transfusion history stratum on both linear and semi-log scale will be provided for Day 1 and EOPT.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety Set. Adverse event summaries, summaries of abnormal assessment results, and shift tables will include both primary and extension treatment periods.

4.4.1. Study Drug Exposure

Duration of study drug exposure will be calculated as the number of days with study drug, as determined below, and will be summarized by cohort and treatment period (Primary, Extension, and Overall) using descriptive statistics based on the following formula.

$$\begin{aligned} &Duration\ of\ \ Study\ Drug\ Exposure \\ &\quad = (Date\ of\ last\ dose\ in\ treatment\ period \\ &\quad - Date\ of first\ dose\ in\ treatment\ period) + 1 \end{aligned}$$

Duration of study drug exposure for each patient will also be provided in a data listing.

4.4.1.1. Drug Exposure and Compliance

Duration of drug exposure will be summarized with descriptive statistics by transfusion history stratum and provided in a by-patient data listing.

Study drug compliance will be assessed by examination of the dispensed and returned tablets. Percent compliance will be calculated based on comparing the returned tablets to the expected number of tablets to be taken until treatment discontinuation per the following definition, where the number of tablets expected to be taken is defined as the duration of study drug exposure multiplied by 2:

$$Percent\ Compliance = \frac{(Number\ of\ tablets\ dispensed - Number\ of\ tablets\ returned)}{(Number\ of\ tablets\ expected\ to\ be\ taken)} \times 100$$

Study drug compliance will be summarized by transfusion history stratum and treatment period (Primary, Extension, and Overall) using descriptive statistics and will be categorized into the following categories: < 80%, 80-100%, > 100 – 120%, and > 120%. Percent compliance will be summarized with descriptive statistics overall and by transfusion history stratum.

The incidence of patients with early discontinuations (before W48D1 visit), dose holds, and dose reductions will be summarized with descriptive statistics.

A by-patient data listing will be presented. Patients who withdrew from the study early will be flagged.

4.4.2. Adverse Events

All AEs will be coded using version 26.1 of MedDRA and will be displayed in tables and data listings using SOC and PT.

Adverse events will be summarized in tables presenting both number and percent of patients as well as number of events and incidence rates (events per 100 patient-years). For the former, a patient is counted once for a given SOC and PT. For the latter, each individual adverse event will be counted separately.

For ongoing patients or patients who have discontinued treatment within 28 days prior to the analysis date, time on study is calculated as (data cut date– date of first dose + 1)/365.25. For patients who have discontinued treatment, time on study is calculated as (date of last dose + 28 – date of first dose + 1)/365.25. Cumulative patient-years are the sum of time on study for all patients in the specified group (e.g. NTD).

Analyses of adverse events will be performed for those events that are considered treatment-emergent, which is defined as any adverse event that emerges or worsens in the period from first dose of study drug to 28 days after the last dose of study drug.

TEAEs will be summarized by SOC and PT by transfusion history stratum and overall for the following categories, unless otherwise noted:

- All TEAEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs

- Grade 3 or higher drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- Serious drug-related TEAEs
- TEAEs requiring dose modification (any dose reduction from 400 mg or temporary interruption in dosing due to an adverse event)

TEAEs will be considered drug-related if assessed by the Investigator as possibly related or related, or if relationship is missing. For summaries of severity, when reporting number and percent of patients, only the maximum severity level will be presented in the severity summaries.

All adverse events occurring on-study will be listed in patient data listings. By-patient listings also will be provided for the following: SAEs, and AEs leading to discontinuation of study drug.

4.4.3. Laboratory Data

Laboratory test results will be presented based on the measurements with Système International (SI) units provided by a central laboratory. Unit conversions to SI units will be performed for test results collected from local labs before the raw data is received by the biostatistics team. Additional conversions may be performed at analysis dataset level with appropriate conversion factors if necessary. If a laboratory value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier, while the original values including non-numeric qualifier will be provided in the data listings.

