Official Title of Study:

A Phase 3, Double-Blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo in Subjects with Myeloproliferative Neoplasm-Associated Myelofibrosis on Concomitant JAK2 Inhibitor Therapy and Who Require Red Blood Cell Transfusions

The “Independence” Trial

NCT Number: NCT04717414

Document Date (Date in which document was last revised): 09 Dec 2022

A PHASE 3, DOUBLE-BLIND, RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS PLACEBO IN SUBJECTS WITH MYELOPROLIFERATIVE NEOPLASM-ASSOCIATED MYELOFIBROSIS ON CONCOMITANT JAK2 INHIBITOR THERAPY AND WHO REQUIRE RED BLOOD CELL TRANSFUSIONS

The "INDEPENDENCE" Trial

PROTOCOL NUMBER:	**ACE-536-MF-002**
COMPOUND NUMBER:	**ACE-536 (BMS-986346)**
DATE FINAL:	**09 Mar 2020**
PROTOCOL AMENDMENT 1.0:	**09 Dec 2022**
EudraCT NUMBER:	**2020-000607-36**
IND NUMBER:	**112,562**
SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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Back-up 24-hour Global Emergency Contact Call Center: +1-877-501-7738

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted] [redacted]

dd mmm yyyy

[redacted]

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 1.0:

The primary reasons for this protocol amendment are:

- Study design has been revised to include subject unblinding after Day 169 for response failures and to allow crossover to open-label luspatercept for placebo subjects only, enabling access to the product earlier.
- To incorporate a risk/benefit assessment section to align with [redacted]
- To introduce a superiority interim analysis (IA) at [redacted] information fraction [redacted]

These revisions have also been made in the Protocol Summary and are not summarized in the table below.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized.

This protocol amendment applies to all subjects in the study.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page Section 1.2: Luspatercept Background	Added the Bristol-Myers Squibb (BMS) compound number.	To align BMS and heritage Celgene compound numbers.
Title Page: Medical Monitor/Emergency Contact Information	Updated the Medical Monitor information.	Based on change in personnel.
Section 1.1: Myeloproliferative Neoplasms-associated Myelofibrosis	Updated the percentage of patients referred to as “triple negative”.	Updated for consistency with the risk/benefit assessment section.
Section 1.1.3.5: Thalidomide, Lenalidomide, and Pomalidomide Section 9.3: Sample Size and Power Considerations	Added number of subjects for the response rates for the primary endpoint.	Clarification of the referenced data discussing a modified intent-to-treat (ITT) population.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2.2: Summary of Clinical Experience	Added details of the study for which the results were presented in this section.	Clarification of the referenced data.
Section 1.3.2.4: Rationale for the Open-label Extension Phase	Added individual unblinding and crossover details for the Extension Phase.	Clarification on the scope of unblinding in the Open-label Extension Phase.
Section 1.3.4: Rationale for Endpoints	Added clarification regarding primary and secondary endpoint time periods.	To clarify the timeframe definition for the endpoints that require response to start during the primary endpoint timeframe.
Section 1.4: Risk/Benefit Assessments	New section and subsections 1.4.1, 1.4.2, and 1.4.3 added.	To align with the [redacted]
Section 2: Study Objectives and Endpoints (Table 1: Study Objectives)	"Treatment satisfaction" was added to the exploratory objective for patient-reported outcomes (PROs). Exposure-response relationship for luspatercept was added as an exploratory objective.	To align with the PRO endpoints listed. To better understand this exposure-response relationship in myelofibrosis.
Section 3.1.1: Screening Period and Randomization	Clarifications were made for maintaining the subject blinding.	To ensure alignment on maintaining subject blinding.
Section 3.1.2: Blinded Core Treatment Period (Weeks 1 Through 24)	Follow-up period was specified for subjects who discontinued Investigational Product (IP) prior to Day 169.	To clarify that all subjects should complete a Day 169 Response Assessment.
Section 3.1.3: Day 169 Response Assessment Section 3.1.5: Unblinding and Open-label Extension Treatment Period Section 6.2.2: Day 169 Response Assessment	Added details regarding timepoint when subjects would be considered for open-label crossover.	To align criteria for unblinding and crossover.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2.4: Open-label Extension Treatment Period (Crossover)		
Section 3.1.5: Unblinding and Open-label Extension Treatment Period Section 6.2.4: Open-label Extension Treatment Period (Crossover)	Added eligibility clarification for subjects randomized to placebo and best supportive care (BSC) group and subjects randomized to luspatercept and BSC group.	To align criteria for unblinding and crossover.
Section 3.1.5: Unblinding and Open-label Extension Treatment Period Table 3: Table of Events Section 6.2.4: Open-label Extension Treatment Period (Crossover)	Added that collection of biomarker samples on Cycle 5 Day 1 and PRO assessments will not be required during the Open-label Extension Treatment Period.	Intermediate timepoint for biomarker samples in a crossover population is not necessary.
Section 3.1.5: Unblinding and Open-label Extension Treatment Period	Added “clinical” to benefit demonstrated.	To clarify that the definition of clinical benefit is any of the 3 criteria.
Section 3.1.6: End of Treatment and Posttreatment Follow-up Period Section 6.4: End of Treatment Visit Section 6.5: Posttreatment Follow-up Period Section 6.5.1: 42-Day Follow-up Period (referred to as the Safety Follow-up)	Added that End of Treatment (EOT) and 42-day Follow-up Period are applicable for both blinded and crossover subjects.	To clarify that EOT and 42-day Follow-up Period are applicable for both blinded and crossover subjects.
Figure 2: Overall Study Design	The schema was updated to reflect the crossover to the Open-label Extension Treatment Period, and	To better represent the overall study design, including

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	abbreviations and footnotes were updated accordingly.	subject unblinding and crossover.
Section 3.2: Study Duration for Subjects	Added details for crossover. Clarified that the Posttreatment Follow-up Period is every 3 months for at least 5 years following the date of first dose of blinded IP.	To include duration details for subjects who may enter crossover. To clarify that the scope of the Posttreatment Follow-up Period may be based on first dose of blinded IP.
Section 4.3: Exclusion Criteria	In criterion 3.e, the estimated glomerular filtration rate was lowered from 40 mL/min/1.73 m^2 to 30 mL/min/1.73 m^2. Added a sub-criterion 11.a, relating to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at study entry.	To align with the approved luspatercept labeling in multiple countries. To clarify study entry criteria related to SARS-CoV-2.
Section 5: Table of Events (Table 3: Table of Events)	Removed the column for "Every 4th Cycle". Table was updated to include the "crossover" timepoint. Row was added for integrated response technology (IRT), "Unblinding via IRT" for the crossover timepoint. Footnotes were updated.	To better align the table of events to represent the overall revised study design, including subject unblinding and crossover.
Section 6.2: Treatment Phase	Removed the statement that subjects who become ineligible after randomization but prior to receiving first dose of IP will be replaced.	To align with the statistical analysis and ITT population definition.
Section 6.7: Pharmacokinetics Section 6.8: Antidrug Antibody	Clarified timepoint for additional sample collection if subject discontinues before samples are collected in the Treatment Phase	To align within the protocol and ensure samples continue to be collected for subjects who discontinue early.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	or does not participate in the Extension Treatment Phase.	
Section 6.9.1: Additional and Optional Research	New section and sub-sections 6.9.1.1 and 6.9.1.2 were added to provide information regarding additional and optional research.	To align with informed consent language and clarify the use of samples for additional and/or optional research.
Section 6.10.3: RBC Transfusion-related Experience Measures and Patient Global Impression of Transfusion Satisfaction (PGI-TS)	Clarifications made to the procedural burden of red blood cell (RBC) transfusions questionnaire.	To align with the actual instrument being used as also described in Protocol Administrative Letter #1.
Section 7.1: Description of Investigational Product(s)	Added wording for obtaining placebo (normal saline) or Janus kinase 2 (JAK2) inhibitor therapy based on local guidelines.	Due to varied country regulations and clinical trial agreements for obtaining placebo or JAK2 inhibitor therapy.
Section 7.3.2: Dose Delay and Dose Reduction (Table 5: Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guidelines)	Footnote 'b' was updated to read as follows "Includes systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg."	To align blood pressure guidance with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3.
Section 7.6.1: Blinding	Added that the subject will remain blinded to treatment unless the subject is unblinded after Day 169.	Clarification to ensure that blind is maintained unless an individual subject has been unblinded.
Section 9.2: Study Population Definitions	Under sub-heading 'Safety Population', added that the estimand framework, handling of intercurrent events, and statistical methods will be described in the statistical analysis plan (SAP).	To acknowledge Committee for Medicinal Products for Human Use (CHMP) advice.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.3: Sample Size and Power Considerations	Added a sentence to accommodate superiority IA.	To describe the impact of the superiority IA on sample size/power.
Section 9.7.1: Primary Efficacy Endpoint	Added that if the stratified Cochran-Mantel-Haenszel (CMH) test is not estimable due to low strata size, the stratified Miettinen-Nurminen (MN) method will be used.	To align with hematology-level standard analyses methods.
Section 9.7.2.2: Additional Secondary Efficacy Endpoints	Added that certain endpoints (ie, duration of red blood cell transfusion independence [RBC-TI] 12, duration of reduction in transfusion burden, RBC-TI ≥ 12 weeks in treatment period, RBC-TI ≥ 16 weeks in treatment period, cumulative duration RBC-transfusion independence, and mean hemoglobin (Hgb) increase ≥ 1 g/dL) will be calculated through EOT or at time of crossover (if applicable).	To align endpoint modifications for unblinding and crossover.
Section 9.9.1: Interim Analysis for Futility	Clarified that the futility IA timing will be based on the primary endpoint and approximately [redacted] randomized subjects. Clarified that an external data monitoring committee (DMC) will review the unblinded data and provide a recommendation.	To elaborate on the details for the futility IA.
Section 9.9.2: Interim Analysis for Superiority	Added a superiority IA at approximately [redacted] randomized subjects.	To maintain the trial completion timelines.
Section 9.9.3: Final Analysis	Added clarification for when the final analysis will be performed.	To clarify the timeframe for the final analysis to align with the amount of follow-up needed to analyze the primary and key secondary endpoints.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added a description of the alpha adjustment on the final analysis.	To describe the impact of the superiority IA on the final analysis.
Section 9.10.2: Patient-reported Outcome Measures	Removed language relating to the handling of missing data and scoring/manual.	Not required in the protocol and will be described in the SAP.
Section 9.10.6: Sensitivity Analysis	Updated the section to state "sensitivity analyses and supplemental estimands will be further described in the SAP".	Sensitivity analyses are being revised [redacted], particularly to re-frame into the estimand framework.
Section 9.10.7: Data Monitoring Committee	Specified that the independent third party is the Statistical Data Analysis Center.	To align terminology with current company standard operating procedures (SOPs).
Section 10.1: Monitoring, Recording and Reporting of Adverse Events	Section was updated to provide instructions on how to report serious adverse events (SAEs) to Drug Safety.	To ensure that instructions provided are clear and align with reporting processes.
Section 10.7: Expedited Reporting of Adverse Events	Added updates for expedited reporting of adverse events (AEs) to Food and Drug Administration (FDA).	To ensure that instructions provided are clear and align with reporting processes.
Section 10.8: COVID-19 Reporting	New section added to provide information on coronavirus disease 2019 (COVID-19) reporting.	Due to the pandemic, sections for COVID-19 reporting were added.
Section 12.2: Emergency Identification of Investigational Products	Clarified that blind must not be broken except for the subject unblinding to determine crossover eligibility.	To ensure emergency unblinding only in cases of emergency. Unblinding related to crossover does not apply.
Section 15.1: Study Monitoring and Source Data Verification	Study monitoring details were added.	To clarify the processes regarding risk-based monitoring.
Section 15.3: Investigational Medicinal Product Quality Issues	Information in this section was updated.	To align with processes for quality issue reporting.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 17: References	Section was updated.	To include new references used.
Appendix A: Table of Abbreviations	List was updated.	To align with updated text in the protocol.

PROTOCOL SUMMARY

Study Title

A Phase 3, Double-Blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo in Subjects with Myeloproliferative Neoplasm-Associated Myelofibrosis on Concomitant JAK2 Inhibitor Therapy and Who Require Red Blood Cell Transfusions

Indication

Treatment of anemia associated with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) in subjects who are on concomitant Janus kinase 2 (JAK2) inhibitor therapy and who require red blood cell (RBC) transfusions.

Objectives

The **primary objective** of this study is:

- to evaluate the efficacy of luspatercept compared with placebo for the treatment of anemia in subjects with MPN-associated MF with concomitant JAK2 inhibitor therapy and who require RBC transfusions.

The **secondary objectives** of this study are to evaluate:

- additional efficacy parameters of luspatercept compared with placebo;
- the safety of luspatercept compared to placebo in subjects with MPN-associated MF as measured by the frequency and severity of adverse events (AEs), serious adverse events (SAEs), antidrug antibodies (ADA), and transformation to blast phase;
- pharmacokinetics (PK) for luspatercept in MPN-associated MF.

The **exploratory objectives** of this are:

- to explore the effect of luspatercept compared with placebo in subjects with MPN-associated MF on:
  - serum ferritin
  - overall survival
  - patient-reported outcomes to measure health-related quality of life, health utility scores, anemia-related symptoms, treatment satisfaction, and RBC transfusion experience
  - healthcare resource utilization
  - biomarker relationships to efficacy, and markers related to the disease and the mechanism of action of luspatercept
  - exposure-response relationships for luspatercept

Study Population and Design

This is a Phase 3, global, multicenter, double-blind, randomized study that will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Key inclusion criteria for this study will include subjects with:

- a diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria or diagnosis of post-essential thrombocythemia (post-ET) or post-polycythemia vera (post-PV) MF according to the International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) 2007 criteria, confirmed by the most recent local pathology report;
- a baseline transfusion burden defined as 4 to 12 RBC units/12 weeks immediately up to the date of randomization, with no interval > 6 weeks (42 days) without ≥ 1 RBC transfusion;
- a continuous (eg, absent of dose interruptions lasting ≥ 2 consecutive weeks) JAK2 inhibitor therapy as approved for the treatment for MPN-associated MF as part of their standard-of-care therapy for at least 32 weeks, while being on stable daily dose for at least 16 weeks immediately up to the date of randomization and anticipated to be on a stable daily dose of that JAK2 inhibitor for at least 24 weeks after randomization.

Overall, the study will enroll approximately 309 subjects globally who will be randomized at a 2:1 ratio to either luspatercept or placebo.

The study will consist of a:

- Screening Period
- Treatment Phase
- Posttreatment Follow-up Period

Refer to Section 3.1 for more information.

Length of Study

The expected duration of the study for an individual subject is approximately 5 years, consisting of a maximum 28-day Screening Period, a Blinded Core Treatment Period of 24 weeks, a Day 169 Response Assessment, a Blinded Extension Treatment Period, an Open-label Extension Treatment Period (if unblinded), and a Posttreatment Follow-up Period of at least 5 years post first dose or at least 3 years post last dose, whichever occurs later.

The Screening Period

Screening procedures are to take place over a maximum of 28 days immediately prior to their randomization date, after which the subject will be randomized using the integrated response technology (IRT) built for this study.

The diagnosis of MPN-associated MF will be confirmed by the Investigator based on review of the most recent local pathology report (including bone marrow biopsy information). The report should come from the most recent local bone marrow biopsy performed and should also contain the mutational status of the disease (eg, Janus kinase 2 [*JAK2*] gene, thrombopoietin receptor [*MPL*] gene, and calreticulin [*CALR*] gene).

Red blood cell (RBC) transfusion history must be available for at least 16 weeks immediately prior to the subject's randomization date. Transfusion data should include, but not be limited to, the type of transfusion (ie, RBC or whole blood), the number of units, volume of transfusion, pretransfusion hemoglobin (Hgb) values, and date of transfusion. Red blood cell (RBC) transfusions given at outside local institutions must also be collected. For the purpose of this study, RBC and whole blood transfusions are regarded as equivalent.

The Blinded Core Treatment Period (Weeks 1 Through 24)

The first dose of investigational product (IP) may be administered no later than 3 days from the date of randomization; however, it can be administered on the same day as randomization.

Subjects will receive a starting dose level of IP at 1.33 mg/kg as a subcutaneous injection every 3 weeks (or an equivalent volume of placebo) on Day 1 of each 21-day treatment cycle (unless there are dose delays). Best supportive care (BSC) may be used in combination with IP when clinically indicated per Investigator. Additional details can be found in Section 8.

Day 169 Response Assessment

The Day 169 Response Assessment is an evaluation for all subjects who received at least 1 dose of IP to confirm clinical benefit and is performed by the Investigator to determine if a subject is eligible to continue receiving IP treatment in the Blinded Extension Treatment Period.

Subjects who do not meet any of the clinical benefit criteria will have the opportunity after completion of the Day 169 visit, End of Treatment (EOT), and subsequent 42-Day Follow-up Period to be considered for optional individual open-label crossover if their blinded treatment was placebo. Subjects randomized to luspatercept will not be eligible.

Additional details can be found in Section 6.2.2.

Blinded Extension Treatment Period (Week 25+)

Subjects who meet the clinical benefit criteria as determined by the Investigator for remaining on double-blind treatment with IP in the Blinded Extension Treatment Period may continue dosing on Day 1 of each 21-day treatment cycle as long as they are benefitting from IP as assessed by the Investigator, or until subjects experience transformation to blast phase or unacceptable toxicities, withdraw consent, or meet any other discontinuation criteria (refer to Section 11.1 for full treatment discontinuation criteria).

Serial measurements of safety and efficacy will continue on scheduled study visits in the Blinded Extension Treatment Period. Refer to Section 6 for a full list of study procedures/assessments.

The same dose titration, delay and/or reduction, and treatment discontinuation criteria will still apply in the Blinded Extension Treatment Period. See Section 7.3 for dose modification rules.

Unblinding and Open-label Extension Treatment Period

Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessment as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive

luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period, as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.

Study unblinding is planned when all subjects have completed or discontinued early from the Blinded Core Treatment Period, the primary endpoint has been analyzed, and the Data Monitoring Committee (DMC) has been consulted.

At the time of subject and study unblinding:

- **subjects randomized to placebo and BSC** who meet the safety-related eligibility criteria of the study (excluding inclusion criteria 1 through 4) may receive luspatercept treatment with a starting dose of 1.33 mg/kg at the next cycle after unblinding. The eligibility criteria must be verified by the Investigator, with appropriate documentation available that may be reviewed by the Sponsor prior to a subject receiving their first luspatercept dose. Upon meeting the eligibility criteria, subjects are eligible for assignment to luspatercept treatment via IRT. Subjects will continue in the study for at least 24 weeks following the schedule of assessments beginning with the Cycle 1 Day 1 assessments, with the exception of PK and antidrug antibodies (ADA) samples that will not be collected. Collection of biomarker samples on Cycle 5 Day 1 will not be required during the Open-label Extension Treatment Period. In addition, patient-reported outcome (PRO) assessments will also not be required during the Open-label Extension Treatment Period.
- **subjects randomized to luspatercept and BSC** who have discontinued treatment will not be eligible for individual crossover to open-label luspatercept after unblinding. They will remain in the Posttreatment Follow-up Period at the time of unblinding as appropriate. Those subjects in the Blinded Extension Treatment Period can continue receiving luspatercept in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment.

<u>End of Treatment and Posttreatment Follow-up Period</u>

All subjects who have received at least 1 dose of IP should undergo end of treatment (EOT) evaluations when IP is discontinued (for both blinded and crossover subjects).

The Posttreatment Follow-up Period includes a 42-Day Follow-up Period starting from the date of last dose of IP (applicable for both blinded and crossover subjects) and Long-term Follow-up Period.

42-Day Follow-up Period

All AEs, including SAEs, regardless of causal relationship to IP, will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of IP (applicable for both blinded and crossover subjects).

Long-term Follow-up Period

For all subjects who receive at least 1 dose of IP, continuation of monitoring for transformation to blast phase will occur in the Posttreatment Follow-up Period, along with assessing adverse events of special interest (AESIs) and SAEs related to IP, data collection of new MPN-associated MF disease therapies, and overall survival every 3 months after the 42-Day Follow-up Period for at least 5 years following the date of first dose of IP or 3 years post last dose of IP, whichever occurs later, unless the subject withdraws consent from the study, dies, or is lost to follow up, whichever occurs first. Refer to Section 6.5 for additional details.

All subjects will be followed for RBC transfusions (occurring at the study site or at outside institutions) for 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed, and the availability of a roll-over protocol exists into which any subjects that remain on study may be consented to continue receiving access to luspatercept if they are deriving clinical benefit or be monitored for long-term safety. Such a protocol would be written for a compound that would not yet be commercially available.

Refer to Section 3.1 for more information.

Study Treatments

Subjects satisfying the eligibility criteria will be randomized by a central randomization procedure using IRT at a 2:1 ratio to either:

- **Experimental Arm**: Luspatercept (ACE-536, also known as BMS-986346) + BSC; luspatercept starting dose of 1.33 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

OR

- **Control Arm**: Placebo + BSC; placebo starting dose with volume equivalent to experimental arm subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

Randomization will be stratified based on the following factors:

- RBC-transfusion burden at baseline
  - 4 to 5 units/12 weeks
  - 6 to 12 units/12 weeks
- Dynamic International Prognostic Scoring System (DIPSS) score at baseline
  - Intermediate-1/Intermediate-2

– High risk

Once randomized, the blind should be maintained for persons responsible for the ongoing conduct of the study until all blinded subjects have completed or discontinued early from the Blinded Core Treatment Period, the primary endpoint has been analyzed, and the DMC has been consulted.

During the Treatment Phase, the starting dose can be titrated (increased) up to a maximum of 1.75 mg/kg, provided that the subject meets the appropriate criteria. The subject's dose may also be delayed, reduced, or discontinued, depending on the specific criteria (refer to Section 7.3).

Overview of Key Efficacy Assessments

Key efficacy assessments include:

- RBC transfusions
- Clinical benefit response assessment

Overview of Key Safety Assessments

Key safety assessments include:

- AE/SAE reporting
- Prior/Concomitant medications/procedures
- Hematology parameters
- Serum chemistry
- Urinalysis
- Pregnancy testing
- 12-lead electrocardiogram (ECG)
- Spleen size assessment via palpation
- Eastern Cooperative Oncology Group (ECOG) performance status
- Vital signs and body weight

Statistical Methods

For more specific information, please refer to Section 9 of the protocol.

A total of 309 subjects (206 in the active treatment group, 103 in the placebo group) will have 90% power to detect the difference [redacted]. The sample size calculation is based on a 2:1 randomization ratio, one-sided alpha of 0.025, test statistics on difference of proportions using an un-pooled estimate of variance with one non-binding interim futility analysis at [redacted] information fraction (eg, approximately [redacted] randomized subjects have completed the Day 169 Response Assessment or have discontinued the IP prior to the end of Week 24). The addition of a superiority interim analysis does not alter the original sample size calculation.

All efficacy analyses will be performed on the intent-to-treat (ITT) population (defined as all randomized subjects regardless of whether or not the subject received IP). Key efficacy analyses will be also performed on the modified ITT (mITT; defined as a sub-set of the ITT population that have no important protocol deviations of inclusion/exclusion criteria and no other important protocol deviations that could impact on efficacy outcome, and take at least one dose of IP) population as supportive evidence and to assess robustness of efficacy findings. Subjects will be analyzed according to their randomized treatment group.

The primary efficacy endpoint of RBC-transfusion independence (RBC-TI) is defined as the proportion of subjects who become RBC transfusion free during any consecutive 12-week period starting during the Blinded Core Treatment Period (the time from randomization up to and including Week 24), referred to as RBC-TI 12.

The key secondary endpoint, defined as the proportion of subjects who become RBC-transfusion free over any consecutive 16-week period starting during the Blinded Core Treatment Period (the time from randomization up to and including Week 24) and referred to as RBC-TI 16, will be tested in the same manner as the primary efficacy endpoint once superiority of luspatercept on the primary endpoint is demonstrated.

Other secondary endpoints will be summarized descriptively, unless otherwise specified, and will be based on the ITT population:

Duration of RBC-TI 12 will be summarized only for subjects who achieved RBC-TI 12 response. It is defined as the maximum duration of an RBC-TI 12 response, calculated from the start of a response (ie, RBC-TI 12) through end of treatment.

Reduction in transfusion burden is defined as the proportion of subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units from baseline over any consecutive 12-week period. It will be calculated from randomization through and including Week 24.

Duration of reduction in transfusion burden is defined as the maximum duration of when subjects reduce their transfusion burden by ≥ 50% and by ≥ 4 units from baseline over any consecutive 12-week period. It will be calculated from the start of the response up through end of treatment.

RBC-TI ≥ 12 weeks in treatment period (RBC-TI 12/TP) is defined as the proportion of subjects who become RBC-transfusion free over any consecutive 12-week period, calculated from the time of randomization up to the end of treatment.

RBC-TI ≥ 16 weeks in treatment period (RBC-TI 16/TP) is defined as the proportion of subjects who become RBC-transfusion free over any consecutive 16-week period, calculated from the time of randomization up to the end of treatment.

Change in RBC transfusion burden is defined as the mean change in transfusion burden (RBC units) from baseline. It will be calculated from randomization up to and including Week 24. This analysis will be conducted in subjects that remain on study (in the Treatment Phase or the Long-term Follow-up Period) at the time of Study Day 169.

Cumulative duration RBC-transfusion independence is defined as the cumulative response duration for subjects achieving multiple episodes of RBC-TI 12, calculated from randomization up through end of treatment.

Mean Hgb increase ≥ 1 g/dL is defined as the proportion of subjects achieving a mean Hgb increase ≥ 1 g/dL from baseline over any consecutive 12-week period in absence of RBC transfusions, calculated from any consecutive "rolling" 12-week period starting from randomization up to and including Week 24, as well as randomization up to end of treatment.

Change in serum ferritin from baseline is calculated from randomization up to and including Week 24, as well as randomization up to end of treatment. This analysis will be conducted in subjects that remain on study (in the Treatment Phase or the Long-term Follow-up Period) at the time of Study Day 169.

An interim analysis (IA) to assess futility will be performed on the primary endpoint in the ITT population when approximately [redacted] randomized subjects have completed the Day 169 Response Assessment or have discontinued IP prior to the end of Week 24 [redacted] information fraction). A conditional power approach is used for the futility analysis; if the interim analysis shows less than [redacted] conditional power, the trial may stop for futility. An external DMC will review the unblinded interim data and provide a futility recommendation.

An IA to test for superiority will be performed on the primary endpoint in the ITT population when approximately [redacted] randomized subjects have been followed for 40 weeks to accommodate the start of the key secondary endpoint of RBC-TI of 16 weeks ([redacted] information fraction). [redacted] An external DMC will review the unblinded interim data and will inform the Sponsor whether the superiority boundary has been crossed.

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1 INTRODUCTION

1.1 Myeloproliferative Neoplasms-associated Myelofibrosis

Myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) is a clonal myeloid neoplasm resulting from a transformed multipotent hematopoietic progenitor cell (Juliana, 2018) and is characterized by defective bone marrow function, bone marrow fibrosis with increased micro-vessel density, ineffective erythropoiesis, extramedullary hematopoiesis, an increased risk for transformation to blast phase (ie, acute myeloid leukemia [AML]), and an inflammatory state. Levels of hematopoietic stem and progenitor cells in the blood are increased, reflecting abnormal homing of hematopoietic stem and progenitor cells. The cause of MPN-associated MF is unknown and there are no known etiological factors (Mughal, 2014).

Myeloproliferative neoplasm (MPN)-associated MF can develop directly (primary myelofibrosis [PMF]) or evolve from other MPNs, including polycythemia vera (PV) and essential thrombocythemia (ET), and represent a group of Philadelphia chromosome-negative MPNs (Tefferi, 2007). Polycythemia vera (PV) and ET are characterized by increased levels of red blood cells (RBCs) and platelets, respectively. However, about 10% of affected patients develop bone marrow fibrosis morphologically indistinguishable from PMF. These conditions are termed post-polycythemia vera MF (post-PV MF) and post-essential thrombocythemia MF (post-ET MF) (Campbell, 2006). For purposes of this study, MPN-associated MF is defined as PMF, post-PV MF, and post-ET MF.

About 50% of patients with MPN-associated MF have a mutation in the Janus kinase 2 (*JAK2*) gene, about 33% of patients have a mutation in the calreticulin (*CALR*) gene, and about 5% of patients have a mutation in the thrombopoietin receptor (*MPL*) gene. Mutations in *JAK2*, *CALR*, and *MPL* (referred to as driver mutations) result in a constitutively active *JAK*/signal transducers and activators of transcription (STAT) signaling pathway that results in cell proliferation and inhibition of cell death, and subsequently clonal expansion (Ihle, 2007). About 10% to 15% of patients have no detectable abnormalities in these driver mutations and are subsequently referred to as "triple-negative" (Langabeer, 2016). Mutations in other genes such as *TET2, ASXL1* and *DMT3A* are also sometimes found and can precede or follow development of the driver mutations, resulting in disease initiation or progression.

1.1.1 Signs and Symptoms

Myeloproliferative neoplasm (MPN)-associated MF is predominately a disease of the elderly with a median age of approximately 65 years at the time of diagnosis (Mughal, 2014).

Erythropoiesis is qualitatively and quantitatively abnormal resulting in anemia in about 40% to 60% of affected patients at diagnosis. However, eventually all affected patients develop anemia (Naymagon, 2017; Tefferi, 2012), which is often confounded by comorbidities typical of an older population like atherosclerotic cardiovascular disease and cerebrovascular disease. Severe anemia unresponsive to therapy can be fatal; as such, anemia is a strong adverse prognostic variable for survival in patients with myelofibrosis (Dupriez, 1996; Tefferi, 2007; Cervantes, 2009; Tefferi, 2009). Furthermore, patients receiving RBC transfusions have a greater negative survival impact than patients who are anemic but not receiving RBC transfusions (Elena, 2011). Typical

signs and symptoms of anemia include pallor, fatigue, malaise, syncope, dyspnea, tachycardia, decreased exercise tolerance, edema, congestive heart failure, infections, and bleeding.

Myelopoiesis is also qualitatively and quantitatively abnormal resulting in decreased or increased granulocytes and/or platelets, which in turn may increase infection risk due to decreased numbers of and/or dysfunctional granulocytes, as well as elevated risk of bleeding due to decreased numbers of and/or dysfunctional platelets.

Extramedullary hematopoiesis, typical of MPN-associated MF, results in spleen and liver enlargement (splenomegaly and hepatomegaly, respectively) in a majority of affected patients at diagnosis, resulting in abdominal pain, early satiety, weight loss, and constitutional symptoms (Mughal, 2014).

Myeloproliferative neoplasm (MPN)-associated MF is a progressive disorder such that many of the signs and symptoms discussed above will develop with time even in patients in whom they are absent at diagnosis.

1.1.2 Prognosis

The median survival of patients with MPN-associated MF is highly variable and dependent on the number of adverse prognostic variables present. In patients who are categorized as either intermediate-2 or intermediate-1 per the Dynamic International Prognostic Scoring System (DIPSS), the median survival is 4 and 14 years, respectively (Passamonti, 2010). The individual prognostic variables that comprise the DIPSS scoring system include age, the presence of constitutional symptoms, hemoglobin, white blood cell count, and presence of peripheral blood blasts, which therefore enables the DIPSS to be utilized at the time of disease diagnosis and at any point during the course of the disease. Patients developing MPN-associated MF after PV or ET have the same prognosis to those with PMF (Cervantes, 2009).

Many of the risk factors mentioned above are also associated with an increased risk of transformation to blast phase (ie, AML), of which the median survival from time of diagnosis ranges from 1.5 to 10 months. The 10-year incidence rates for development of transformation to blast phase in PMF, post-ET MF, and post-PV MF is 10% to 20%, 2.3%, and < 1%, respectively (Yogarajah, 2017).

Recently, associations have been reported between prognosis and the patient's mutational landscape. For example, the presence of a *CALR* mutation has a favorable impact on a patient's prognosis whereas the absence of a detectable mutation in the driver mutations (triple negative) has an unfavorable impact on a patient's prognosis (Tefferi, 2018). The concomitant presence of *non-driver* mutations, such as those in *ASXL1*, *TET2* and *DNMT3A*, are also associated with an unfavorable impact on a patient's prognosis, independent of risk stratification by various prognostic tools (Guglielmelli, 2014), as these mutations can be associated with disease initiation and even progression. However, the prognostic impact of these mutations has not yet been used in clinical practice for patient management.

1.1.3 Treatment of MPN-associated Myelofibrosis

Treatment of MPN-associated MF is complex, with three goals of therapy: (1) those directed towards treatment of splenomegaly; (2) those directed towards the signs and symptoms of the disease; and (3) treatment of anemia. Most of the existing therapy is supportive and is aimed at reversing and alleviating the signs and symptoms of MPN-associated MF instead of treating the underlying cancer. Splenectomy and/or spleen radiation are also sometimes done, whereas hematopoietic cell transplants (considered the only curative treatment that can induce long-term remission) are rarely used because of advanced age and co-morbidities.

In 2011 and 2012, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), respectively, approved ruxolitinib, a Janus kinase (*JAK*) inhibitor intended for therapy of MPN-associated MF. Currently, it is the standard of care for treating splenomegaly and constitutional symptoms, offering significant improvements in spleen shrinkage, and symptom mitigation. However, therapy-induced cytopenias like anemia may impair administration of ruxolitinib to attain optimal therapeutic doses.

In August 2019, the US FDA approved fedratinib, a JAK2 kinase inhibitor indicated for the treatment of adult patients with DIPSS intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF to treat splenomegaly and constitutional symptoms. However, like ruxolitinib, fedratinib has also been shown to cause therapy-induced cytopenias including anemia.

Other *JAK* or STAT inhibitors are currently in development, in addition to other drug classes that are being assessed such as telomerase inhibitors and anti-fibrotic drugs (eg, pentraxin).

The only curative treatment that can induce long-term remission, resolution of bone marrow fibrosis, molecular remission, and restoration of normal hematopoiesis is allogenic stem cell transplantation (ASCT). Myeloablative and reduced-intensity conditioning ASCT are feasible and potentially of benefit for some patients with PMF, post-ET MF, and post-PV MF, although broad application of these treatment modalities is limited by the typically advanced age of the patients and the presence of comorbidities. Generally, < 5% of PMF subjects undergo ASCT (Tefferi 2012; Vannucchi, 2015).

1.1.3.1 Treatment for Anemia

Moderate to severe anemia (defined as hemoglobin [Hgb] < 10 g/dL) is present at diagnosis in about 40% of patients with MPN-associated MF at the time of diagnosis and develops in almost all patients (Tefferi, 2012). The etiology of anemia in MPN-associated MF is complex, as several mechanisms may operate in an affected person (Barosi, 2010), while some drugs used to treat MPN-associated MF, such as hydroxyurea (hydroxycarbamide) and ruxolitinib, worsen anemia.

Overall, anemia and RBC-transfusion dependence are strong, independent negative prognostic variables for survival and for risk of transformation to blast phase (Passamonti, 2010; Elena, 2011).

In summary, no therapy has been proven safe and effective to treat anemia in patients with MPN-associated MF. As patients who are RBC-transfusion dependent have a worse survival compared with those who are RBC-transfusion independent, there is an unmet medical need in this patient population.

1.1.3.2 Erythropoiesis Stimulating Agents

Erythropoiesis stimulating agents (ESAs) are widely used for the treatment of anemia associated with both lymphoid and myeloid neoplasms. In general, serum erythropoietin (EPO) levels in patients with MPN-associated MF are elevated for the degree of anemia and exogenous use of ESAs are of limited value (Barosi, 1993).

Some patients with EPO levels < 500 IU/L receive recombinant human EPO. Currently, there are no randomized clinical trials of recombinant human EPO in patients with MPN-associated MF who are RBC-transfusion dependent. Retrospective series in such patients treated with EPO or darbepoetin reported occasional responses, with response rates (defined as RBC-transfusion independence [RBC-TI] of ≥ 8 weeks) of around 20% and 30% (Cervantes, 2004; Cervantes, 2006; Rodriguez, 1998; Tsiara, 2007). The data suggest ESAs have limited therapeutic activity in RBC-transfusion dependent patients with MPN-associated MF and anemia regardless of serum EPO levels (Huang, 2009).

1.1.3.3 Androgenic Steroids

Androgenic steroids are sometimes used to treat anemia in patients with MPN-associated MF. A retrospective analysis of case reports identified 5 of 27 (18%) subjects with MPN-associated MF and RBC-transfusion dependence responding to treatment with danazol, defined as becoming free of RBC transfusions for ≥ 12 weeks (Cervantes, 2015). Additionally, androgenic steroids are associated with risks of liver toxicity and liver and prostate cancers. Based on these data, use of androgenic steroids in this setting is not proven safe and effective in patients with MPN-associated MF who are RBC-transfusion dependent (Branda, 1977; Brubaker, 1982; Cervantes, 2005; Lévy, 1996).

1.1.3.4 Corticosteroids

Corticosteroids do not produce sustained improvement in hemoglobin concentrations in patients with MPN-associated MF. Corticosteroids are poorly-tolerated, especially in older patients, and increase infection risk in patients with decreased normal spleen function and in patients who have been splenectomized (Odenike, 2005).

1.1.3.5 Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide and other immunomodulatory compounds, such as lenalidomide and pomalidomide, modulate levels of cytokines and growth factors in the bone marrow and may be of benefit in patients with MPN-associated MF. Thalidomide and lenalidomide are reported to improve outcomes with MPN-associated MF in nonrandomized clinical trials. However, the efficacy of thalidomide and lenalidomide are severely limited by adverse effects, toxicities that are uncommon with pomalidomide. Furthermore, pomalidomide is more active in modulating levels of inflammatory cytokines and growth factors. In a large Phase 3, randomized trial comparing pomalidomide versus placebo, 168 MPN-associated MF subjects were randomized to pomalidomide and 84 MPN-associated MF subjects were randomized to placebo and the study did not show a difference between pomalidomide and placebo. The primary endpoint (defined as RBC-TI for ≥ 12 weeks) response rates were 16% (n = 152, 95% confidence interval [CI]: 11% to 23%)

with pomalidomide and 16% (n = 77, 95% CI: 8% to 26%) with placebo (Tefferi, 2017) in the modified intent to treat population (n = 229). However, other investigational studies of pomalidomide and corticosteroids report contradictory data (Schlenk, 2017).

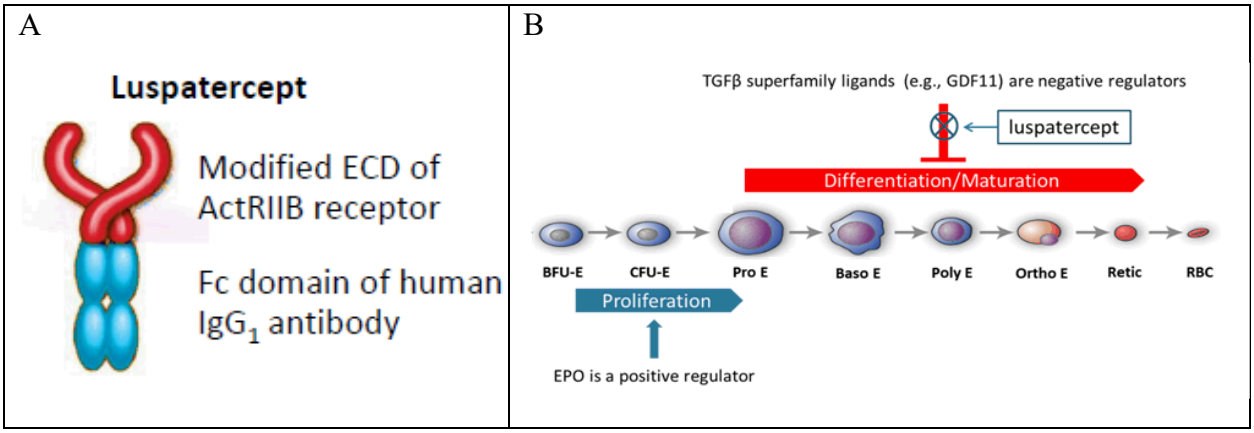
1.2 Luspatercept Background

Luspatercept (ACE-536, also known as BMS-986346) is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the Immunoglobulin G1 (IgG1) Fc domain (Figure 1A). The ActRIIB receptor and its ligands are members of the transforming growth factor-β (TGF-β) superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various tissues. No species differences have been described in the ligand-receptor interactions among members of the TGF-β superfamily as the ligands and receptors are highly conserved across species (Massagué, 1998). Thus, observations from pharmacology studies of luspatercept or its murine ortholog RAP-536 in animal models provide significant insight into the potential of luspatercept to treat human disease.

Transforming growth factor (TGF)-β ligands, through their binding to activin receptors, are involved in modulating the differentiation of late-stage erythrocyte precursors (normoblasts) in the bone marrow. In particular, luspatercept acts as a ligand trap for growth differentiation factor 11 (GDF11) and other TGF-β superfamily ligands to suppress Smad2/3 signaling. In nonclinical experiments, luspatercept has been shown to bind with high affinity to some TGF-β superfamily ligands (eg, GDF11, bone morphogenetic protein 6 [BMP6] and activin B) but substantially less to others (eg, bone morphogenetic protein 9 [BMP9] and activin A). The mechanism of action of luspatercept is independent from that of EPO (Suragani, 2014). While EPO stimulates proliferation and differentiation of early erythroid progenitors, luspatercept promotes stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow (refer to Figure 1B).

During normal erythropoiesis, GDF11 appears to inhibit differentiation and maintain the survival of immature erythroid progenitors, but its expression is decreased as cells mature, and thus its effect is transient. In a mouse model of thalassemia, defects in erythroid differentiation led to an accumulation of GDF11 expressing cells that maintained their own survival (Dussiot, 2014). Recent studies (Dussiot, 2014; Suragani, 2014) identified GDF11 as a regulator of erythropoiesis and showed that its inhibition in mouse models of anemia with ineffective erythropoiesis restores normal erythropoietic differentiation and improves anemia.

Figure 1: Luspatercept Schematic Representation and Mechanism of Action



ActRIIB = activin receptor type IIB; ECD = extracellular domain; EPO = erythropoietin; GDF11 = growth differentiation factor 11; IgG1 = immunoglobulin G1; RBC = red blood cell; TGFβ = transforming growth factor-beta.

Please refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of luspatercept.

1.2.1 Summary of Nonclinical Studies With Luspatercept

A brief summary of key findings from pharmacology and toxicology studies is provided below. Please refer to the most recent version of the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of luspatercept prior to initiating the study.

1.2.1.1 Toxicology Studies

Repeat-dose toxicology studies of up to 3- and 6-month duration have been conducted with luspatercept in Sprague-Dawley rats and cynomolgus monkeys, respectively. Recovery periods of up to 10 weeks were included as part of these studies. In addition, studies to assess potential effects on reproduction, fertility, and embryo-fetal development have been conducted in rats and rabbits. Findings from toxicology studies are described in more detail in the IB.

1.2.2 Summary of Clinical Experience

Overall, preliminary results from a Phase 2 study of luspatercept in subjects with myelofibrosis-associated anemia as of 10 May 2019 are reported as the following with respect to the primary endpoint (Gerds, 2019):

- In the anemia-only cohorts (Cohorts 1 and 3A), 2 out of 20 subjects (10%) in Cohort 1 compared to 3 out of 14 subjects (21%) in Cohort 3A achieved a ≥ 1.5 g/dL Hgb increase from baseline in all assessments in the absence of RBC transfusions for ≥ 84 days.
- In the RBC transfusion-dependent cohorts (Cohorts 2 and 3B), 2 out of 21 subjects (10%) in Cohort 2 and 6 out of 19 subjects (32%) in Cohort 3B achieved RBC-TI for ≥ 84 days.