Results and change from baseline will be summarized with descriptive statistics by transfusion history stratum, nominal time point, laboratory panel (hematology, chemistry, coagulation, urinalysis, and Hb electrophoresis) and parameter. In the event of multiple entries by time point, the latest non-missing value will be used. Only the pre-specified parameters for the Hb electrophoresis panel will be summarized; additional Hb variants reported will be presented in listings only.

All available laboratory data for hematology, chemistry, Hb electrophoresis, coagulation, serology, urinalysis, and pregnancy tests (See Appendix E of the study protocol for further details) will be provided in data listings. Summaries will be done for the listed parameters below only:

- Hematology: Hb, Hematocrit, RBCs, RBW, Absolute Reticulocytes, Reticulocytes (%), MCHC, MCV, Platelets, WBC, Absolute Neutrophils, Neutrophils (%), Abs Lymphocytes, Lymphocytes (%), Abs Eosinophils, Eosinophils (%), Abs Monocytes, Monocytes (%), Abs Basophils, Basophils (%)
- Hb electrophoresis: Hgb A, Hgb A2, Hgb C, Hgb F, and Hgb S
- Chemistry: Albumin, Total Protein, Sodium, Potassium, Calcium, Phosphorus, Chloride, Bicarbonate/CO2, BUN, Creatinine, Magnesium, Glucose, Amylase, Lipase,

LDH, ALT, AST, Alkaline Phosphatase, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, eGFR, and GGT
- Coagulation: INR, Prothrombin time, and PTT
- Urinalysis: pH, Specific Gravity

Line plots with mean ± SE over nominal visits will be included for liver function tests (ALT, AST, ALP, and total bilirubin). eDISH plots of peak AST and ALT versus total bilirubin at the same visit of peak ALT/AST will be included.

4.4.4. Vital Signs and Physical Examination

Vital sign results and change from baseline will be summarized with descriptive statistics by nominal time point and transfusion history stratum. Results summarized will include systolic and diastolic blood pressure (BP), pulse, respiratory rate, and temperature.

All physical examination findings and vital sign measurements will be presented in data listings.

4.4.5. Cardiac Monitoring

ECG results (absolute value and change from baseline) will be summarized using descriptive statistics by transfusion history stratum and nominal time point for: RR, PR, QT, QRS, HR, and QT interval corrected using Fridericia's correction formula (QTcF).

ECG data for each patient will be provided in a data listing.

5. CHANGES FROM PROTOCOL

5.1. Endpoint Phrasing Clarifications

No clarifications need to be made.

5.2. Changes to Planned Analyses

For the purpose to support an abbreviated CSR, a selected set of endpoints are included in this SAP. The following analysis populations and endpoints mentioned in the protocol are not included:

Protocol Section 3.2:

- The HI-E for ≥ 8 weeks within 16 and 48 weeks of etavopivat
- The HI-E for ≥ 16 weeks within 24 and 48 weeks of etavopivat
- Overall response rate (2006 International Working Group [IWG] Criteria) (see protocol Appendix A)
- Duration of response (2006 IWG Criteria)
- Increase in neutrophils and/or platelets counts
- Decrease in ferritin and transferrin saturation (TSAT)
- Decrease in iron chelation therapy
- Overall survival

Protocol Section 3.3:

- PK: 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 (AUC0-last), from time zero to infinity (AUC0-inf), for a dosing interval (AUCtau/AUC0-24).
- RBC 2,3-DPG and ATP levels over time

Protocol Section 3.4:

- 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
- 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

Protocol Section 9.2:

- Interim Assessment Set and Per-Protocol Set

5.3. Additional Changes

No patients were anticipated to enter the optional prolonged treatment period. Therefore, related information such as treatment exposure definition and schedule of events are not applicable and are not included in this SAP.

6. REFERENCES

Nordin Å, Taft C, Lundgren-Nilsson Å, Dencker A. Minimal important differences for fatigue patient reported outcome measures − a systematic review. BMC Med Res Methodology. 2016; 16:62.

PROMIS. PROMIS Fatigue scoring manual. Accessed July 21, 2022. https://www.fda.gov/media/137977/download

Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol*. 2011;64(5):507-516. doi:10.1016/j.jclinepi.2010.11.018