Additionally, luspatercept has been in clinical development for myelodysplastic syndrome (MDS) and β-thalassemia.

Study ACE-536-MDS-001 (MEDALIST) is an ongoing Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept versus placebo in subjects with anemia due to International Prognostic Scoring System – Revised (IPSS-R) very low-, low-, or intermediate-risk MDS with ring sideroblasts who required RBC transfusions. The primary efficacy endpoint of RBC-TI ≥ 8 weeks from Week 1 through Week 24 was defined as the absence of any RBC transfusion for at least 8 weeks during the Primary Phase of the Treatment Period (first 24 weeks of double-blind treatment). A statistically significantly and clinically meaningfully greater proportion of luspatercept-treated subjects achieved the primary endpoint of RBC-TI ≥ 8 weeks from Week 1 through Week 24 compared with placebo (37.9% versus 13.2%, respectively; $p < 0.001$) (Fenaux, 2020).

Another study that is currently ongoing in MDS is COMMANDS, a Phase 3 trial that is an open-label, randomized study to compare the efficacy and safety of luspatercept versus epoetin alfa in subjects with anemia due to IPSS-R very low-, low-, or intermediate-risk MDS who are ESA-naïve and require RBC transfusions.

Study ACE-536-B-THAL-001 (BELIEVE) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of luspatercept in adults with anemia who required regular RBC transfusions due to β-thalassemia. The primary efficacy endpoint of the study was the proportion of subjects with hematologic improvement, defined as ≥ 33% reduction from baseline in RBC transfusion burden with a reduction of ≥ 2 units from Week 13 to Week 24 compared with the 12-week interval prior to randomization for luspatercept + best supportive care (BSC) versus placebo + BSC. A greater proportion of subjects achieved the primary efficacy endpoint (subjects with ≥ 33% reduction in RBC transfusion burden during the fixed Week 13 to Week 24 interval) in the luspatercept + BSC treatment group than in the placebo + BSC treatment group (21.4% versus 4.5%, $p < 0.0001$). Luspatercept was approved for β-thalassemia patients who are RBC-transfusion dependent by the FDA in November 2019.

Another study that is currently ongoing in β-thalassemia is BEYOND, a Phase 2 trial that is a double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept versus placebo in adults with nontransfusion dependent β-thalassemia.

Additional information regarding clinical experience with luspatercept is summarized in the current version of the luspatercept IB.

1.2.3 Potential Risks of Human Use

Increases in hematologic parameters (ie, RBC, Hgb, hematocrit, reticulocytes) are expected pharmacologic effects of luspatercept treatment. Increases in systolic and diastolic blood pressures may occur in concert with increases in hemoglobin values. Excessive or rapid increases in hemoglobin or blood pressure may occur and will be monitored. Dose modification rules for individual subjects, including dose delay and/or dose reduction, will be utilized to minimize risks associated with increased RBC parameters.

Adverse events observed in the Phase 1 study in healthy volunteers and the ongoing Phase 2 studies that were considered probably or possibly related to investigational product included injection site

reactions (hemorrhage, pruritus, rash), skin rash, hyperesthesia, muscle spasms, myalgia, pruritus, and hyperkalemia.

As with all biologics, there is the potential for antidrug antibodies (ADA) that can be associated with increased drug clearance and hypersensitivity reactions. Antidrug antibody (ADA) formation against luspatercept as well as human ActRIIB protein will be monitored.

Luspatercept has exhibited maternal and developmental toxicity in reproductive toxicity studies in preclinical species and therefore luspatercept should not be administered to pregnant or nursing women. Male and female subjects of childbearing potential participating in studies of luspatercept must be willing to abstain from sexual intercourse or use adequate contraception during the treatment and follow-up period of the study. Please refer to the IB for additional information regarding findings from toxicology studies. It is unknown if humans will experience any of the effects of luspatercept that were noted in the rat and monkey toxicology studies. Safety effects will be monitored closely through AE reporting, clinical laboratory tests, vital signs, and spleen assessments.

A comprehensive review of luspatercept, as well as details regarding the information summarized above, is provided in the IB. The most recent version of the luspatercept IB should be reviewed prior to initiating the study.

1.3 Rationale

1.3.1 Study Rationale and Purpose

Anemia and related symptoms are important features of MPN-associated MF. Patients with anemia and those receiving RBC transfusions have significantly worse survival and an increased risk of transformation to blast phase (ie, AML). Therapies such as ESAs, androgenic steroids, and corticosteroids are rarely effective with most responses transient, while data regarding efficacy of pomalidomide is controversial. Currently, no drug is approved to treat anemia in patients with MPN-associated MF, resulting in an unmet medical need in this patient population.

Luspatercept is a novel recombinant fusion protein consisting of a modified form of the ECD of the human ActRIIB. Luspatercept stimulates the later, maturation phase of erythropoiesis and improves anemia in patients with MDS and β-thalassemia. Luspatercept has also been shown to be clinically active in a Phase 2, open-label study in subjects with MPN-associated MF and anemia who may or may not be receiving RBC transfusions.

The purpose of this Phase 3 study is to evaluate the efficacy and safety of luspatercept compared with placebo in subjects with MPN-associated MF and anemia on concomitant JAK2 inhibitor therapy and who require RBC transfusions.

1.3.2 Rationale for the Study Design

ACE-536-MF-002 is a global Phase 3, multicenter, randomized, double-blind, placebo-controlled study. The multicenter nature of the study means results are likely to be widely applicable whereas the remaining study-design elements (eg, randomized, double-blinded, placebo-controlled, and parallel-group) will reduce biases in data reporting and interpretation.

1.3.2.1 Rationale for Placebo Control

The current treatment options for anemia in MPN-associated MF include ESAs, corticosteroids, androgenic steroids, and immunomodulatory compounds such as pomalidomide and thalidomide; however, none of these drugs are approved for the treatment of anemia in MPN-associated MF. While these treatments are used to treat anemia, none have demonstrated efficacy in terms of reduction or independence from RBC transfusions and all have drug-related toxicities. Thus, in this setting, placebo in addition to RBC transfusions is an appropriate comparator. Furthermore, utilizing placebo as the comparator will allow for a blinded study design in the context of RBC-transfusion endpoints.

1.3.2.2 Rationale for a Concomitant JAK2 Inhibitor and Best Supportive Care (BSC) With Allowed Concomitant Therapies

The protocol will allow BSC (eg, RBC transfusions, nutritional support) in combination with luspatercept or placebo. Other specified potential therapies for anemia (eg, ESAs, thalidomide, immunomodulatory compounds, and androgenic steroids) are not allowed to be used in combination with investigational product (IP). Additionally, all subjects are required to be on a stable dose of concomitant JAK2 inhibitor therapy as approved in the country of the study site for the treatment for MPN-associated MF and as per their local standard-of-care for at least 32 weeks and on a stable daily dose for at least 16 weeks immediately up to the date of randomization. As one of the primary adverse drug reactions associated with JAK2 inhibition is anemia, it is critical to control for the use and dose of the concomitant JAK2 inhibitor. Refer to Section 1.3.3 below for additional details on JAK2 inhibitor requirements.

1.3.2.3 Rationale for 2:1 Randomization and Stratification Factors

Subjects will be randomized to receive luspatercept and BSC or placebo and BSC at a 2:1 ratio as MPN-associated MF is an orphan disease with a limited number of subjects and therapies available.

Randomization will be stratified based on a subject's RBC-transfusion burden and DIPSS score:

- The magnitude of the hematopoietic effect of luspatercept has shown to be dependent on the baseline RBC-transfusion burden (ie, luspatercept in MDS). Subjects with 6 to 12 RBC units/12 weeks are regarded to be RBC-transfusion dependent, while subjects with 4 to 5 RBC units/12 weeks are considered as requiring regular RBC transfusions and are not regarded to be RBC-transfusion dependent. Stratifying at randomization for a baseline RBC-transfusion burden of 4 to 5 RBC units/12 weeks versus 6 to 12 RBC units/12 weeks will ensure a proper distribution across the treatment arms.
- The DIPSS prognostic risk score will be used in the study for stratification of subjects during randomization because it is an established prognostic scoring system in MPN-associated MF and is broadly used in clinical trials. The DIPSS scoring system predicts survival in patients with MPN-associated MF and is comprised of several individual prognostic variables such as age, constitutional symptoms, hemoglobin, white blood cell count, and presence of peripheral blood blasts. This scoring system can be utilized at the time of diagnosis and at any point through the course of a subject's disease, in which these factors and associated point values stratify patients into one of four different prognostic risk categories: low risk (0 points),

intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points), and high risk (5 or 6 points) (Passamonti, 2010). Stratifying at randomization for DIPSS intermediate-1/intermediate-2 and high risk will ensure a proper distribution of subjects with intermediate or high risk across the treatment arms.

Subjects randomized to either arm may remain on IP following the Day 169 Response Assessment if they are continuing to receive benefit from treatment defined as follows:

- absence of any IP discontinuation criteria (eg, excessive toxicities, transformation to blast phase, subject withdrawal) and
  - RBC-TI for any consecutive ≥ 12-week period over the first 24 weeks from Cycle 1 Day 1 in the Blinded Core Treatment Period,
  - reduced RBC-transfusion burden by ≥ 50% and by ≥ 4 units compared to baseline for ≥ 12 weeks immediately up to Study Day 169, or
  - an incomplete duration of response defined as being free from RBC transfusions for ≥ 4 weeks immediately up to Study Day 169.

1.3.2.4 Rationale for the Open-label Extension Phase

Subjects randomized to the placebo arm will be allowed to receive luspatercept as part of individual unblinding and crossover if they do not meet any Day 169 clinical benefit criteria or when all blinded subjects have completed or discontinued early from the Blinded Core Treatment Period, the primary endpoint has been analyzed, and the data monitoring committee (DMC) has been consulted. This will ensure blinding and the integrity of the study through the primary endpoint at Day 169, although it may impact any responses that begin on Day 169 and the long-term comparison of efficacy and safety.

1.3.3 Rationale for Study Population

RBC-transfusion Requirement

The intended study population includes patients with MPN-associated MF who require RBC transfusions. In the context of this study, requiring RBC transfusions at baseline is defined as receiving an average of 4 to 12 RBC units/12 weeks, with no interval of greater than 6 weeks (42 days) without receiving an RBC transfusion. Of note, in order to establish a conservative assessment of the baseline RBC-transfusion burden and to ensure that the baseline RBC-transfusion burden is not overestimated, RBC transfusions will only be counted toward the baseline RBC-transfusion burden requirements for eligibility and determination of improvements from baseline when the:

- pretransfusion Hgb is ≤ 9.5 g/dL in subjects with symptomatic anemia; or the
- pretransfusion Hgb is ≤ 7 g/dL in subjects with asymptomatic anemia.

Red blood cell (RBC) transfusions given for worsening of anemia due to bleeding or infections will not be counted toward the baseline RBC-transfusion burden.

Anemia in MPN-associated MF subjects is an unfavorable prognostic factor, starting with a Hgb < 10 g/dL and regardless of the need for RBC transfusions. Myeloproliferative neoplasm (MPN)-associated MF is a progressive disease with a goal of therapy to prevent subjects from becoming RBC-transfusion dependent. Subjects requiring regular transfusions of 4 to 12 RBC units/12 weeks with no transfusion-free interval > 6 weeks (42 days) describe a patient population in need of therapy.

The magnitude of the hematopoietic effect of luspatercept has shown to be dependent on the baseline RBC-transfusion burden (ie, luspatercept in MDS). Subjects with an RBC transfusion burden of > 12 units/12 weeks will be excluded as they may not become RBC transfusion-free during treatment.

For the purpose of the study, RBC and whole blood transfusions are regarded as equivalent.

Concomitant JAK2 Inhibitor Therapy

JAK2 inhibitors, like ruxolitinib or fedratinib, are standard-of-care for treating splenomegaly and constitutional symptoms and are used in most subjects with intermediate- or high-risk MPN-associated MF.

Subjects are required to be on concomitant JAK2 inhibitor therapy as approved for the treatment of MPN-associated MF in the country in which the subject is enrolled in the trial as part of their standard-of-care therapy.

In the ACE-536-MF-001 Phase 2 study, luspatercept has demonstrated the most pronounced anti-anemic effect in subjects that are on ruxolitinib treatment (requirement was 16 weeks stable dose of ruxolitinib prior to enrollment), with a median time on ruxolitinib treatment before enrollment of 69 weeks (minimum: 30 weeks, maximum: 411 weeks) in all Cohort 3B subjects (RBC-transfusion dependent). For subjects identified as responders in Cohort 3B, the median time on ruxolitinib treatment before enrollment was 138 weeks.

In order to most conservatively estimate baseline transfusion burden and ensure that improvements in anemia and/or RBC-transfusion requirements are not influenced by recovery from the Hgb nadir due to JAK2 inhibitor therapy (ie, ruxolitinib and fedratinib), subjects are required to have been treated for at least 32 weeks and be treated on a stable daily dose for at least 16 weeks immediately up to the date of randomization.

Exclusionary Laboratory Values

Laboratory exclusion criteria were chosen to ensure that subjects can tolerate treatment and are evaluable for anemia response and can be treated with a JAK2 inhibitor. With respect to excluding subjects with peripheral blood myeloblasts > 5%, these subjects are excluded because they have an elevated risk of progression by transformation to blast phase.

Other eligibility criteria are consistent with those in other studies of this population.

1.3.4 Rationale for Endpoints

The primary endpoint for the Phase 3 study is RBC-TI defined as the proportion of subjects who become RBC-transfusion free for at least 12 consecutive weeks in the luspatercept arm compared

with the placebo arm, where the 12-week period starts from randomization up to and including Week 24 (named RBC-TI 12).

Red blood cell (RBC)-transfusion dependency, whether present at the time of diagnosis or developing over time, is an adverse prognostic variable on survival in patients with MPN-associated MF and anemia (Elena, 2011). Red blood cell (RBC)-TI (defined as the absence of RBC transfusions given over 12 weeks) is a clinically meaningful endpoint that supports the evaluation of various anemia therapies within clinical trials (Gale, 2011), is in line with the definition of anemia response according to the Revised International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) response criteria for MPN-associated MF (Tefferi, 2013), and has also been used in previous studies in this indication (Tefferi, 2017).

The key secondary endpoint of the study will be the proportion of subjects achieving RBC-TI with duration ≥ 16 consecutive weeks, where the 16-week period starts from randomization up to and including Week 24 (named RBC-TI 16). The comparison between the two groups will enable the evaluation of extended clinical benefit achieved with luspatercept therapy and confirmation of the primary endpoint.

1.3.5 Rationale for Dose, Schedule, and Regimen Selection

The starting dose level for luspatercept is 1.33 mg/kg every 3 weeks, which can be increased to a maximum dose level of 1.75 mg/kg every 3 weeks in cases where a lack or loss of response is observed.

Preliminary results from the ACE-536-MF-001 Phase 2 study showed anemia-only subjects had a greater and more sustained Hgb increase at higher luspatercept exposure. Furthermore, most RBC transfusion-dependent subjects who eventually responded required a dose of 1.33 mg/kg or higher to achieve or maintain a 12-week response duration in the first 24 weeks of the study. Additionally, these preliminary results suggest that the time to response in MPN-associated MF subjects appeared longer at a starting dose of 1 mg/kg compared to what was observed in the Phase 3 study with luspatercept in MDS (MEDALIST, ACE-536-MDS-001).

Results from other luspatercept studies show doses up to 1.75 mg/kg are safe and well-tolerated. In MDS, a higher response rate, including hematologic improvement – erythroid response (HI-E) and RBC-TI, was seen in the higher dose groups (0.75 to 1.75 mg/kg subcutaneous every 3 weeks) compared with lower doses (0.125 to 0.5 mg/kg subcutaneous every 3 weeks) (Platzbecker, 2017).

Selection of the dosing schedule (every 3 weeks) is based on the duration of the luspatercept responses as well as pharmacokinetic (PK) parameters for luspatercept in subjects in other studies with MPN-associated MF and MDS.

1.3.6 Rationale for Patient-reported Outcomes and Healthcare Resource Utilization

Patients with the MPN-associated MF are at increased risk for thrombotic and cardiovascular events and experience a variety of burdensome, debilitating symptoms (Emanuel, 2012), such as early satiety, abdominal discomfort, weight loss, fatigue, night sweats, bone pain, itching,

concentration problems, and splenomegaly-related symptoms (ie, pain under the ribs on the left-hand side of the body), which compromise activities of daily living and quality of life (Mesa, 2016; Gregory, 2011; Mesa, 2011; Verstovsek, 2012).

Demonstrating an improvement or not worsening in these symptoms is an important area of research in clinical trials. The current study includes several patient-reported outcome (PRO) measures to assess and compare the quality of life associated with the two arms of treatment. Two instruments were selected for this purpose. The first one is the Myelofibrosis Symptom Assessment Form (MF-SAF) v4.0 – an instrument developed specifically to assess symptom burden for patients with MPN-associated MF. The second one is the Functional Assessment of Cancer Therapy – Anemia (FACT-An) – a widely used instrument that assesses multi-dimensional health-related quality of life (HRQoL) of cancer patients with a specific module designed to assess anemia-related symptoms and treatment side-effects. A combination of these two instruments will provide a comprehensive assessment of HRQoL among patients with the MPN-associated MF.

Although questionnaires that assess HRQoL offer valuable information about treatment impact of cancer and therapy-related side-effects, they do not address patients' satisfaction, expectations, and preferences concerning the occurrence and management of adverse events, the choice and type of therapy, and the efficacy of the treatment. Such information provides opportunities for physicians to improve therapy compliance, personalize the course of treatment, and develop interventions designed to prevent or effectively treat adverse events and thus improve HRQoL. To close this gap, an assessment of treatment satisfaction to address patients' overall feelings about treatment in addition to the HRQoL instruments was included. As no validated tool to capture the overall treatment satisfaction in hematological malignancies is available, the Global Satisfaction domain items of the Treatment Satisfaction Questionnaire: Medication (TSQM) was modified (Atkinson 2004; Atkinson 2005) to assess study treatment (rather than medication) satisfaction. Finally, the Patient Global Impression of Transfusion Satisfaction (PGI-TS) was included to assess patients' impression of transfusion experiences, complemented by RBC transfusion-related experience measures (ie, several additional items designed specifically for this study that will measure subjects' transfusion frequency and procedural burden).

The EuroQol Group 5 Dimensions – 5 Levels (EQ-5D-5L) instrument is included to explore utility scores, as recommended by key health technology assessment bodies (National Institute for Health and Care Excellence [NICE] guidelines, 2013; NICE guidelines, 2019).

More information about all PRO instruments can be found in the Section 6.10.

Myeloproliferative neoplasm (MPN)-associated MF is generally associated with high disease burden and reduced quality of life (Harrison, 2017). Management of MPN-associated MF-related anemia has been a key aspect of disease treatment. However, no drug has been approved to treat anemia in patients with MPN-associated MF. Many patients are RBC-transfusion dependent, which can result in time and resource burden. Healthcare resource utilization was also included in this trial to support understanding of the impact of luspatercept + BSC during the data collection period.

1.3.7 Rationale for Exploratory Biomarkers

MPN-associated MF is a clonal disease resulting from mutations in hematopoietic stem cells that promote abnormal proliferation and myeloid differentiation (Mead, 2017). Mutated genes in MPN-associated MF include *JAK2*, *CALR*, *MPL*, *ASXL1*, *SRFS2*, *IDH1/2*, and others. Specific mutations and number of mutations have prognostic value (Guglielmelli, 2017) and are associated with response and resistance to ruxolitinib (Newberry, 2017; Patel, 2015; Spiegel, 2017).

Inflammation, abnormal cytokine expression and bone marrow (BM) fibrosis are hallmarks of MPN-associated MF (Mondet, 2015; Vainchenker, 2017). Dysregulated expression of pro-inflammatory cytokines has been reported to contribute to BM stromal changes, ineffective erythropoiesis, extramedullary hematopoiesis, and constitutional symptoms (Mondet, 2015; Tefferi, 2011). Circulating cytokines including interleukin (IL)-6, IL-8, IL-2, IL-12, IL-15 and tumor necrosis factor-alpha (TNF-α) have been found to be elevated in patients with MPN-associated MF (Vainchenker, 2016; Zahr, 2016). Ruxolitinib is reported to modulate cytokines in MPN-associated MF patients, some of which have been associated with spleen and symptom response (Harrison, 2012).

Non-clinical data indicate that luspatercept acts as an erythroid maturation agent by trapping some TGF-β superfamily ligands that normally modulate differentiation of late-stage erythroid precursors, which promotes their differentiation into RBCs (Suragani, 2014). We intend to explore associations between luspatercept efficacy and frequencies of blood cells (ie, erythroid cells), levels of potential luspatercept ligands (eg, Activin B, GDF11) and circulating proteins related to erythropoiesis (eg, hepcidin, transferrin, and ferritin). Peripheral blood will be collected for evaluation of mutations, cytokines and circulating blood cell profiles at baseline and during treatment. Exploratory biomarker analyses will be performed to understand disease characteristics of the study population at baseline, and to explore relationships of baseline levels of biomarkers, and changes in biomarker levels during treatment, with clinical response to treatments. Lastly, analysis of pharmacogenetic variants from saliva DNA will be evaluated in association with clinical response.

1.3.8 Rationale for Pharmacokinetic Assessments

Pharmacokinetic (PK) analysis will be conducted to quantify serum luspatercept exposure in the presence of concurrent JAK2 inhibitor therapy. The relationship between serum luspatercept exposure and measures of effectiveness and safety may be explored to better understand the luspatercept dosing regimen in MPN-associated MF population. In addition, serum drug concentration will be used to assist in the interpretation of results from ADA tests.

1.4 Risk/Benefit Assessments

1.4.1 Potential Benefits

This trial (ACE-536-MF-002) is a Phase 3, double-blind, randomized study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo in subjects with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) on concomitant JAK2 inhibitor therapy and who require red blood cell transfusions.

Approximately 309 subjects with MPN-associated MF (primary myelofibrosis [PMF], postpolycythemia vera [post-PV], or post-essential thrombocythemia myelofibrosis [post-ET MF]), on concomitant JAK2 inhibitor therapy and who require RBC transfusions will be randomized globally at a 2:1 ratio to either:

- Experimental Arm: luspatercept (ACE-536) + BSC; luspatercept starting dose of 1.33 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

OR

- Control Arm: placebo + BSC; placebo starting dose with volume equivalent to experimental arm subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

Luspatercept (ACE-536) is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the Immunoglobulin G1 (IgG1) Fc domain. The ActRIIB receptor and its ligands are members of the transforming growth factor-β (TGF-β) superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various tissues.

Transforming growth factor (TGF)-β ligands, through their binding to activin receptors, are involved in modulating the differentiation of late-stage erythrocyte precursors (normoblasts) in the bone marrow. In particular, luspatercept acts as a ligand trap for growth differentiation factor 11 (GDF11) and other TGF-β superfamily ligands to suppress Smad2/3 signaling. During normal erythropoiesis, GDF11 appears to inhibit differentiation and maintain the survival of immature erythroid progenitors, but its expression is decreased as cells mature, and thus its effect is transient. Some studies (Dussiot, 2014; Suragani, 2014) identified GDF11 as a regulator of erythropoiesis and showed that its inhibition in mouse models of anemia with ineffective erythropoiesis restores normal erythropoietic differentiation and improves anemia. The mechanism of action of luspatercept is independent from that of EPO (Suragani, 2014). While EPO stimulates proliferation and differentiation of early erythroid progenitors, luspatercept promotes stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow.

Myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) is a clonal myeloid neoplasm resulting from a transformed multipotent hematopoietic progenitor cell (Juliana, 2018) and is characterized by defective bone marrow function, bone marrow fibrosis with increased micro-vessel density, ineffective erythropoiesis, extramedullary hematopoiesis, an increased risk for transformation to blast phase (ie, acute myeloid leukemia [AML]), and an inflammatory state. The cause of MPN-associated MF is unknown, and there are no known etiological factors (Mughal, 2014).

Myeloproliferative neoplasm (MPN)-associated MF can develop directly (primary myelofibrosis [PMF]) or evolve from other MPNs, including polycythemia vera (PV) and essential thrombocythemia (ET) (Tefferi, 2007). About 10% of patients affected with PV and ET develop bone marrow fibrosis morphologically indistinguishable from PMF. These conditions are termed post-polycythemia vera MF (post-PV MF) and post-essential thrombocythemia MF (post-ET MF)

(Campbell, 2006). For the purposes of this study, MPN-associated MF is defined as PMF, post-PV MF, and post-ET MF.

About 50% of patients with MPN-associated MF have a mutation in the Janus kinase 2 (JAK2) gene, about 33% of patients in the calreticulin (CALR) gene, and about 5% of patients in the thrombopoietin receptor (MPL) gene. Mutations in JAK2, CALR, and MPL (referred to as driver mutations) result in a constitutively active JAK/signal transducers and activators of transcription (STAT) signaling pathway that results in cell proliferation and inhibition of cell death, and subsequently clonal expansion (Ihle, 2007). About 10% to 15% of patients have no detectable abnormalities in these driver mutations and are subsequently referred to as "triple-negative" (Langabeer, 2016).

Moderate to severe anemia (defined as hemoglobin [Hgb] < 10 g/dL) is present at diagnosis in about 40% of patients with MPN-associated MF at the time of diagnosis and develops in almost all patients (Tefferi, 2012). The etiology of anemia in MPN-associated MF is complex, as several mechanisms may operate in an affected person (Barosi, 2010), while some drugs used to treat MPN-associated MF, such as hydroxyurea (hydroxycarbamide) and ruxolitinib, may worsen anemia.

Overall, anemia and RBC-transfusion dependence are strong, independent negative prognostic variables for survival and for risk of transformation to blast phase (Passamonti, 2010; Elena, 2011).

Preliminary results from a Phase 2 study of luspatercept in subjects with myelofibrosis-associated anemia as of 10 May 2019 are reported as RBC transfusion-dependent Cohorts 3B achieved RBC-TI for ≥ 84 days (primary endpoint) in 6 out of 19 subjects (32%) (Gerds, 2019).

In summary, no therapy has been proven safe and effective to treat anemia in patients with MPN-associated MF. As patients who are RBC-transfusion dependent have a worse survival compared with those who are RBC-transfusion independent, there is an unmet medical need in this patient population.

1.4.2 Potential Risks and Precautions

As of [redacted] Luspatercept (ACE-536) is being co-developed by Acceleron Pharma Inc. (Acceleron) and Celgene Corporation (Celgene). Acceleron is the Sponsor of a completed Phase 1 study conducted in healthy volunteers (Study A536-02), a completed Phase 2 study conducted in subjects with myelodysplastic syndromes (MDS) (Study A536-03), a completed Phase 2 study conducted in subjects with β-thalassemia (Study A536-04), and completed Phase 2 extension studies conducted in subjects with MDS (Study A536-05) and β-thalassemia (Study A536-06) with findings summarized in clinical study reports. Celgene is the Sponsor of ongoing Phase 2 studies conducted in subjects with MDS (Study ACE-536-MDS-003 [Japanese subjects] and Study ACE-536-MDS-004 [Japanese and Chinese subjects]), β-thalassemia (Study ACE-536-B-THAL-002 [BEYOND]), and myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) (Study ACE-536-MF-001); an ongoing Phase 2a study in pediatric subjects with β-thalassemia (Study ACE-536-B-THAL-004); an ongoing Phase 3 clinical study in subjects with MDS (Study ACE-536-MDS-002 [COMMANDS]); a completed Phase 3 study conducted in subjects with MDS (Study ACE-536-MDS-001 [MEDALIST]); a completed Phase 3 study

conducted in subjects with β-thalassemia (Study ACE-536-B-THAL-001 [BELIEVE]); a completed non-interventional study conducted in subjects with β-thalassemia (Study ACE-536-B-THAL-003); an ongoing non-interventional study (ACE-536-MDS-005); and an ongoing, long-term open-label study conducted in subjects who participated in other luspatercept clinical trials (ACE-536-LTFU-001).

In terms of clinical safety, AEs considered probably or possibly related to IP that were reported in ≥ 5% of subjects in the Phase 1 study in healthy volunteers include injection site hemorrhage and injection site macules. Adverse events reported in ≥ 15% of subjects regardless of causality in the open-label Phase 2 studies in MDS include (in order of decreasing frequency in the extension study) hypertension, viral upper respiratory tract infection, fatigue, cough, diarrhea, urinary tract infection, and peripheral edema. Adverse events reported in ≥ 15% of luspatercept-treated subjects regardless of causality in the Phase 3 study in MDS include (in order of decreasing frequency) fatigue, diarrhea, asthenia, edema peripheral, back pain, cough, dizziness, nausea, dyspnea, fall, and headache. Adverse events reported in ≥ 15% of subjects regardless of causality in the open-label Phase 2 studies in β-thalassemia include (in order of decreasing frequency) headache, pyrexia, asthenia, bone pain, diarrhea, arthralgia, oropharyngeal pain, back pain, cough, myalgia, influenza, musculoskeletal pain, viral upper respiratory tract infection, pain in extremity, rhinitis, vomiting, dizziness, abdominal pain, gastroenteritis, pharyngitis, abdominal pain upper, nausea, epistaxis, and upper respiratory tract infection. Adverse events reported in ≥ 15% of luspatercept-treated subjects regardless of causality in the Phase 3 study in β-thalassemia include (in order of decreasing frequency) upper respiratory tract infection, headache, back pain, arthralgia, bone pain, cough, pyrexia, and oropharyngeal pain.

1.4.2.1 Additional Precautions

No dosing information is available on administration to pediatric, adolescent, or pregnant subjects, and subjects with metabolic or organ impairment.

Splenectomized β-thalassemia subjects are at increased risk of developing thromboembolic complications. Caution is advised when treating splenectomized subjects who had at least 1 other risk factor for developing thromboembolic events such as a history of thrombocytosis or concomitant use of hormone replacement therapy. The occurrence of thromboembolic events was not correlated with elevated hemoglobin levels. No imbalance in thromboembolic events was observed in adult subjects with MDS in a Celgene-sponsored controlled clinical trial.

Extramedullary hematopoiesis (EMH) is a common disease-related condition in patients with β-thalassemia that has infrequently resulted in significant medical complications such as spinal compressions or neurologic symptoms. These symptoms are generally dependent on the location of the masses. A recent cumulative evaluation of all case reports of EMH in the luspatercept clinical development program identified EMH as a new risk in patients with β-thalassemia receiving treatment with luspatercept. Most events were Grade 1 or 2 in severity with infrequent complications requiring interventions, and most patients continued luspatercept treatment despite these events. Based on the identification of this new risk, administration of luspatercept in patients with prior therapies to control EMH masses is no longer recommended. There have been no reports

of EMH from the luspatercept myelodysplastic syndromes and myelofibrosis clinical development programs.

In Celgene-sponsored controlled clinical trials in adult subjects with MDS and β-thalassemia, subjects treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline not observed in placebo. Hypertension was reported as an adverse reaction in 8.1% of subjects treated with luspatercept and 2.8% of subjects who received placebo in the Celgene-sponsored controlled clinical trial in β-thalassemia. In the Celgene-sponsored controlled clinical trial in MDS, hypertension was reported as an adverse reaction in 8.5% of subjects treated with luspatercept and 7.9% of subjects who received placebo. Blood pressure should be monitored prior to each luspatercept administration. In case of new-onset hypertension or exacerbations of pre-existing hypertension, subjects should be treated for hypertension as per current clinical guidelines.

There have been no studies conducted in humans evaluating the effects of luspatercept on reproductive capacity or fetal outcomes. However, studies have been conducted with luspatercept in pregnant rats and rabbits. The data indicate that luspatercept produced developmental toxicity that included reductions in numbers of live fetuses and fetal body weights and increases in resorptions, post-implantation loss, and skeletal variations. Luspatercept administered to the pregnant mother was found in the blood of the rat and rabbit fetuses. Based on these data, luspatercept may be hazardous to the fetus, and precautions should be taken to protect females of childbearing potential. Therefore, all Celgene-sponsored luspatercept study protocols describe pregnancy prevention requiring females of childbearing potential to use highly effective methods of birth control. Females of childbearing potential must have a negative urine or blood pregnancy test prior to and during their participation in Celgene-sponsored luspatercept clinical studies. Luspatercept must not be given to a pregnant female or a female who intends to become pregnant. If a female becomes pregnant while taking luspatercept, the medication must be stopped immediately. If luspatercept is taken during pregnancy, a teratogenic effect in humans cannot be ruled out.

It is not known whether luspatercept is excreted in human breast milk or absorbed systemically after ingestion by a nursing infant; however, luspatercept was detected in the milk of treated lactating rats. Therefore, a decision should be made whether to discontinue nursing during treatment with luspatercept and for 3 months after the final dose or to discontinue luspatercept treatment.

There have been no Celgene-sponsored studies conducted in humans evaluating the effects of luspatercept on fertility. However, in a fertility and early embryonic development study in rats, higher doses in females produced significant reductions in the average numbers of corpora lutea, implantations, and viable embryos. Effects on fertility in female rats were reversible after a 14-week recovery period. There were no effects on male reproductive parameters (reproductive organ weights, sperm counts, sperm motility, mating, or fertility) or on litter parameters when untreated female rats were mated with luspatercept-treated male rats.

1.4.3 Overall Benefit-Risk Conclusion

Based on the previous description of potential benefits and risks, the overall investigational benefit-risk balance of luspatercept remains favorable in this study.

Current available information supports an acceptable benefit-risk profile for luspatercept when used in accordance with the precautions, dosing, and safety monitoring outlined in the study protocol and the routine pharmacovigilance practices.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy of luspatercept compared with placebo for the treatment of anemia in subjects with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) with concomitant JAK2 inhibitor therapy and who require red blood cell (RBC) transfusions.
Secondary Objective(s)
The secondary objectives of the study are to evaluate: • additional efficacy parameters of luspatercept compared with placebo • the safety of luspatercept compared to placebo in subjects with MPN-associated MF as measured by the frequency and severity of adverse events (AEs), serious adverse events (SAEs), antidrug antibodies (ADA), and transformation to blast phase • pharmacokinetics (PK) for luspatercept in MPN-associated MF
Exploratory Objective(s)
The exploratory objectives of the study are to explore the effect of luspatercept compared with placebo in subjects with MPN-associated MF on: • serum ferritin • overall survival • patient-reported outcomes to measure health-related quality of life, health utility scores, anemia-related symptoms, treatment satisfaction, and RBC transfusion experience • healthcare resource utilization • biomarker relationships to efficacy, and markers related to the disease and the mechanism of action of luspatercept • exposure-response relationships for luspatercept

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Endpoint	Red blood cell-transfusion independence (RBC-TI) ≥ 12 weeks (RBC-TI 12)	Proportion of subjects who become RBC-transfusion free over any consecutive 12-week period	Any consecutive "rolling" 12-week period starting from randomization up to and including Week 24
Key Secondary Endpoint	RBC-TI ≥ 16 weeks (RBC-TI 16)	Proportion of subjects who become RBC-transfusion free over any consecutive 16-week period	Any consecutive "rolling" 16-week period starting from randomization up to and including Week 24
Secondary Endpoints	Duration of RBC-TI 12	Maximum duration of RBC-TI response	Randomization up to end of treatment
	Reduction in transfusion burden	Proportion of subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units/12 weeks from baseline over any consecutive 12-week period	Randomization up to and including Week 24
	Duration of reduction in transfusion burden	Maximum duration of when RBC-transfusion dependent subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units/12 weeks from baseline over any consecutive 12-week period	Randomization up to end of treatment
	RBC-TI ≥ 12 weeks in treatment period (RBC-TI 12/TP)	Proportion of subjects who become RBC-transfusion free over any consecutive 12-week period	Any consecutive "rolling" 12-week period from randomization up to end of treatment
	RBC-TI ≥ 16 weeks in treatment period (RBC-TI 16/TP)	Proportion of subjects who become RBC-transfusion free over any consecutive 16-week period	Any consecutive "rolling" 16-week period from randomization up to end of treatment
	Change in RBC transfusion burden	Mean change in transfusion burden (RBC units) from baseline	Randomization up to and including Week 24
	Cumulative duration of RBC-transfusion independence	Cumulative response duration for subjects achieving multiple episodes of RBC-TI 12	Randomization up to end of treatment
	Mean hemoglobin (Hgb) increase ≥ 1 g/dL	Proportion of subjects achieving a mean Hgb increase ≥ 1 g/dL from baseline over any consecutive 12-week period in absence of RBC transfusions	Any consecutive "rolling" 12-week period starting from randomization up to and including Week 24; Randomization up to end of treatment
	Change in serum ferritin from baseline	Change in serum ferritin	Randomization up to and including Week 24; Randomization up to end of treatment

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Secondary Endpoints – Safety	Safety, including: Type, frequency, severity, and seriousness of adverse events (AEs) and relationship of AEs to luspatercept/placebo	Frequency/severity/seriousness of AEs	Screening up to 42 days post last dose
	Transformation to blast phase	Number and percentage of subjects who transform to blast phase (eg, acute myeloid leukemia [AML])	Randomization up to at least 5 years post first dose or 3 years post last dose (whichever occurs later)
	Antidrug antibodies (ADA)	Frequency of ADA	Randomization up to and including 48 weeks post first dose
	Pharmacokinetics (PK)	Serum concentration of luspatercept	Randomization up to and including 48 weeks post first dose
Exploratory Endpoints	Overall survival	Time from date of randomization to death due to any cause	Randomization up to at least 5 years post first dose or 3 years post last dose (whichever occurs later)
	Exposure-response	PK model that describe the PK exposure of luspatercept and associated variability. Exposure-response for selected efficacy endpoints and AEs of interest.	Randomization up to and including 48 weeks post first dose
	Total symptom score	Mean change in total symptom score by the Myelofibrosis Symptom Assessment Form (MF-SAF v4.0)	Cycle 1 Day 1 up to and including Week 24; Cycle 1 Day 1 up to 42 days post last dose
	EuroQol Group 5 Dimensions – 5 Levels (EQ-5D-5L)	Health Utility Scores and general health measured by multiple-choice items and Visual Analog Scale of EQ-5D	Cycle 1 Day 1 up to and including Week 24; Cycle 1 Day 1 up to 42 days post last dose
	Functional Assessment of Cancer Therapy – Anemia (FACT-An)	Evaluation of anemia-related quality of life	Cycle 1 Day 1 up to and including Week 24; Cycle 1 Day 1 up to 42 days post last dose

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
	RBC transfusion-related experience measures	Captures health-related quality of life specific to RBC transfusions	Cycle 1 Day 1 up to and including Week 24; Cycle 1 Day 1 up to 42 days post last dose
	Patient Global Impression of Treatment Satisfaction (PGI-TS)	Single item measure of a subject's overall satisfaction with their transfusion experience	Cycle 1 Day 1 up to and including Week 24; Cycle 1 Day 1 up to 42 days post last dose
	Global Treatment Satisfaction	Two-item measure of a subject's overall satisfaction with the study treatment	Cycle 1 Day 1 up to and including Week 24; Cycle 1 Day 1 up to 42 days post last dose
	Healthcare resource utilization	Evaluation of healthcare resource use (eg, hospitalization, clinic visits, medications, diagnostic procedures, treatment for AEs) associated with investigational product (IP) during study	Screening up to 42 days post last dose
	Circulating proteins such as inflammatory cytokines (eg, interleukin [IL]-6, IL-8, tumor necrosis factor-alpha [TNF-α) and C-reactive protein (CRP), proteins related to erythropoiesis (eg, hepcidin, transferrin, and ferritin), as well as potential luspatercept ligands (eg, Activin B, growth differentiation factor 11 [GDF11]). Peripheral blood and gene profiling (eg, erythroid, immune cells, prognostic mutations, genetic variants, gene expression) related to drug mechanism of action and efficacy	Evaluation of biomarkers at baseline and during treatment. Associations of biomarkers with treatment response.	Randomization up to end of treatment

3 OVERALL STUDY DESIGN

3.1 Study Design

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

This is a Phase 3, global, double-blind, randomized, multicenter study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo in subjects with MPN-associated MF and anemia on concomitant JAK2 inhibitor therapy and who require RBC transfusions.

The study is divided into Screening Period, a Treatment Phase (consisting of a Blinded Core Treatment Period, a Day 169 Response Assessment, a Blinded Extension Treatment Period, and an Open-label Extension Treatment Period), and a Posttreatment Follow-up Period. The overall study design is described in Figure 2, with more detailed descriptions for each phase of the study design found in Section 6.

3.1.1 Screening Period and Randomization

Upon giving written informed consent, subjects will enter the maximum 28-day Screening Period to determine eligibility (the full eligibility criteria can be found in Section 4), in which a subject's eligibility will be reviewed with the Sponsor prior to the subject's randomization via the integrated response technology (IRT). Subjects satisfying the eligibility criteria will be randomized by a central randomization procedure using IRT at a 2:1 ratio to either:

- **Experimental Arm**: Luspatercept (ACE-536) + BSC; luspatercept starting dose of 1.33 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

OR

- **Control Arm**: Placebo + BSC; placebo starting dose with volume equivalent to experimental arm subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

Randomization will be stratified based on the following factors:

- RBC-transfusion burden at baseline
  - 4 to 5 units/12 weeks
  - 6 to 12 units/12 weeks
- DIPSS score at baseline
  - Intermediate-1/Intermediate-2
  - High risk

Once randomized, the blind should be maintained for persons responsible for the ongoing conduct of the study until all blinded subjects have completed or discontinued early from the Blinded Core Treatment Period, the primary endpoint has been analyzed, and the DMC has been consulted. Blinded persons may include but are not limited to: the Clinical Research Physician(s), Clinical

Research Scientist(s), Clinical Trial Manager(s), Study Statistician(s), Data Manager(s), Programmers, and Clinical Research Associates. If a subject is unblinded after Day 169 due to unblinding and crossover, the persons responsible for the ongoing conduct of the study will be unblinded for this subject only.

3.1.2 Blinded Core Treatment Period (Weeks 1 Through 24)

The first dose of IP may be administered no later than 3 days from the date of randomization; however, it can be administered on the same day as randomization.

Subjects will receive a starting dose level of IP at 1.33 mg/kg as a subcutaneous injection every 3 weeks (or an equivalent volume of placebo). The starting dose can be titrated (increased), reduced, or delayed during the Treatment Phase. Please refer to Section 7.3 for more information regarding dose modifications.

In both treatment arms and throughout the Treatment Phase, BSC may be used in combination with IP when clinically indicated per investigator. Best supportive care includes, but is not limited to, treatment with transfusions (eg, RBC, platelet, whole blood), iron chelation therapy (ICT), antibiotic, antiviral and/or antifungal therapy, and nutritional support as needed. Best supportive care (BSC) for this study excludes the use of ESAs, androgenic steroids, and immunomodulatory compounds such as pomalidomide, and thalidomide. Please refer to Section 8 for additional details.

Subjects should receive IP through to a minimum of the Day 169 Response Assessment, unless the subject experiences transformation to blast phase, unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (Section 11.1). Subjects who discontinue IP prior to the Day 169 Response Assessment but remain on study are expected to be followed through at least Week 24 in order to be evaluated for the primary and key secondary endpoints. In cases where a subject withdraws consent for IP or assessments, every effort will be made to retain permission to continue to follow the subject for safety and long-term follow-up.

3.1.3 Day 169 Response Assessment

For subjects reaching the end of Week 24 (168 days), a Response Assessment evaluation to confirm clinical benefit performed by the Investigator is required for eligibility of a subject to continue IP in the Blinded Extension Treatment Period at Study Day 169 (regardless of dose delays).

Clinical benefit as determined by the Investigator is defined as demonstrating one of the following:

- RBC-TI for any consecutive ≥ 12-week period during the Blinded Core Treatment Period,
- reduced RBC-transfusion burden by ≥ 50% and by ≥ 4 units for ≥ 12 weeks immediately up to Study Day 169, or
- an incomplete duration of response defined as being free from RBC transfusions for ≥ 4 weeks immediately up to Study Day 169.

Subjects who do not meet any of the clinical benefit criteria above (Day 169 Response Assessment of "no") will have the opportunity after completion of the Day 169 visit, End of Treatment (EOT),

and subsequent 42-Day Follow-up Period to be considered for optional individual open-label crossover if their blinded treatment was placebo. Subjects randomized to luspatercept will not be eligible.

3.1.4 Blinded Extension Treatment Period (Week 25+)

Subjects completing their Day 169 Response Assessment and assessed as having clinical benefit can continue receiving IP in the Blinded Extension Treatment Period. Subjects will continue receiving IP on Day 1 of each 21-day treatment cycle as long as the subject is benefitting from IP according to the Investigator's assessment or until they experience transformation to blast phase, unacceptable toxicities, withdraws consent, or meet any other criteria for treatment discontinuation (Section 11.1).

3.1.5 Unblinding and Open-label Extension Treatment Period

Subjects who do not meet any of the clinical benefit criteria (Section 3.1.3; defined in the Day 169 Response Assessment as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period, as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.

Study unblinding is planned when all subjects have completed or discontinued early from the Blinded Core Treatment Period, the primary endpoint has been analyzed, and the DMC has been consulted.

At the time of subject and study unblinding:

- **subjects randomized to placebo and BSC** who meet the safety-related eligibility criteria (excluding inclusion criteria 1 through 4) of the study may receive luspatercept treatment with a starting dose of 1.33 mg/kg at the next cycle after unblinding. The eligibility criteria must be verified by the Investigator, with appropriate documentation available that may be reviewed by the Sponsor prior to a subject receiving their first luspatercept dose. Upon meeting the eligibility criteria, subjects are eligible for assignment to luspatercept treatment via IRT. Subjects will continue in the study for at least 24 weeks following the schedule of assessments beginning with the Cycle 1 Day 1 (C1D1) assessments, with the exception of PK and ADA samples that will not be collected. Collection of biomarker samples on Cycle 5 Day 1 will not be required during the Open-label Extension Treatment Period. In addition, PRO assessments will also not be required during the Open-label Extension Treatment Period.
- **subjects randomized to luspatercept and BSC** who have discontinued treatment will not be eligible for individual crossover to open-label luspatercept after unblinding. They will remain in the Posttreatment Follow-up Period at the time of unblinding as appropriate. Those subjects in the Blinded Extension Treatment Period can continue receiving luspatercept and completing

assessments and procedures as scheduled in Section 5, Table 3 in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment.

3.1.6 End of Treatment and Posttreatment Follow-up Period

All subjects who have received at least 1 dose of IP should undergo end of treatment (EOT) evaluations when IP is discontinued (for both blinded and crossover subjects).

All subjects will be followed for RBC transfusions (occurring at the study site or at outside institutions) for 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later. Subjects will enter the Posttreatment Follow-up Period following their last dose of IP, which will be inclusive of a 42-Day Follow-up Period starting from the last dose of IP (applicable for both blinded and crossover subjects) and Long-term Follow-up Period, where subjects will be followed (which may consist of telephone contact from site) every 3 months after the 42-Day Follow-up Period for at least 5 years following the date of first dose of IP or 3 years post last dose of IP, whichever occurs later.

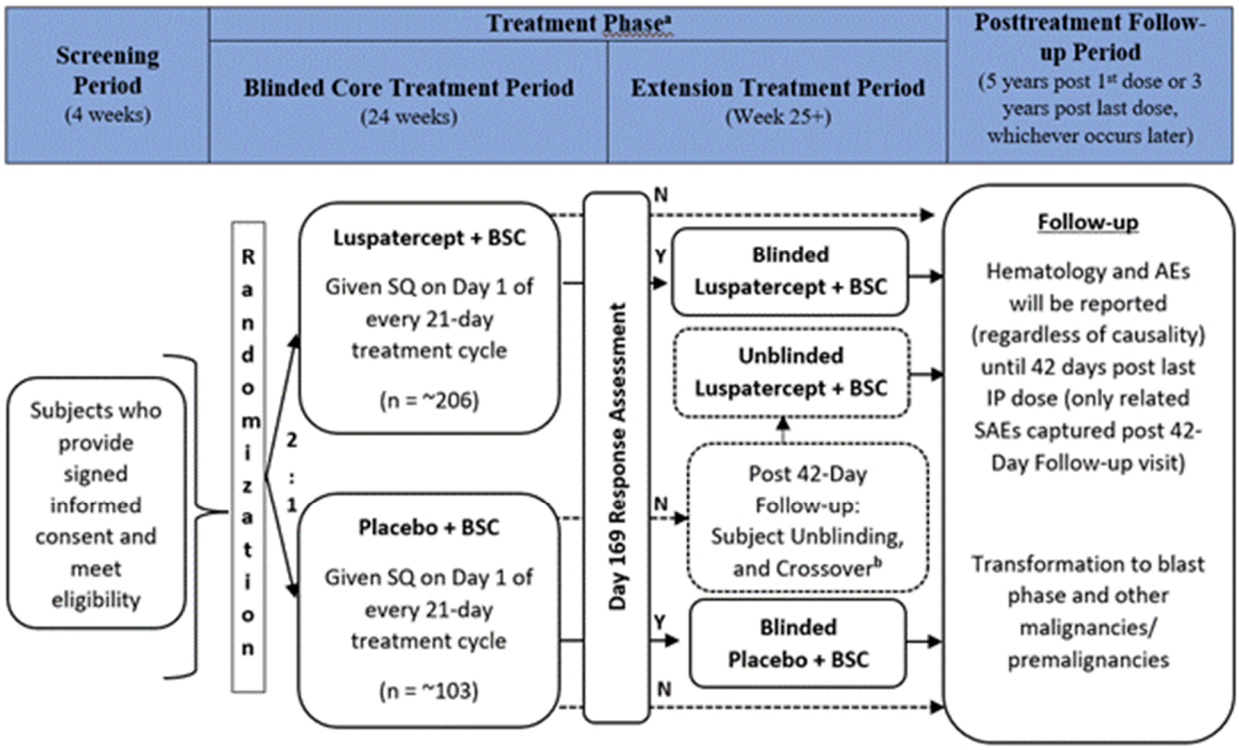
3.1.7 Data Monitoring Committee (DMC)

Operational details for the DMC will be detailed in the DMC charter. Refer to Section 9.10.7 for additional details.

3.1.8 Steering Committee (SC)

Operational details for the steering committee (SC) will be detailed in the SC charter. Refer to Section 9.10.8 for additional details.

Figure 2: Overall Study Design



AEs = adverse events; BSC = best supportive care; EOT = end of treatment; IP = investigational product; n = number of subjects;N = did not meet Day 169 Response Assessment criteria; SAEs = serious adverse events; SQ = subcutaneously; Y = met Day 169 Response Assessment criteria.

[a] Study unblinding will occur after analysis of the primary endpoint and with data monitoring committee (DMC) consultation.

[b] Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessment as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities or meet any other criteria for treatment discontinuation.

3.2 Study Duration for Subjects

After a Screening Period of at most 28 days from the time of signing the informed consent form (ICF), eligible subjects who are randomized to receive IP should continue double-blind treatment through at least the first 24 weeks (168 days) of the study in the Blinded Core Treatment Period unless the subject experiences transformation to blast phase, unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (Section 11.1).

Subjects who experience clinical benefit as determined by the Day 169 Response Assessment (Section 6.2.2) may continue double-blind treatment in the Blinded Extension Treatment Period until the subject experiences transformation to blast phase, unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (Section 11.1).

Subjects who do not meet any of the clinical benefit criteria will have the opportunity after completion of the Day 169 visit, EOT, and subsequent 42-Day Follow-up Period to be considered for optional individual open-label crossover if their blinded treatment was placebo. Crossover subjects may be treated for at least 24 weeks in the Open-label Extension Treatment Period, as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation. Subjects randomized to luspatercept will not be eligible.

Upon treatment discontinuation, all subjects who receive at least one dose of IP will undergo EOT evaluations and then enter the Posttreatment Follow-up Period, which will be inclusive of a 42-Day Follow-up Period starting from the last dose of IP and Long-term Follow-up Period, where subjects will be followed (which may consist of telephone contact from site) every 3 months for at least 5 years following the date of first dose of blinded IP or 3 years post last dose of IP, whichever occurs later. Refer to Section 6.5 for additional details.

3.3 End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is

required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed, and the availability of a roll-over protocol exists into which any subjects that remain on study may be consented to continue receiving access to luspatercept if they are deriving clinical benefit or be monitored for long-term safety. Such a protocol would be written for a compound that would not yet be commercially available.

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 309 subjects with MPN-associated MF (primary myelofibrosis [PMF], post-polycythemia vera [post-PV], or post-essential thrombocythemia myelofibrosis [post-ET MF]; APPENDIX B) on concomitant JAK2 inhibitor therapy and who require RBC transfusions will be randomized globally.

4.2 Inclusion Criteria

Subjects must satisfy the following criteria to be randomized in the study:

1. Subject is ≥ 18 years of age at the time of signing the ICF.
2. Subject has a diagnosis of PMF according to the 2016 World Health Organization (WHO) criteria (APPENDIX C) or diagnosis of post-ET or post-PV MF according to the IWG-MRT 2007 criteria (APPENDIX D), confirmed by the most recent local pathology report.
3. Subject is requiring RBC transfusions as defined as:
   a. Average RBC-transfusion frequency: 4 to 12 RBC units/12 weeks immediately up to randomization. There must be no interval > 6 weeks (42 days) without ≥ 1 RBC transfusion.
   b. RBC transfusions are scored in determining eligibility when given for treatment of:
      - Symptomatic (ie, fatigue or shortness of breath) anemia with a pretransfusion Hgb ≤ 9.5 g/dL or
      - Asymptomatic anemia with a pretransfusion Hgb ≤ 7 g/dL
   c. RBC transfusions given for worsening of anemia due to bleeding or infections are not scored in determining eligibility.
4. Subjects on continuous (eg, absent of dose interruptions lasting ≥ 2 consecutive weeks) JAK2 inhibitor therapy as approved in the country of the study site for the treatment for MPN-associated MF as part of their standard-of-care therapy for at least 32 weeks, on stable daily dose for at least 16 weeks immediately up to the date of randomization and anticipated to be on a stable daily dose of that JAK2 inhibitor for at least 24 weeks after randomization.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
6. A female of childbearing potential (FCBP) for this study is defined as a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (eg, has had menses at any time in the preceding 24 consecutive months). Females of childbearing potential (FCBP) participating in the study must:
   a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the study, and after end of IP. This applies even if the subject practices true abstinence* from heterosexual contact.
   b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception** without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 12 weeks (approximately 5 times the mean

terminal half-life of IP based on multiple-dose PK data) after discontinuation of study therapy.

7. Male subjects must:

   Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential** while participating in the study, during dose interruptions and for at least 12 weeks (approximately 5 times the mean terminal half-life of IP based on multiple-dose PK data) following IP discontinuation, even if he has undergone a successful vasectomy.

   * True abstinence is acceptable when it is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.]

   ** Agreement to use highly effective methods of contraception that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly throughout the course of the study. Such methods include: Combined (estrogen and progestogen containing) hormonal contraception: Oral, Intravaginal, Transdermal; Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral, Injectable hormonal contraception, Implantable hormonal contraception; Placement of an intrauterine device (IUD); Placement of an intrauterine hormone-releasing system (IUS); Bilateral tubal occlusion; Vasectomized partner; Sexual Abstinence.

8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements including the use of the electronic patient reported outcomes device.

4.3 Exclusion Criteria

The presence of any of the following will exclude a subject from randomization:

1. Subject with anemia from cause other than MPN-associated MF or JAK2 inhibitor therapy (eg, iron deficiency, vitamin B12 and/or folate deficiencies, autoimmune or hemolytic anemia, infection, or any type of known clinically significant bleeding or sequestration).
2. Subject use of hydroxyurea, immunomodulatory compounds such as pomalidomide, thalidomide, ESAs, androgenic steroids or other drugs with potential effects on hematopoiesis ≤ 8 weeks immediately up to the date of randomization.
   a. Systemic corticosteroids are permitted for nonhematological conditions providing the subject is receiving a constant dose equivalent to ≤ 10 mg prednisone for the 4 weeks immediately up to randomization.
   b. Iron chelation therapy (ICT) is permitted providing the subject is receiving a stable dose for the 8 weeks immediately up to randomization.
3. Subject with any of the following laboratory abnormalities at screening:
   a. Neutrophils: $< 1 \times 10^9$/L
   b. White blood count (WBC): $> 100 \times 10^9$/L
   c. Platelets: the lowest allowable level as approved for the concomitant JAK2 inhibitor but not $< 25 \times 10^9$/L or $> 1000 \times 10^9$/L
   d. Peripheral blood myeloblasts: > 5%

e. Estimated glomerular filtration rate: < 30 mL/min/1.73 m^2 (via the 4-variable modification of diet in renal disease [MDRD] formula) or nephrotic subjects (eg, urine albumin-to-creatinine ratio > 3500 mg/g)

f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT): > 3.0 x upper limit of normal (ULN)

g. Direct bilirubin: ≥ 2 x ULN

- Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (eg, ineffective erythropoiesis)

4. Subject with uncontrolled hypertension, defined as repeated elevations of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, that is not resolved at the time of randomization.
5. Subject with prior history of malignancies, other than disease under study, unless the subject has been free of the disease for ≥ 3 years. However, subject with the following history/concurrent conditions is allowed:
   a. Basal or squamous cell carcinoma of the skin
   b. Carcinoma in situ of the cervix
   c. Carcinoma in situ of the breast
   d. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
6. Subject with prior hematopoietic cell transplant or subject anticipated to receive a hematopoietic cell transplant during the 24 weeks from the date of randomization.
7. Subject with stroke, myocardial infarction, deep venous thrombosis, pulmonary or arterial embolism within 6 months immediately up to the date of randomization.
8. Subject with major surgery within 2 months up to the date of randomization. Subject must have completely recovered from any previous surgery immediately up to the date of randomization.
9. Subject with a major bleeding event (defined as symptomatic bleeding in a critical area or organ and/or bleeding causing a decrease in Hgb of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed red cells) in the last 6 months prior to the date of randomization.
10. Subject with inadequately controlled heart disease and/or have a known left ventricular ejection fraction < 35%.
11. Subject with uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment).
    a. History of active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 4 weeks prior to screening, unless the subject has adequately recovered from coronavirus disease 2019 (COVID-19) symptoms and related complications as per Investigator's discretion and following a discussion with the Medical Monitor. Use of a live COVID-19 vaccine is prohibited within 4 weeks prior to randomization.
12. Subject with known human immunodeficiency virus (HIV), evidence of active Hepatitis B (HepB) as demonstrated by the presence of Hepatitis B surface antigen (HBsAg) and/or positive for Hepatitis B virus DNA (HBVDNA-positive), and/or evidence of active Hepatitis C (HepC) as demonstrated by a positive Hepatitis C virus RNA (HCV-RNA) test of sufficient sensitivity.

13. Subject with prior therapy of luspatercept or sotatercept.
14. Subject with history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (see luspatercept IB).
15. Pregnant or breastfeeding females.
16. Subject participation in any other clinical protocol or investigational trial that involves use of experimental therapy (including investigational agents) and/or therapeutic devices within 30 days or for investigational agents within five half-lives, whichever comes later, immediately up to the date of randomization.
17. Subject with any significant medical condition, laboratory abnormality, psychiatric illness, or is considered vulnerable by local regulations (eg, imprisoned or institutionalized) that would prevent the subject from participating in the study or places the subject at unacceptable risk if he/she were to participate in the study.
18. Subject with any condition or concomitant medication that confounds the ability to interpret data from the study.

5 TABLE OF EVENTS

Table 3: Table of Events

	Reference Section	Screening Period[b]	Treatment Phase[a]						Posttreatment Follow-up Period (± 14 days)		
			Blinded Core Treatment Period Blinded Extension Treatment Period Open-label Extension Treatment Period[c] *The Day 169 Response Assessment must be completed to move into the (Blinded or Open-label) Extension Treatment Period* (± 3 days)			Day 169[d] (Week 24) Response Assessment (± 14 days)	EOT Visit[d]	Cross-over[c] (42-day Follow-up +14 days)	• **42-Day Follow-up Period =** Occurs 42 days from last dose of IP • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up Period until at least 5 years post first dose/3 years post last dose of IP (whichever occurs later)		
		Day -28 to Randomization	Cycle 1 Day 1	Every Cycle (eg, 2, 3, 4, etc) Day 1	Every Other Cycle Only (eg, 3, 5, 7, etc) Day 1				42-Day Follow-up Period[e]	Long-term Follow-up Period	End of Study
STUDY ENTRY											
Informed consent	6.1	X	--	--	--	--	--	--	--	--	--
Inclusion/Exclusion evaluations[a]	6.1	X	--	--	--	--	--	X	--	--	--
Demographics	6.1	X	--	--	--	--	--	--	--	--	--
Medical history and bone marrow assessment	6.1	X	--	--	--	--	--	--	--	--	--
Assessment of HepB/HepC status[f]	6.1	X	--	--	--	--	--	--	--	--	--
DIPSS evaluation	6.1	X	--	--	--	--	--	--	--	--	--
Prior RBC transfusion history for 16 weeks[g] and anemia treatment	6.1	X	--	--	--	--	--	--	--	--	--

Table 3: Table of Events

	Reference Section	Screening Period[b]	Treatment Phase[a]						Posttreatment Follow-up Period (± 14 days)		
			Blinded Core Treatment Period Blinded Extension Treatment Period Open-label Extension Treatment Period[c] *The Day 169 Response Assessment must be completed to move into the (Blinded or Open-label) Extension Treatment Period* (± 3 days)			Day 169[d] (Week 24) Response Assessment (± 14 days)	EOT Visit[d]	Cross-over[c] (42-day Follow-up +14 days)	• **42-Day Follow-up Period =** Occurs 42 days from last dose of IP • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up Period until at least 5 years post first dose/3 years post last dose of IP (whichever occurs later)		
		Day -28 to Randomization	Cycle 1 Day 1	Every Cycle (eg, 2, 3, 4, etc) Day 1	Every Other Cycle Only (eg, 3, 5, 7, etc) Day 1				42-Day Follow-up Period[e]	Long-term Follow-up Period	End of Study
GENERAL ASSESSMENTS											
Healthcare resource utilization	6.11	Continuous until 42 days after last IP administration or Study Day 169 (whichever occurs later)								--	--
Spleen size assessment by palpation	6.2	--	X	--	X	X	X	--	--	--	--
IP administration and accountability[h]	6.2	--	X	X	--	--	--	--	--	--	--
ECOG performance status	6.1	X	--	--	--	X	X	--	--	--	--
Urinalysis	6.1	X	X	--	X	--	--	--	--	--	--
Electrocardiogram (ECG), 12-lead	6.1	X	--	--	--	--	--	--	--	--	--
Pregnancy testing	6.1	X	X	X	--	X	X	--	--	--	--
Adverse events	6.1	Continuous, from signing informed consent until 42 days after last IP administration, after which only AESIs and SAEs related to IP will be captured									
Prior and concomitant medications/procedures	6.1	Continuous until 42 days after last IP administration, Study Day 169 or until the EOT visit, whichever occurs later								--	--

Table 3: Table of Events

	Reference Section	Screening Period[b]	Treatment Phase[a]						Posttreatment Follow-up Period (± 14 days)		
			Blinded Core Treatment Period / Blinded Extension Treatment Period / Open-label Extension Treatment Period[c] *The Day 169 Response Assessment must be completed to move into the (Blinded or Open-label) Extension Treatment Period* (± 3 days)			Day 169[d] (Week 24) Response Assessment (± 14 days)	EOT Visit[d]	Cross-over[c] (42-day Follow-up +14 days)	• 42-Day Follow-up Period = Occurs 42 days from last dose of IP • Long-term Follow-up Period = Occurs every 3 months after 42-Day Follow-up Period until at least 5 years post first dose/3 years post last dose of IP (whichever occurs later)		
		Day -28 to Randomization	Cycle 1 Day 1	Every Cycle (eg, 2, 3, 4, etc) Day 1	Every Other Cycle Only (eg, 3, 5, 7, etc) Day 1				42-Day Follow-up Period[e]	Long-term Follow-up Period	End of Study
Vital signs, height (measured at screening only), weight (measured at screening and prior to every IP administration)	6.1	X	X	X	--	X	X	--	--	--	--
Serum chemistry	6.1	X	X	--	X	X	X	--	--	--	--
Hematology	6.1	X	X	X	--	X	X	--	X	--	--
Serum erythropoietin (EPO)	6.1	X	X	--	--	X	X	--	--	--	--
Serum ferritin	6.1	X	X	--	--	X	X	--	--	--	--
Transfusion data collection and assessment[i]	6.2	--	Assess and record on ongoing basis (prior to each dose of IP) for 168 days from the date of C1D1 (ie, Study Day 169) or 12 weeks after last dose of IP, whichever occurs later								--
Clinical benefit assessment[j]	6.2.2	--	--	--	--	X	X	--	--	--	--
EXPLORATORY/BIOMARKER ASSESSMENTS											
Blood for mutational analysis	6.9	--	X	--	--	X	X	--	--	--	--

Table 3: Table of Events

	Reference Section	Screening Period[b]	Treatment Phase[a]						Posttreatment Follow-up Period (± 14 days)		
			Blinded Core Treatment Period Blinded Extension Treatment Period Open-label Extension Treatment Period[c] *The Day 169 Response Assessment must be completed to move into the (Blinded or Open-label) Extension Treatment Period* (± 3 days)			Day 169[d] (Week 24) Response Assessment (± 14 days)	EOT Visit[d]	Cross-over[c] (42-day Follow-up +14 days)	• **42-Day Follow-up Period =** Occurs 42 days from last dose of IP • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up Period until at least 5 years post first dose/3 years post last dose of IP (whichever occurs later)		
		Day -28 to Randomization	Cycle 1 Day 1	Every Cycle (eg, 2, 3, 4, etc) Day 1	Every Other Cycle Only (eg, 3, 5, 7, etc) Day 1				42-Day Follow-up Period[e]	Long-term Follow-up Period	End of Study
Serum (or plasma) for circulating proteins	6.9	--	X	--	C5D1 only[k]	X	X	--	--	--	--
Blood for cytogenetics analysis	6.9	--	X	--	--	X	X	--	--	--	--
Blood for cell profiling	6.9	--	X	--	C5D1 only[k]	X	X	--	--	--	--
Blood for gene expression profiling	6.9	X	X	--	C5D1 only[k]	X	X	--	--	--	--
Saliva for pharmacogenomics	6.9	X	--	--	--	--	--	--	--	--	--
PK AND ADA											
PK sample collection	6.7	--	Day 1 of C1*, C2, C4, C6, C8, C12, and C16 only *Collect C1D1 sample prior to IP dose			X	--	--	X[l]	PK and ADA sample	--

Table 3: Table of Events

	Reference Section	Screening Period[b]	Treatment Phase[a]						Posttreatment Follow-up Period (± 14 days) • **42-Day Follow-up Period** = Occurs 42 days from last dose of IP • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up Period until at least 5 years post first dose/3 years post last dose of IP (whichever occurs later)		
			Blinded Core Treatment Period **Blinded Extension Treatment Period** **Open-label Extension Treatment Period**[c] *The Day 169 Response Assessment must be completed to move into the (Blinded or Open-label) Extension Treatment Period* **(± 3 days)**			**Day 169[d] (Week 24) Response Assessment (± 14 days)**	**EOT Visit[d]**	**Cross-over[c] (42-day Follow-up +14 days)**			
		Day -28 to Randomization	**Cycle 1 Day 1**	**Every Cycle** (eg, 2, 3, 4, etc) **Day 1**	**Every Other Cycle Only** (eg, 3, 5, 7, etc) **Day 1**				**42-Day Follow-up Period[e]**	**Long-term Follow-up Period**	**End of Study**
ADA sample collection	6.8	--	Day 1 of C1*, C2, C4, C6, C8, C12, and C16 only *Collect C1D1 sample prior to IP dose			X	--	--	X[l]	collection to continue every 12 weeks for up to 48 weeks post first dose of IP[l]	--
QUALITY OF LIFE[m]											
MF-SAF v4.0[n]	6.10.1	--	Completed every treatment cycle during the Blinded Core Treatment Period and then every other cycle in the Blinded Extension Treatment Period			X	X	--	X	--	--
FACT-An[n]	6.10.2	--	X	--	X	X	X	--	X	--	--
RBC transfusion-related experience measures, including PGI-TS[n]	6.10.3	--	X	--	X	X	X	--	X	--	--

Table 3: Table of Events

	Reference Section	Screening Period[b]	Treatment Phase[a]						Posttreatment Follow-up Period (± 14 days)		
			Blinded Core Treatment Period Blinded Extension Treatment Period Open-label Extension Treatment Period[c] *The Day 169 Response Assessment must be completed to move into the (Blinded or Open-label) Extension Treatment Period* (± 3 days)			Day 169[d] (Week 24) Response Assessment (± 14 days)	EOT Visit[d]	Cross-over[c] (42-day Follow-up +14 days)	• **42-Day Follow-up Period =** Occurs 42 days from last dose of IP • **Long-term Follow-up Period** = Occurs every 3 months after 42-Day Follow-up Period until at least 5 years post first dose/3 years post last dose of IP (whichever occurs later)		
		Day -28 to Randomization	Cycle 1 Day 1	Every Cycle (eg, 2, 3, 4, etc) Day 1	Every Other Cycle Only (eg, 3, 5, 7, etc) Day 1				42-Day Follow-up Period[e]	Long-term Follow-up Period	End of Study
Global Treatment Satisfaction[n]	6.10.4	--	X	--	X	X	X	--	X	--	--
EQ-5D-5L[n]	6.10.5	--	X	--	--	X	X	--	X	--	--
FOLLOW UP											
Unblinding via IRT	6.2.4	--	--	--	--	--	--	X[a]	--	--	--
Monitoring for transformation to blast phase and other malignancies/ premalignancies[o]	6.1	After signing ICF and until at least 5 years post first dose of IP or 3 years post last dose of IP (whichever occurs later) or until death, lost to follow up, withdrawal of consent for further data collection.									
Posttreatment myelofibrosis therapies[o]	6.5	--	--	--	--	--	--	--	X	X	X
Survival follow up[o]	6.5	--	--	--	--	--	--	--	X	X	X

ADA = antidrug antibody; AESIs = adverse events of special interest; BSC = best supportive care; CxDx = Cycle x Day x; DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; EQ-5D-5L = EuroQol 5 Dimensions – 5 Levels; FACT-An = Functional Assessment of Cancer Therapy – Anemia; HepB = Hepatitis B; HepC = Hepatitis C; Hgb = hemoglobin; ICF = informed consent form; IP =

investigational product; IRT = integrated response technology; MF-SAF v4.0 = Myelofibrosis Symptom Assessment Form v4.0; PGI-TS = Patient Global Impression of Transfusion Satisfaction; PK = pharmacokinetic; PROs = patient-reported outcomes; RBC = red blood cell; SAE = serious adverse event; WBC = white blood count.

[a] Following subject unblinding (completing Day 169, EOT, and 42-day Follow-up), subjects randomized to placebo and BSC who meet the safety-related eligibility criteria of the study are eligible to crossover and receive luspatercept treatment with a starting dose of 1.33 mg/kg. The eligibility criteria must be verified by the Investigator, with appropriate documentation available that may be reviewed by the Sponsor prior to a subject receiving their first luspatercept dose. Upon meeting the eligibility criteria, subjects are eligible for assignment to luspatercept treatment via IRT. Subjects will continue in the study for at least 24 weeks following the schedule of assessments beginning with the C1D1 assessments, with the exception of PK and ADA samples that will not be collected. In addition, PRO assessments will also not be required during the Open-label Extension Treatment Period.

[b] If screening assessments are performed within 3 days of the C1D1 date, safety laboratory and spleen assessments do not need to be repeated during the C1D1 date, with the exception of blood pressure measurements, hematology, serum ferritin, and serum erythropoietin sample collection.

[c] Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessment as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.

[d] All subjects (regardless if they discontinue early from the Blinded Core Treatment Period) will need to complete procedures/assessments as part of the Day 169 Response Assessment. Day 169 Response Assessment (Week 24) visit procedures/assessments do not need to be repeated if performed within ± 7 days of the scheduled visit. End of Treatment (EOT) Visit procedures/assessments will be performed for subjects who are withdrawn from treatment for any reason as soon as possible (but, at the latest, at the next projected planned study visit) after the decision to permanently discontinue treatment has been made. Furthermore, the EOT evaluations do not need to be repeated if performed within ± 7 days of EOT visit (with the exception of blood pressure assessment and sample collection for hematology, chemistry, and urinalysis). If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit.

[e] For subjects that discontinue treatment in the Blinded Core Treatment Period, if procedures/assessments of the 42-Day Follow-up Period visit fall within 4 weeks of the anticipated Day 169 Response Assessment, then the 42-Day Follow-up Period visit procedures/assessments can be completed at the Day 169 Response Assessment visit.

[f] Central assessments are not required when local test results HepB and HepC are available within 8 weeks immediately prior to the randomization date.

[g] Prior RBC transfusion history (eg, any RBC transfusions given at the study site or an outside institution) should be collected for the 16 weeks immediately prior to the date of randomization.

[h] On dosing days, a local laboratory sample will be collected, with WBC and Hgb levels assessed prior to each IP administration to ensure dose modification rules are followed. Blood myeloblasts should also be assessed prior to IP dosing. Generally, it suffices to assess the blood myeloblast count from the previous treatment cycle. In case a subject had an elevated blood myeloblast percentage at the previous treatment cycle (≥ 10%), the blood myeloblast percentage needs to be assessed within a week prior to the next treatment cycle. In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis. Subjects must have blood pressure assessed prior to each IP administration. Should a dose delay occur on the day of dosing, refer to Section 6.3 for more information.

[i] Clinical site staff should confirm if any transfusions were received by the subject (including any at outside institutions in between study visits) prior to each IP administration via use of a transfusion diary or other local procedure in place at the investigational site. Subjects should record information relating to transfusions (eg, date of transfusion, pretransfusion Hgb levels, number of units transfused, volume of transfusion, etc.) they may have received outside the study site. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject.

[j] Clinical benefit, defined as demonstrating one of the following: RBC-TI for any consecutive ≥ 12-week period during the Blinded Core Treatment Period, reduced RBC-transfusion burden by ≥ 50% and by ≥ 4 units for ≥ 12 weeks immediately up to Study Day 169, or an incomplete duration of response defined as being free from RBC transfusions for ≥ 4 weeks immediately up to Study Day 169, will be assessed at the Day 169 Response Assessment timepoint, regardless of dose delays. In circumstances where the subject receives the IP dose prior to confirmation of clinical benefit, the Investigator must confirm clinical benefit prior to the next IP administration.

[k] After crossover, C5D1 biomarker samples will not be collected for unblinded subjects.

[l] If the subject discontinues before all PK/ADA samples are collected during the Treatment Phase, sample collection should continue at the 42-Day Follow-up Period and for every 12 weeks thereafter for up to 48 weeks after the first dose of IP. PK/ADA collection is not required after crossover.

[m] Patient-reported outcome (PRO) assessments should be completed prior to IP administration, with the exception of the 2 procedural-burden items of the RBC transfusion-related experience measure instrument, which should be completed before or after an RBC transfusion is administered, as appropriate. All PRO assessments are to be completed exclusively on the electronic device provided.

[n] For subjects who crossover into the Open-Label Extension Treatment Period, all PRO assessments will not be collected after the blinded 42-day Follow-up.

[o] The Long-term Follow-up Period for transformation to blast phase, other malignancies/premalignancies, and data collection for subsequent myelofibrosis therapies may be conducted by record review (including public records if allowed by local regulations) and/or telephone contact with the subject, family, or the subject's treating physician. The Investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow up.

6 PROCEDURES

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

The protocol required assessments are listed in Section 5, Table 3, with an "X" indicating at which visits the assessments are to be performed. All data obtained from these assessments must be recorded in the subject's source documentation. Except for the Day 169 Response Assessment, all study visits during the Treatment Phase must occur within ± 3 days of the scheduled day. A 14-day window is allowed for the Day 169 Response Assessment and Posttreatment Follow-up Period assessments (ie, transformation to blast phase, posttreatment myelofibrosis therapies). Procedures are described in detail below for each study phase.

Safety laboratory analyses and all laboratory assessments will be performed centrally (except otherwise stated in this section) during the Screening Period and Treatment Phase.

Local laboratories are only allowed in cases when timely results are needed (eg, IP dosing decisions, hematology assessments between clinic visits, adverse events). In these circumstances, a split sample should still be collected and sent to the central laboratory for analysis. When applicable, local laboratories may also be used to determine study eligibility if central laboratory results are not available (ie, hemolyzed sample) or if there is a discrepancy between local and central laboratory results impacting study eligibility. Local laboratory data should be collected in the electronic case report form (eCRF) if relevant to dose administration, dose modification, an AE, or when no central laboratory results were obtained.

Refer to the eCRF completion guidelines for additional information related to data entry requirements of local laboratories.

Sample collection, processing, storage, and shipment procedures will be provided in the Study Laboratory Manual.

6.1 Screening Period

Upon giving written informed consent, subjects enter the Screening Period to determine eligibility. Subject screening procedures (refer to Section 5, Table 3 for further information) are to take place over a maximum of 28 days immediately prior to their randomization date (unless otherwise noted below), which will be defined in this protocol as the date in which they have been randomized via IRT. The first dose of IP (designated as the C1D1 date) should be administered as soon as possible (at the latest 3 calendar days) following the randomization date. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study. Screening laboratory values must demonstrate subject eligibility but may be repeated within the screening window if clinically justified. Subjects that have met all eligibility criteria during the Screening Period will be eligible for randomization.

The diagnosis of MPN-associated MF will be confirmed by the Investigator based on review of the most recent local pathology report (including bone marrow biopsy information). The report should come from the most recent local bone marrow biopsy performed and should also contain the mutational status of the disease (eg, *JAK2*, *MPL*, and *CALR*).

Red blood cell (RBC)-transfusion history must be available for at least 16 weeks immediately prior to the subject's randomization date. Transfusion data should include, but not be limited to, the type of transfusion (ie, RBC or whole blood), the number of units, volume of transfusion, pretransfusion hemoglobin values, and date of transfusion. Red blood cell (RBC) transfusions given at outside local institutions must also be collected. For the purpose of this study, RBC and whole blood transfusions are regarded as equivalent.

These data will be recorded in the subject's eCRF. Subjects who do not meet the eligibility criteria prior to randomization will be considered screening failures and will not be eligible for randomization. Subjects who fail screening may undergo rescreening as per the Investigator discretion.

In the event that a subject is rescreened, a new subject number will be assigned by IRT. All screening assessments that were completed prior to the subject being declared a screen fail (ie, within 28 days after the ICF signature) can be entered in the eCRF under the new assigned subject ID number provided that they are within the validity windows as indicated per Section 5, Table 3. The only exceptions are the following:

- Electrocardiograms (ECG) will not need to be repeated if it was performed within 6 months of the projected randomization date.
- Testing for HepB and HepC will not need to be repeated if local labs are available within 8 weeks of the projected randomization date or central labs are available within 28 days of the projected randomization date.

Waivers to the protocol eligibility criteria will not be granted during the conduct of this trial.

The following will be performed during the 28-day Screening Period as specified in the Table of Events (Section 5, Table 3) after informed consent has been obtained:

- **Assessment of inclusion/exclusion criteria for study eligibility**

Screening evaluations will be performed for all subjects to determine eligibility. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

- **Demographics and medical history**

Information about the subject's demographics (if allowed per local country regulations; including, but not limited to: date of birth, sex, race, and ethnicity) to be recorded on the appropriate eCRF.

Complete medical history documenting specific information regarding all relevant medical conditions diagnosed (occurring prior to Screening Period) to be recorded on the appropriate eCRF.

- **Hepatitis B (HepB) and Hepatitis C (HepC) status**

Testing for HepB and HepC will be completed by the central laboratory unless local lab results are available within 8 weeks immediately prior to the randomization date. Subjects receiving antiviral therapies should have 2 negative HCV-RNA tests approximately three months apart (ie, one test

at the end of the antiviral therapy and a second test approximately three months following the first test).

- **DIPSS evaluation**

A DIPSS evaluation will be performed and captured on the appropriate eCRF using the criteria in APPENDIX E.

- **RBC transfusion history**

Information regarding RBC transfusion history (≥ 16 weeks prior to and including the randomization date), including, but not limited to, pretransfusion Hgb levels, number of units transfused, volume of transfusion, and dates of transfusions, will be collected and reported in the appropriate eCRF. Any transfusions given at outside institutions must also be collected. Source documentation of RBC transfusion history must be available for source document verification. Transfusions given for symptomatic anemia with a pretransfusion Hgb of ≤ 9.5 g/dL **or** asymptomatic anemia with a pretransfusion Hgb of ≤ 7 g/dL will be scored in determining the baseline transfusion requirements for eligibility. Transfusions given for worsening of anemia due to bleeding or infections will not be scored in determining eligibility.

- **Healthcare resource utilization**

Refer to Section 6.11 for more information.

- **Eastern Cooperative Oncology Group (ECOG) performance status**

Performance status will be assessed by the Investigator using the ECOG criteria provided in APPENDIX F.

- **Urinalysis**

Information regarding urinalysis to include microscopic, quantitative analysis of urine (eg, albumin, protein, creatinine, albumin/creatinine ratio), and will be tested by the central laboratory.

- **Electrocardiogram (ECG)**

A 12-lead ECG to be performed locally at site. The following ECG parameters will be recorded on the respective eCRF(s): heart rate (HR), PR interval, QRS duration, QT, and QTc. The Investigator will review the results and assess as normal, abnormal – not clinically significant, or abnormal – clinically significant, and report the abnormal finding(s) on the appropriate eCRF. If the ECG is abnormal, the Investigator should consult a cardiologist if deemed appropriate.

- **Pregnancy testing**

Pregnancy testing (conducted at the central laboratory or locally) to be completed for all female subjects of childbearing potential (FCBP), in which the urine beta subunit of the human chorionic gonadotropic (β-hCG) pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL will be performed. This assessment will be used to confirm eligibility. A urine pregnancy test will be performed to assess subject eligibility within 72 hours prior to the C1D1 date, if the initial urine pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration). During the Treatment Period, urine pregnancy tests will be assessed. The Investigator will appraise a female subject as a FCBP according to the definition

provided in Section 4.2. Justification must be recorded in the eCRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

- **Adverse event assessment**

Information regarding adverse event assessment and reporting initiated from the time the subject signs the informed consent form will occur on an ongoing basis and must be documented on the appropriate eCRF. Refer to Section 10 for more information.

- **Prior/concomitant medications and procedures**

Information relating to prior/concomitant medications and procedures to be reported on the appropriate eCRF. Refer to Section 8 for more information.

- **Vital signs, height, and weight**

Information regarding vital signs including height (measured only during screening), weight (measured during screening and prior to each IP administration), seated blood pressure (documented as mean of 2 readings obtained approximately 10 minutes apart with the subject seated for approximately 10 minutes prior to initial reading; on dosing days, blood pressure must be assessed prior to IP administration), temperature, heart rate, and respiratory rate are to be reported on the appropriate eCRF.

- **Serum chemistry**

Information regarding serum chemistry including labs such as sodium, potassium, chloride, bicarbonate (if available), calcium, magnesium, phosphorus, blood urea nitrogen, creatinine and creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, direct/indirect total bilirubin, AST/serum glutamic oxaloacetic transaminase (SGOT) or ALT/serum glutamic pyruvic transaminase (SGPT), lactate dehydrogenase, and uric acid are to be reported on the appropriate eCRF and will be tested by the central laboratory.

- **Hematology**

Information regarding hematology assessments including RBC count, complete blood count, WBC with differential (including myeloblasts), Hgb, hematocrit, nucleated red blood cells, absolute reticulocyte count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell distribution width are to be reported on the appropriate eCRF and will be tested by the central laboratory.

- **Serum erythropoietin (EPO)**

Serum EPO collected during the Screening Period should be collected on the same day as a planned RBC transfusion, prior to the transfusion, or 7 days after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. Serum EPO samples will be analyzed by the central laboratory.

- **Serum ferritin**

Serum ferritin should be collected within the Screening Period and analyzed by the central laboratory. Historic serum ferritin levels from previous local laboratory reports (within the 84-

day window prior to and including the randomization date) should be collected, if available in the medical records, and entered on the appropriate eCRF.

On dosing days, serum ferritin samples should be collected prior to IP administration and analyzed by the central laboratory.

- **Exploratory/biomarker sample collection**

Refer to Section 6.9 for more information.

- **Monitoring for transformation to blast phase and other malignancies/premalignancies**

Monitoring for transformation to blast phase as per International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria (Tefferi, 2013) will be included as part of the safety assessment throughout the course of the study. Transformation to blast phase should be monitored from time of signing of informed consent through at least 3 years after last dose of IP or until death, lost to follow up, or withdrawal of consent from the study, whichever occurs first. The occurrence of a new malignancy or premalignant lesion will be monitored as an event of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the development of any new malignancy or premalignant lesion as a serious adverse event, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF for up to and including at least 3 years of long-term follow up, or until death, lost to follow up, or withdrawal of consent for further data collection. Documentation supporting the diagnosis of transformation to blast phase and other malignancies/pre-malignancies (eg, confirmatory histology or cytology results) may be requested. Appropriate information related to the diagnosis of transformation to blast phase and other malignancies/premalignancies should be captured on the eCRF and in the subject's source documents.

6.2 Treatment Phase

The subject must be randomized at the latest 28 days from signing the ICF. The first dose of IP (designated as C1D1) should be administered as soon as possible (at the latest 3 calendar days) following the randomization date. In case a subject should become ineligible after being randomized but prior to receiving the first dose of IP, they must be discontinued from the study.

If screening assessments are performed within 72 hours of the C1D1 date, safety laboratory and spleen assessments would not need to be repeated during the C1D1 date, with the exception of blood pressure measurements, hematology, serum ferritin, and serum EPO sample collections.

On dosing days, local laboratory WBC and Hgb levels should be assessed prior to each IP administration. In case a subject had an elevated blood myeloblast percentage at the previous treatment cycle, the blood myeloblast percentage needs to be assessed within a week prior to the next treatment cycle. These parameters are to ensure the dose modification rules are followed as outlined in Section 7.3.

In these circumstances, a split sample should also be collected and sent to the central laboratory for analysis. Subjects should also have blood pressure assessed (as detailed in Section 6.1).

The clinical site must confirm with the subject if any transfusions were received at outside local centers in between study visits prior to each IP administration.

6.2.1 Blinded Core Treatment Period

Subjects will receive IP on Day 1 of each 21-day treatment cycle (unless there are dose delays) through at least Day 168 following the C1D1 date unless the subject experiences transformation to blast phase, unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria (refer to Section 11.1) prior to the Day 169 Response Assessment. Treatment cycles are 21 days in duration.

The following procedures/evaluations will be performed at the frequency specified in the Table of Events (Section 5, Table 3) during the Blinded Core Treatment Period. The procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Spleen size assessment by palpation
- Healthcare resource utilization (as detailed in Section 6.11)
- Administration/accountability of IP
- Urinalysis (as detailed in Section 6.1)
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)
- Serum EPO level
- Serum ferritin level
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.

- Exploratory/Biomarker sample collection (as detailed in Section 6.9)
- PK and ADA sample collection (as detailed in Sections 6.7 and 6.8)
- PRO instrument completion (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies

6.2.2 Day 169 Response Assessment

All subjects (regardless if they discontinue early from the Blinded Core Treatment Period) will need to complete procedures/assessments as part of the Day 169 Response Assessment.

The Day 169 Response Assessment should be completed 169 days after the C1D1 date, regardless of dose delays, with a 14-day window to allow for completion of other assessments and procedures.

For subjects to remain on IP treatment beyond Study Day 169, one of the following criteria must be confirmed upon the completion of the Response Assessment by the Investigator:

Clinical benefit is defined as demonstrating one of the following:

- RBC-TI for any consecutive ≥ 12-week period during the Blinded Core Treatment Period,
- reduced RBC-transfusion burden by ≥ 50% and by ≥ 4 units for ≥ 12 weeks immediately up to Study Day 169, or
- an incomplete duration of response defined as being free from RBC transfusions for ≥ 4 weeks immediately up to Study Day 169.

In circumstances where the subject does receive the first Blinded Extension Treatment Period IP dose prior to confirmation of clinical benefit, the Investigator must confirm clinical benefit prior to the next IP administration.

Should subjects not meet any of the clinical benefit criteria outlined above, they should discontinue treatment with IP and enter the Posttreatment Follow-up Period. These subjects will have the opportunity after completion of the Day 169 visit, EOT, and subsequent 42-Day Follow-up Period to be considered for optional individual open-label crossover if their blinded treatment was placebo. Subjects randomized to luspatercept will not be eligible (see Section 6.2.4).

Subjects who meet at least one of the clinical benefit criteria may begin IP treatment in the Blinded Extension Treatment Period at the Investigator's discretion as long as the subject is benefitting from IP, or the subject experiences transformation to blast phase or any of the other criteria for treatment discontinuation are met (Section 11.1). Subjects who enter the Blinded Extension Treatment Period will not be eligible for open-label crossover.

The following procedures/evaluations will be performed for the Day 169 Response Assessment:

- Spleen size assessment by palpation
- Healthcare resource utilization (as detailed in Section 6.11)
- ECOG performance status
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)

- Serum EPO level
- Serum ferritin level
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.

- Exploratory/Biomarker sample collection (as detailed in Section 6.9)
- PK and ADA sample collection (as detailed in Sections 6.7 and 6.8)
- PRO instrument completion (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies

6.2.3 *Blinded Extension Treatment Period*

Subjects who meet the clinical benefit criteria and remain on IP treatment after completion of the Day 169 Response Assessment may continue dosing on Day 1 of each 21-day treatment cycle in the Blinded Extension Treatment Period as long as the subject is benefitting from IP according to the Investigator's assessment, or they experience unacceptable toxicities, have transformation to blast phase, withdraw consent, or meet any other discontinuation criteria (Section 11.1).

All subjects who have received at least 1 dose of IP should undergo EOT evaluations when IP is discontinued (refer to Section 6.4 for more information). The reason for discontinuation will be recorded in the eCRF pages and in the source documents.

Serial measurements of safety and efficacy will continue on scheduled study visits in the Blinded Extension Treatment Period, of which the following procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Spleen size assessment by palpation
- Healthcare resource utilization (as detailed in Section 6.11)
- Administration/accountability of IP
- Urinalysis (as detailed in Section 6.1)
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)

- Serum EPO level
- Serum ferritin level
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.

- Exploratory/Biomarker sample collection (as detailed in Section 6.9)
- PK and ADA sample collection (as detailed in Sections 6.7 and 6.8)
- PRO instrument completion (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies

6.2.4 Open-label Extension Treatment Period (Crossover)

Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessment as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation. This also applies to subjects who have previously completed the Blinded Core Treatment Period, did not meet clinical benefit criteria at Day 169, and entered the Posttreatment Follow-up Period.

Following study unblinding, eligible subjects may enter the Open-label Extension Treatment Period to begin receiving luspatercept therapy or continue receiving luspatercept therapy if they were experiencing clinical benefit in the blinded study.

Subjects randomized to placebo and BSC will need to meet the safety-related eligibility criteria of the study (excluding inclusion criteria 1 through 4) which must be verified by the Investigator, with appropriate documentation available that may be reviewed by the Sponsor prior to a subject receiving their first luspatercept dose. Upon meeting the eligibility criteria, subjects are eligible for assignment to luspatercept treatment via IRT, in which they will receive a starting dose of 1.33 mg/kg at the next treatment cycle after unblinding. Subjects will continue in the study for at least 24 weeks following the schedule of assessments beginning with the Cycle 1 Day 1 assessments,

with the exception of PK and ADA samples that will not be collected. Collection of biomarker samples on Cycle 5 Day 1 will not be required during the Open-label Extension Treatment Period. In addition, PRO assessments will also not be required during the Open-label Extension Treatment Period (Section 6.10).

Subjects randomized to luspatercept and BSC who have discontinued treatment will not be eligible for individual crossover to open-label luspatercept after unblinding. They will remain in the Posttreatment Follow-up Period at the time of unblinding as appropriate. Those subjects in the Blinded Extension Treatment Period can continue receiving luspatercept and completing assessments and procedures as scheduled in Section 5, Table 3 in the Open-label Treatment Period as long as they continue to demonstrate clinical benefit from treatment (refer to Section 6.2.2).

6.3 Dose Delays in the Treatment Phase

On days when subjects return to the investigational site for IP administration, but IP is not administered (eg, due to protocol dose modification, dose delay rules [Section 7.3]), all required assessments and procedures should be performed, regardless if IP is administered. During the time period of dose delay, the following assessments/procedures should be performed:

- If dose delay is due to a laboratory or vital signs abnormality, the assessment that was the reason for the dose delay should be repeated at least on a weekly basis.
- If dose delay is due to increased Hgb level, perform hematology assessments at least weekly.
- If dose delay is due to an AE, perform hematology, serum chemistry, and serum ferritin assessments at least every 3 weeks thereafter and before next dose administration.
- Pharmacokinetic (PK)/ADA samples should be collected on the first day of dose delay and prior to IP administration on day dosing resumes.
- Refer to the eCRF completion guidelines for detailed instructions related to eCRF data entry.

6.4 End of Treatment Visit

An EOT evaluation will be performed as soon as possible for subjects (both blinded and crossover subjects) who are withdrawn from treatment for any reason (but, at the latest, at the next projected planned study visit) after the decision to permanently discontinue treatment has been made. Evaluations will be performed as specified in Section 5, Table 3.

If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit. If a procedure had been performed within ± 7 days of the EOT visit, it does not need to be repeated unless clinically indicated per Investigator discretion (with the exception of blood pressure assessment and sample collection for hematology, chemistry, and urinalysis).

The reason for discontinuation will be recorded in the eCRF and in the source documentation for all randomized subjects, regardless of whether they are dosed or not. Reasons for treatment discontinuation are provided in Section 11.1.

The following procedures/evaluations (including a Response Assessment evaluation) should be performed:

- Spleen size assessment by palpation

- Healthcare resource utilization (as detailed in Section 6.11)
- ECOG performance status
- Pregnancy testing (as detailed in Section 6.1)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures on an ongoing basis
- Vital signs (as detailed in Section 6.1)
- Serum chemistry (as detailed in Section 6.1)
- Hematology assessments (as detailed in Section 6.1)
- Serum EPO level
- Serum ferritin level
- Response assessment (as detailed in Section 6.2.2)
- Transfusion data collection and assessment

  During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.

- Exploratory/Biomarker sample collection (as detailed in Section 6.9)
- PRO instrument completion (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/premalignancies

6.5 Posttreatment Follow-up Period

The Posttreatment Follow-up Period will be inclusive of a 42-Day Follow-up Period starting from the last dose of IP (applicable for both blinded and crossover subjects) and a Long-term Follow-up Period, beginning from the date of last dose of IP.

6.5.1 42-Day Follow-up Period (referred to as the Safety Follow-up)

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of IP as well as those serious adverse events (SAEs) made known to the Investigator at any time that are suspected of being related to IP (applicable for both blinded and crossover subjects).

Females of childbearing potential (FCBPs) will be advised to avoid becoming pregnant during study and for 12 weeks after the last dose of IP. Males will be advised to use a latex condom during any sexual contact with an FCBP prior to study entry and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy. Refer to Section 10.5.

Pharmacokinetic (PK) and ADA sample(s) may be required in the Posttreatment Follow-up Period. Refer to Sections 6.7 and 6.8.

Additionally, the following should also be captured:

- Healthcare resource utilization (as detailed in Section 6.11)
- Adverse event assessment and reporting on an ongoing basis
- Concomitant medications and procedures
- Hematology assessments (as detailed in Section 6.1)
- Transfusion data collection and assessment

During the study, the following, but not limited to, information will be recorded for all transfusions (including any transfusions received at outside institutions in between study visits) the subject receives 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later: date of transfusion, pretransfusion Hgb levels, number of units transfused, and volume of transfusion. In addition to local procedures that may be in place at the site to capture this information, a transfusion diary will be provided to all subjects and will be reviewed by the site when/if returned by the subject. Source documentation of transfusions given during the study must be available for source document verification.

- PRO instrument completion (as detailed in Section 6.10)
- Monitoring for transformation to blast phase and other malignancies/pre-malignancies
- Post-IP treatment MPN-associated MF therapies
- Survival follow up

6.5.2 Long-term Follow-up and End of Study

After the 42-Day Follow-up Period, only adverse events of special interest (AESI) and those SAEs made known to the Investigator that are suspected of being related to IP will be recorded by the Investigator.

Females of childbearing potential (FCBPs) will be advised to avoid becoming pregnant during study and for 12 weeks after the last dose of IP. Males will be advised to use a latex condom during any sexual contact with an FCBP prior to study entry and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy. Refer to Section 10.5.

For all subjects who receive at least 1 dose of IP, continuation of monitoring for transformation to blast phase will occur in the Posttreatment Follow-up Period, along with data collection of new MPN-associated MF disease therapies and overall survival every 3 months after the 42-Day Follow-up Period for at least 5 years following the date of first dose of IP or 3 years post last dose of IP, whichever occurs later, unless the subject withdraws consent from the study, dies, or is lost to follow up, whichever occurs first. This information will be collected until the End of Study and recorded in the eCRF. During this time, all subjects will be followed approximately every 3 months following the 42-Day Follow-up Period. The Investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow up. Survival follow up can be performed via the telephone.

All subjects will be followed for RBC transfusions (occurring at the study site or at outside institutions) for 168 days from the date of Cycle 1 Day 1 (ie, Study Day 169) or 12 weeks after the last dose of IP, whichever occurs later.

Long-term follow up may be conducted by record review (including public records, if available and allowed by local regulations) and/or telephone contact with the subject, family, or the subject's treating physician.

6.6 Unscheduled Visits

An unscheduled visit in this protocol refers to any assessment or procedure that is completed outside of the designated time points and frequencies outlined in Section 5, Table 3. Should it become necessary to repeat an evaluation (eg, laboratory tests or vital signs), the results of the repeat evaluation should be entered as an additional unscheduled visit in the eCRF.

Refer to the eCRF completion guidelines for detailed instructions related to eCRF data entry.

6.7 Pharmacokinetics

Blood samples will be collected to analyze IP concentrations in serum in all subjects as indicated in Section 5, Table 3. At each PK time point, approximately 3 mL of blood will be collected and serum prepared as described in the study reference guide. Blood samples for PK will be taken at the following visits during the study: C1D1 (must be collected before the first dose), C2D1, C4D1, C6D1, C8D1, Day 169 Response Assessment, C12D1, and C16D1 only.

If the subject discontinues before all samples are collected during the Treatment Phase, or does not participate in the Extension Treatment Phase, or discontinues the Extension Treatment Phase with less than 48 weeks of monitoring, additional samples should be collected at the 42-Day Follow-up Period and for every 12 weeks thereafter for up to 48 weeks post the first dose of blinded IP.

The dose level and dosing time of IP on the PK visit days should be recorded in eCRF.

Detailed procedures of PK sample collection, processing, and shipping are provided in the study reference guide.

6.7.1 Unscheduled Pharmacokinetic Visits

Pharmacokinetic (PK) sampling per Investigator's or Sponsor's discretion is allowed and should be recorded as an unscheduled visit.

6.8 Antidrug Antibody

Blood samples will be collected for assessment of ADA against IP in serum in all subjects. The maximum ADA monitoring period will be 48 weeks post the first dose of IP. At each ADA time point, approximately 3 mL of blood will be collected and serum prepared as described in the study reference guide. However, during the first year of treatment, an additional blood draw may not be needed for the ADA test, as the ADA test may be conducted utilizing the PK samples obtained at the same visit. Blood samples for ADA will be taken at the following visits during the study (also see Section 5, Table 3): C1D1 (must be collected before the first dose), C2D1, C4D1, C6D1, C8D1, Day 169 Response Assessment, C12D1, and C16D1 only.

If the subject discontinues before all samples are collected during the Treatment Phase, or does not participate in the Extension Treatment Phase, or discontinues the Extension Treatment Phase with less than 48 weeks of monitoring, additional samples should be collected at the 42-Day Follow-up Period and for every 12 weeks thereafter for up to 48 weeks post the first dose of blinded IP.

Antidrug antibodies (ADA) sampling per Investigator's or Sponsor's discretion is allowed and should be recorded as an unscheduled visit.

Detailed procedures of ADA sample collection, processing, and shipping are provided in the study reference guide.

6.9 Exploratory/Biomarker Assessments

Blood and saliva samples for evaluation of biomarkers, such as, but not limited to, gene expression profiling, ActRIIB ligands, inflammatory cytokines, immune and erythroid cells, molecular mutations, and serum markers related to erythropoiesis and fibrogenesis, will be collected at screening and throughout the study as indicated in Section 5, Table 3. If required on IP dosing days, samples should be obtained prior to IP administration. Evaluation of some of the samples may require blood samples to be collected and processed as multiple samples to allow for the possibility of future analyses.

Other biomarkers may be evaluated as determined by additional data.

6.9.1 Additional and Optional Research

Additional and optional research as described below may be performed using leftover samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.9.1.1 Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.9.1.2 Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact the subject's ability to participate in the main study.

6.10 Patient-reported Outcome (PRO) Measures

All PRO measures will be completed prior to every IP administration, apart from two items pertaining to the procedural burden of RBC transfusions that are comprising the RBC transfusion-related experience measures (these two items will be administered immediately after an RBC transfusion). Furthermore, except for the EQ-5D-5L and MF-SAF v4.0 instruments, all PRO measures will be completed starting on Cycle 1 Day 1 and every other cycle thereafter, in addition

to the Day 169 Response Assessment, the End of Treatment Visit, and the 42-day Follow-up Period.

The EQ-5D-5L instrument will be completed starting on Cycle 1 Day 1, the Day 169 Response Assessment, the End of Treatment Visit, and the 42-day Follow-up Period.

The MF-SAF v4.0 instrument will be completed on Cycle 1 Day 1 and every treatment cycle thereafter in the Blinded Core Treatment Period, followed by every other cycle thereafter in the Blinded Extension Treatment Period, the Day 169 Response Assessment, the End of Treatment Visit, and the 42-day Follow-up Period.

For subjects who crossover into the Open-label Extension Treatment Period, no PRO measures will be collected during this open-label period. This includes the MF-SAF v4.0, FACT-An, RBC Transfusion-related Experience Measures, PGI-TS, TSQM, and EQ-5D-5L.

Refer to Section 5, Table 3 for more information.

6.10.1 Overview of Myelofibrosis Symptom Assessment Form (MF-SAF v4.0)

Myelofibrosis Symptom Assessment Form, version 4.0 (MF-SAF v4.0) was developed and validated by The Patient-Reported Outcome (PRO) Consortium's MF Working Group as an instrument to be used in clinical trials on myelofibrosis (Gwaltney, 2017). The instrument focuses on seven core symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain.

The resulting MF-SAF v4.0 asks respondents to report symptom severity at its worst for each of the seven items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale. The MF-SAF v4.0 has two recall formats: 24-hour and 7-days and will be maintained and licensed. The 7-day recall format will be used in this study. The total symptom score for the 7-day recall format of the MF-SAF v4.0 is calculated as the average of the observed individual item responses on the 0 to 10 scale multiplied by 7, resulting in a weekly total symptom score range of 0 to 70, with the higher score indicating overall worse symptoms.

See APPENDIX G for the full list of items.

6.10.2 Overview of Functional Assessment of Cancer Therapy – Anemia (FACT-An)

The FACT-An is a 47-item, cancer-specific questionnaire consisting of a core 27-item general questionnaire (ie, the Functional Assessment of Cancer Therapy-General [FACT-G]) and an additional 20-item anemia questionnaire (ie, the Anemia Subscale [AnS]) (Yellen, 1997). This instrument has been validated and widely used in clinical trials to assess the effect of treatments in various therapeutic areas, including MPN-associated MF (Tefferi, 2014). The FACT-G measures the following domains on a five-point scale ranging from 0 ("not at all") to 4 ("very much"):

- Physical Well-being (PWB; 7 items; score range, 0 to 28),
- Social/Family Well-being (SWB; 7 items; score range, 0 to 28),
- Emotional Well-being (EWB; 6 items; score range, 0 to 24), and

- Functional Well-being (FWB; 7 items; score range, 0 to 28).

The AnS consists of 20 items on the same five-point scale, with 13 of them measuring fatigue-related symptoms (FS) and seven measuring non-FS. The AnS and FS scores can range from 0 to 80 and 0 to 52, respectively.

Three summary scales can also be calculated from the FACT-An:

- FACT-G (score range, 0 to 108), a summary scale composed of PWB, SWB, EWB, and FWB
- FACT-An Trial Output Index (TOI) (score range, 0 to 136), a summary scale composed of the PWB, FWB, and AnS
- FACT-An Total score (score range, 0 to 188), the sum of the FACT-G score and the AnS score

For all domains and summary scales, a higher score indicates better HRQoL or lower level of symptoms.

See APPENDIX H for the full list of items.

6.10.3 RBC Transfusion-related Experience Measures and Patient Global Impression of Transfusion Satisfaction (PGI-TS)

Six items were built specifically for this study to measure RBC transfusion-related experience, with 4 of these items built to measure the burden associated with the frequency of RBC transfusions, while 2 additional items will measure the burden associated with the procedural aspects of RBC transfusions. The latter 2 items pertaining to the procedural burden of RBC transfusions are intended to be completed before or after an RBC transfusion is administered, as appropriate, to better understand the subject's experience with RBC transfusions. Frequency of administration of these 6 items is defined in Section 5, Table 3.

Additionally, the PGI-TS 2-item measure was included to capture subjects' overall satisfaction with their RBC-transfusion experience and was built specifically for this study. The first item asks subjects to indicate how satisfied or dissatisfied they are with their overall RBC transfusion experience over the past 3 months, and the second item asks about their satisfaction with the number of transfusions over the past 3 months.

See APPENDIX I for the full list of items.

6.10.4 Global Treatment Satisfaction Questionnaire for Medication (TSQM)

The Global Treatment Satisfaction assessment was modified after a Global Satisfaction domain of the TSQM (Atkinson, 2004). The original Global Satisfaction domain of the TSQM contained 3 items that measured confidence in benefits, balance between good and bad things, and global satisfaction. The confidence in benefits item was dropped off in the revised version, TSQM v II (Atkinson, 2005). We used this modified version and adopted it to the current study needs to evaluate a patient's overall satisfaction with the IP rather than a single medication.

See APPENDIX J for the full list of items.

6.10.5 Overview of EQ-5D-5L

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L (Herdman, 2011) consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems).

See APPENDIX K for the full list of items.

6.11 Healthcare Resource Utilization

An exploratory objective of this study is to characterize the medical resource utilization among subjects treated with luspatercept compared with subjects receiving placebo treatment. To facilitate this aim, certain healthcare resource utilization data will be collected.

Healthcare resource utilization information will be collected after a subject signs informed consent and through 42 days after the last dose of IP or until the date of last study visit, whichever period is longer. Healthcare resource utilization data, includes, but are not limited to:

- Hospitalizations;
- Medications;
- Clinic visits;
- Medical/diagnostic procedures; and
- Treatment for AEs.

Information on each hospitalization event will be collected utilizing an eCRF designed for this purpose that collected information on reason for hospitalization (eg, transformation to blast phase, MPN-associated MF-related illness, treatment-related AEs), and days of hospitalization by treatment setting (regular hospital ward versus higher level care units such as intensive care unit).

Other disease- and treatment-related forms of healthcare resource utilization will be collected through routine study activities. These may include RBC transfusions, emergency room visits, or significant diagnostic procedures. The number of RBC transfusion events will be evaluated in detail, as these relate directly to time devoted to receiving RBC transfusions that can impact patients' quality of life. Additionally, information on concomitant medications (eg, antibiotics, antiviral medications, ICTs) and resource use associated with treatment administration for MF or comorbidities will be collected.

6.12 Screen Failures

For all subjects determined as screen failures, the following information is to be captured in the subject's source documents and eCRF page(s): the date the ICF was signed, demographics, the reason subject did not qualify for the study, and the Investigator's signature for the eCRF pages. The adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed as a screen failure. Other relevant information will also be recorded as applicable.

7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Product(s)

Luspatercept will be provided by the Sponsor. Luspatercept for injection is formulated as a sterile, preservative-free, lyophilized cake/powder. Luspatercept for injection is available in 25-mg and 75-mg vials and when reconstituted with water for injection, each consists of 50 mg/mL luspatercept in a 10 mM citrate buffer-based solution (10 mM citrate, pH 6.5, 9% sucrose, 0.02% polysorbate 80).

It is recommended that the reconstituted luspatercept for injection, at room temperature, be used immediately after reconstitution.

- In case the reconstituted luspatercept cannot be administered immediately, it may be stored in either the vial or syringe for up to 8 hours at room temperature. It is suggested that for long hold periods it be kept in the vial rather than transferred to a syringe. The total in-use time of the reconstituted luspatercept for injection, from reconstitution to administration, must not exceed 8 hours when stored at room temperature. The time the IP was reconstituted should be noted on the syringe, study records, source documents and IP dispensation log.
- Alternately, in case the reconstituted luspatercept cannot be administered immediately, it may be stored in either the vial or syringe at 2°C to 8°C for up to 24 hours prior to administration. It is suggested that for long hold periods it be kept in the vial rather than transferred to a syringe. Prior to administration it should be allowed to reach room temperature for at least 15 minutes. The total in-use time of the reconstituted luspatercept for injection, from reconstitution to administration, must not exceed 24 hours. The time the IP was reconstituted should be noted on the syringe, study records, source documents and IP dispensation log.

Samples of luspatercept drug product, held at the recommended storage condition, have been shown to be stable through the labeled shelf-life.

Placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered subcutaneously. Sterile, normal saline will be obtained according to the site's clinical trial agreement and in accordance with local guidelines. The investigational site's designated separate and unblinded personnel will prepare the placebo syringes to match the active syringes. All other site staff and the subject will be blinded. The manufacturer's directions for storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

Investigational product will be administered on Day 1 of every 21-day treatment cycle.

Subjects that are randomized will be receiving JAK2 inhibitor therapy for the treatment of MPN-associated MF as prescribed by their physician. JAK2 inhibitor therapy will be obtained according to the site's clinical trial agreement and in accordance with local guidelines.

7.2 Treatment Administration and Schedule

Investigational product (IP) will be administered on Day 1 of every 21-day cycle, at an initial dose level of 1.33 mg/kg. Doses may be titrated up starting in Cycle 3 as described in Section 7.3. Investigational product (IP) will be administered as a subcutaneous injection to subjects by the study staff at the clinical site and administration will be documented in the subject's source record

and eCRF. Subjects must have their Hgb, WBC, blood myeloblast percentage, and blood pressure assessed prior to each IP administration.

Subcutaneous injections will be given in the upper arm, thigh, and/or abdomen. Calculated doses requiring reconstituted volume greater than 1.2 mL should be divided into separate, similar volume injections across separate sites using the same anatomical location, but on opposite sides of the body (example left thigh and right thigh). The maximum volume per subcutaneous injection should not exceed 1.2 mL. The injection sites can be rotated according to Investigator judgment, and the injections can be given in the following order as needed, for example: 1) right upper arm, 2) left upper arm, 3) right upper thigh, 4) left upper thigh.

7.3 Dose Modifications: Dose Titration, Dose Reduction, and Dose Delay

Starting dose with dose increases and reductions are presented below for reference (refer to Table 4).

Table 4: Starting Dose Level With Dose Reductions and Dose Titrations

3rd Dose Reduction	2nd Dose Reduction	1st Dose Reduction	**Starting Dose Level**	1st Dose Titration Increase
0.6 mg/kg	0.8 mg/kg	1.0 mg/kg	**1.33 mg/kg**	1.75 mg/kg

7.3.1 Dose Titration

As soon as Cycle 3 Day 1 and assessed by the Investigator prior to every subsequent treatment cycle, subjects may have the dose level increased from the starting dose level of 1.33 mg/kg up to a maximum of 1.75 mg/kg during the Treatment Phase.

If the subject has 2 of the most recent prior treatment cycles assessed at the same dose level and if the subject has not met any protocol dose delay and/or reduction criteria in the 2 most prior treatment cycles, they may be eligible for a dose titration. The dose level may be increased by 1 dose level if 1 or more of the following criteria are met:

- Subject has ≥ 1 RBC transfusion event (for pretransfusion Hgb of ≤ 9.5 g/dL) during the 2 most recent prior treatment cycles (~6 weeks)
- Hgb decrease of ≥ 1 g/dL is observed in a transfusion-free period of approximately 6 weeks and this decrease is not preceded by an RBC transfusion (the Hgb decrease occurs ≥ 14 days after the last RBC transfusion)
- Hgb value is not exceeding 1 g/dL increase from the baseline mean pretransfusion Hgb value

The dose level should be titrated individually for each subject.

7.3.2 Dose Delay and Dose Reduction

Dose delay and/or reduction or discontinuation may be required due to increased hemoglobin or adverse events. Table 5 below provides guidelines for dose modifications and dose delay.

Table 5: Dose Modification - Dose Delay, Dose Reduction, and Discontinuation Guidelines

Event at the Day of Dosing (Assessed prior to each IP administration)	Action
Any suspected related adverse event (AE) ≥ Grade 3[a,b]	Dose delay[c] investigational product (IP) until resolved to ≤ Grade 1 or baseline, and then reduce dose by 1 dose level
≥ 2 dose reductions suspected related AE[a]	Discontinue IP treatment
Change in hemoglobin (Hgb) ≥ 2 g/dL compared to predose Hgb of previous treatment cycle	Reduce dose by 1 dose level[d] if change in Hgb not influenced by red blood cell (RBC) transfusions
Predose Hgb[d] ≥ 12 g/dL	Dose delay IP until Hgb ≤ 11.5 g/dL
Blood myeloblast percentage[e] *(based on either local or central lab hematology sample)*	If the blood myeloblast percentage at the first day of a dosing cycle is ≥ 10% conduct retesting within a week before the next dosing cycle: • If the retest has a myeloblast percentage that is still ≥ 10%, discontinue IP • If the retest has a myeloblast percentage < 10%, the subject may continue IP
Transformation to blast phase *(based on either local or central lab)*	If there is transformation to blast phase confirmed by a bone marrow blast count of ≥ 20% **or** an increase in blood myeloblast percentage of ≥ 20% associated with an absolute blast count ≥ 1 x 10^9/L that lasts for at least 2 weeks, discontinue IP.
White blood count (WBC) is: • ≥ 120 x 10^9/L **or** • ≥ 3 x baseline and ≥ 30 x 10^9/L[f] *(based on either local or central lab hematology sample)*	Dose delay[c] IP with weekly WBC monitoring until WBC is: • < 120 x 10^9/L **or** • < 3 x baseline **or** < 30 x 10^9/L If WBC continues to be elevated for 3 consecutive determinations, discontinue IP
Leukopenia, Neutropenia and/or Thrombocytopenia A shift (worsening) by ≥ 2 grades[g] leukopenia, neutropenia or thrombocytopenia to ≥ Grade 3 during treatment with IP not clearly and solely related to an extraneous case such as advancing MPN-associated MF or an infectious event. **Worsening of Anemia:** A ≥ 50% increase from baseline in transfusion burden in combination with an unexplained shift from baseline (worsening) of ≥ 2 grades[g] leukopenia, neutropenia or thrombocytopenia.	Dose delay[c] IP and repeat WBC, neutrophils and platelet count weekly for two consecutive weeks • If WBC, neutrophils and platelet counts are resolved to ≤ Grade 1, baseline, or shifts by at least one toxicity grade (improvement) and if cytopenia is not regarded as related to IP and the myeloblast percentage is < 10% (follow the myeloblast percentage rule above), then discuss the dose level for continuation of IP with the Medical Monitor. • If WBC, neutrophils and platelet counts are not resolved to ≤ Grade 1, baseline or does not shift by at least one toxicity grade (improvement) and an alternative cause cannot be identified, then consider additional bone marrow assessments and discuss next steps with the Medical Monitor.

[a] Possibly, probably or definitely related to IP.

[b] Includes systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg.

[c] If dose delay is > 12 consecutive weeks, IP should be discontinued.

[d] Predose Hgb value not being influenced by red blood cell (RBC) transfusion (eg, hemoglobin [Hgb] result > 14 days after last RBC transfusion); Hgb should be rechecked weekly during dose delay.

[e] The Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion prior to making decision regarding IP discontinuation.

[f] Corrected WBC should be used to establish the baseline white blood count (WBC). Baseline = highest WBC between Screening WBC and Cycle 1 Day 1 (C1D1).

[g] Thrombocytopenia, leukopenia, and neutropenia toxicity grades as defined by Common Terminology Criteria for Adverse Events (CTCAE) criteria.

7.4 Overdose

Overdose, as defined for this protocol, refers to luspatercept dosing only. On a per dose basis, an overdose is defined as being 10% or higher over the protocol-specified dose of luspatercept assigned to a given subject, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 10.1 for the reporting of adverse events associated with overdose.

7.5 Method of Treatment Assignment

The treatment assignment (randomization) will occur at the end of the Screening Period, once all the required screening procedures have been completed and all required data have been submitted to the Sponsor or its authorized representative. Upon receiving acknowledgment of subject's eligibility review from the Sponsor or its authorized representative, the subject can be randomized using the IRT built for this study.

Designated research personnel at each investigational site will be assigned password protected, coded identification numbers which gives them authorization to call into IRT to randomize subjects. For drug assignment at each dose start and in the event of any dose reduction or dose titrations, site staff must contact IRT to record the new dose level and obtain the new IP assignment.

The relationship of the randomization number to the subject identification (ID) number will be described by a randomization algorithm. The randomization algorithm will be employed by the IRT system to assign a subject to a treatment based on the prespecified rules, such us a double-blind study, stratified randomization with a randomization ratio of active versus placebo at 2:1; subjects will be placed into the appropriate stratum per the responses/data entered/collected for questions collecting stratification and based on the combination of these data points, the IRT will place the subject in the next available slot within the appropriate stratum for that subject. The IRT will be utilized to ensure an equal weight central randomization based on the randomization method according to stratification factors defined in Section 3.1. The randomization number corresponds to a particular treatment arm within a stratum. The randomization number, by itself, will not unblind a user to the subject's treatment. The randomization number should be coupled with all the unblinded code information in order for the subject to become unblinded.

7.6 Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations/requirements.

7.6.1 Blinding

For this trial, all subjects, study site staff, and Sponsor representatives with the exception of designated individuals (eg, the pharmacist at the investigational site), will remain blinded to all treatment assignments (except if a specific subject is unblinded after Day 169), until all blinded subjects have completed or discontinued early from the Blinded Core Treatment Period, the primary endpoint has been analyzed, the DMC has been consulted, and the study has become unblinded.

The designated site individual (eg, the pharmacist) at the investigational site will use a syringe (that exactly matches the syringe used for reconstituted luspatercept) and sterile normal saline (0.9% sodium chloride for injection) to prepare a matching placebo. Thus, the designated site individual at the investigational site will be unblinded and will give Investigators and their staff luspatercept and placebo in a blinded manner.

Randomization, drug dispensing, dose reduction/titration, and drug discontinuation will be accomplished by an IRT system. Authorized site personnel must contact the IRT for randomization, IP assignment at the beginning of each cycle, registering dose reductions or titrations, and treatment discontinuation. Confirmation of each call will be sent to the investigational site and Celgene.

For emergency unblinding refer to Section 12.2.

7.7 Investigational Product Accountability and Disposal

Accountability for IP that is administrated during the course of the study is the responsibility of the Investigator or designee. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of IP received, to whom it was administered (subject-by-subject accounting), and accounts of any luspatercept accidentally or deliberately destroyed or returned. Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents. Unless otherwise notified, all vials of luspatercept, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The Investigator must return all unused vials of luspatercept to the Sponsor at the end of the study, or the luspatercept may be destroyed at the clinical site with the permission of the Sponsor. For either scenario, the outcome must be documented on the drug accountability log. The Sponsor will provide direction for the outcome of all unused vials.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for luspatercept return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.8 Investigational Product Compliance

Investigational product will be administered as a subcutaneous injection at the clinical site by the study staff. Monitoring for subject compliance with the treatment regimen is therefore unnecessary.

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents.

The Investigator or designee is responsible for accounting for all IP that is administered during the course of the study.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.

The following must be recorded on the appropriate eCRF(s):

- Prior/concomitant treatments used from **28 days** prior to randomization until 42 days after the last dose of IP, Study Day 169, or until the EOT visit (whichever occurs later).
- Prior therapies used for anemia (ie, ESAs, androgenic steroids, immunomodulatory compounds, thalidomide) will be captured regardless of time of treatment discontinuation.
- Prior/concomitant treatments with a potential effect on the hematopoietic system should be captured from **8 weeks** prior to randomization until 42 days after the last dose of IP.
- Prior medical procedures from **8 weeks** prior to randomization until 42 days after the last dose of IP.
- All RBC transfusions from **at least 16 weeks (112 days)** prior to randomization until 12 weeks after the last dose of IP (including any RBC transfusions conducted outside the study site). For the purpose of this study, RBC and whole blood transfusions are regarded as equivalent.
- Prior and/or current JAK2 inhibitor therapies and other treatments for MPN-associated MF and anemia regardless of treatment start/discontinuation.
- Prior anti-cancer treatments regardless of treatment discontinuation/procedure date.

If a subject requires treatment with any new medications that are specifically excluded in Section 8.2, the subject will be discontinued from treatment and should complete the End of Treatment Visit and enter the Posttreatment Follow-up Period. The Investigator should consult the Medical Monitor regarding any questions about whether a new medication or dosage of existing medication would require the subject to discontinue from the study.

For information regarding other drugs that may interact with IP and affect its metabolism, PK, or excretion, please see the IB and/or local package insert.

8.1 Permitted Concomitant Medications and Procedures

Subjects are receiving a JAK2 inhibitor for the treatment of MPN-associated MF that is approved in the country where the study is being conducted. JAK2 inhibitors are to be used according to their respective label and as prescribed as part of the subject's standard-of-care therapy as prescribed by their physician prior to study entry. If the JAK2 inhibitor label permits, the daily JAK2 inhibitor dose should be kept stable during at least the first 24 weeks of IP. The Sponsor will not be supplying approved JAK2 inhibitors for this study. Approved JAK2 inhibitors will be obtained by the sites according to the local clinical study agreement and in accordance with local guidelines.

Best supportive care (BSC) includes, but is not limited to, treatment with transfusions (eg, RBC, platelet, whole blood), ICTs, antibiotic, antiviral and/or antifungal therapy, and nutritional support as needed.

Granulocyte colony-stimulating factors (ie, G-CSF, granulocyte macrophage colony-stimulating factor [GM-CSF]) are allowed only in cases of neutropenic fever or as clinically indicated per product label.

Prophylactic antithrombotic therapy is permitted.

Thrombopoietin and platelet transfusions are permitted.

Treatment with systemic corticosteroids is permitted for nonhematological conditions providing the subject is receiving a constant dose equivalent to ≤ 10 mg prednisone during the study.

Administration of attenuated vaccines (eg, influenza vaccine) is allowed if clinically indicated per Investigator discretion.

Iron chelation therapy (ICT) is to be used according to the product label. If the label permits, the ICT dose should be stable during at least the first 24 weeks of IP. Initiation of ICT while within the first 24 weeks of IP should be clinically indicated to treat an AE.

8.1.1 RBC Transfusions

Red blood cell-transfusion practices based on Hgb levels and symptoms should not change for an individual subject during the Screening Period and the Treatment Phase.

For any RBC transfusions received during the study (at either the study site or an outside institution), the Hgb value just prior to transfusion should be collected, along with several other parameters (ie, number of units transfused, volume transfused, date of transfusion).

Each subject will have a "pretransfusion hemoglobin threshold" for requiring transfusion during the study which will be determined based on transfusion history. The baseline pretransfusion hemoglobin threshold will be the mean of all documented pretransfusion hemoglobin values during the 12 weeks prior to Dose 1 Day 1. During treatment, if the pretransfusion hemoglobin level is increased by ≥ 1 g/dL (at the time of a next anticipated transfusion event) compared to the pretransfusion hemoglobin threshold for that subject, the transfusion should be delayed by a minimum of 7 days and/or the number of units transfused should be reduced by 1 or more RBC units.

Subjects may be transfused at the Investigator's discretion for symptoms related to anemia or other requirements (eg, infection).

8.2 Prohibited Concomitant Medications and Procedures

The following concomitant medications are specifically excluded during the course of study treatment:

- Cytotoxic, chemotherapeutic, targeted, or investigational agents/therapies (excluding JAK2 inhibitor therapy)
- Azacitidine, decitabine, or other hypomethylating agents
- Lenalidomide, thalidomide, and pomalidomide
- Erythropoietin stimulating agents (ESAs) and other RBC hematopoietic growth factors (eg, IL-3)

- Hydroxyurea or other alkylating agents
- Androgens (unless given to treat hypogonadism)
- Oral retinoids (topical retinoids are permitted)
- Arsenic trioxide
- Interferon
- Anagrelide
- Systemic corticosteroids at a dose equivalent to > 10 mg prednisone
- Investigational products for the treatment of MPN-associated MF

The following procedures are specifically excluded during the Treatment Phase:

- Splenectomy
- Radiotherapy
- Hematopoietic cell transplant

8.3 Required Concomitant Medications and Procedures

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

This is a Phase 3, global, double-blind, randomized, multicenter study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo in subjects with MPN-associated MF and anemia on concomitant JAK2 inhibitor therapy and who require RBC transfusions.

The design of the study, including the proposed targeted subject population, study endpoints, and statistical plan, is discussed below.

9.2 Study Population Definitions

Study populations to be analyzed are defined as follows:

Intent-to-treat (ITT) Population:

The intent-to-treat (ITT) population will consist of all randomized subjects regardless of whether or not the subject received IP.

Modified Intent-to-treat (mITT) Population:

The modified intent-to-treat (mITT) population, a sub-set of the ITT population, includes all ITT subjects who

- have no important protocol deviation of inclusion/exclusion criteria and no other important protocol deviation that could impact on efficacy outcome.
- take at least one dose of IP.

The analyses based on mITT will be conducted to support the primary findings.

Safety Population:

The Safety Population will consist of all subjects who were randomized and received at least 1 dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received.

The estimand framework, the handling of intercurrent events, and statistical methods to handle missing data will be described in the statistical analysis plan (SAP). The SAP will describe any predefined rules for including/excluding any subjects with data from any analyses (eg, time windows, visit by visit analysis, endpoint analysis, important protocol deviation).

9.3 Sample Size and Power Considerations

A total of 309 subjects (206 in the active treatment group, 103 in the placebo group) will have 90% power to detect the difference [redacted]

The assumption for the luspatercept arm response rate is derived from the preliminary Phase 2 data results, where, as of the 10 May 2019 data cutoff date, 6 out of 19 subjects (32%) in Cohort 3B achieved RBC-TI for ≥ 84 days within the first 24 weeks on study. Considering that the ACE-536-MF-002 study will allow enrollment of subjects with a slightly lower RBC- transfusion burden

(ie, allowing subjects with 4 to 12 RBC units/12 weeks immediately up to randomization) and a higher luspatercept starting dose compared to the ACE-536-MF-001 study (ie, 1.33 mg/kg versus 1 mg/kg), it is anticipated that the luspatercept arm response rate will be at least 35%.

The assumption of the placebo arm response rate is a conservative assessment derived from available evidence from the limited number of placebo-controlled studies in this indication and previous experiences with luspatercept in other indications and available data from other drugs.

In a large Phase 3, double-blind, randomized trial in MPN-associated MF subjects comparing pomalidomide versus placebo, 168 subjects were randomized to pomalidomide and 84 subjects were randomized to placebo. The study did not show a difference between pomalidomide and placebo, as the primary endpoint (defined as RBC-TI for ≥ 12 weeks) response rates were 16% (n = 152, 95% CI: 11% to 23%) with pomalidomide and 16% (n = 77, 95% CI: 8% to 26%) with placebo (Tefferi, 2017) in the mITT population (n = 229).

In the ACE-536-MDS-001 (MEDALIST) study, a double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept versus placebo in subjects with anemia due to MDS who require RBC transfusions, the secondary efficacy endpoint of RBC-TI ≥ 12 weeks from Week 1 through Week 24 was achieved in 8% (6 out of 76 subjects; 95% CI: 2.95 to 16.4) of all placebo subjects.

The sample size calculation is based on a 2:1 randomization ratio, one-sided alpha of 0.025, test statistics on difference of proportions using an un-pooled estimate of variance with one non-binding interim futility analysis at [redacted] information time (eg, approximately [redacted] randomized subjects have completed the Day 169 Response Assessment or have discontinued the IP prior to the end of Week 24).

The addition of a superiority interim analysis does not alter the original sample size calculation. The power of the superiority interim analysis is [redacted] and the overall study power remains at [redacted] with 309 subjects. [redacted] will be used to control the overall one-sided alpha at 0.025.

9.4 Randomization and Stratification

A 2:1 randomization of luspatercept to placebo will be used as MPN-associated MF is an orphan disease with a limited number of subjects and therapies available.

Randomization will be accomplished by IRT to ensure timely registration and randomization. A stratified randomization schedule will be implemented.

Stratification will be based on the following factors:

- RBC-transfusion burden at baseline
  - 4 to 5 units/12 weeks
  - 6 to 12 units/12 weeks
- DIPSS score at baseline
  - Intermediate-1/Intermediate-2

– High risk`

9.5 Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations by treatment group. Prior transfusion history will be summarized. Myeloproliferative neoplasm (MPN)-associated MF diagnoses as well as RBC-transfusion dependence will be summarized using frequency tabulations.

Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. All prior medications and procedures will be summarized using frequency tabulations. The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

Prior anti-MPN-associated MF treatments will be summarized as appropriate.

9.6 Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for treatment and both follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.7 Efficacy Analysis

All efficacy analyses will be performed on the ITT population. Key efficacy analyses will be performed on the mITT population as supportive evidence and to assess robustness of efficacy findings. Subjects will be analyzed according to their randomized treatment group.

9.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint of RBC-TI is defined as the absence of any RBC transfusions during any consecutive 12-week period starting during the Blinded Core Treatment Period (or the time from randomization up to and including Week 24). Examples of any consecutive 12-week period are from Day 1 to 84, Day 2 to 85, Day 3 to 86, etc. Subjects discontinued without achieving at least 12 consecutive weeks of RBC-TI will be counted as nonresponders.

The primary endpoint will be compared between the two treatment arms based on the ITT population. The Cochran–Mantel–Haenszel (CMH) test will be applied to test the difference in response rates between the two treatment arms at a 1-sided significance level of 0.025 with randomization factors as strata. If the stratified CMH test is not estimable due to low strata size, the stratified Miettinen-Nurminen (MN) method (Miettinen, 1985) will then be used. An analysis based on the mITT population will be confirmative and supportive.

As ruxolitinib is the JAK2 inhibitor expected to be predominantly used, comparison between the two treatment arms might be performed in a pre-specified subgroup of subjects who are receiving ruxolitinib for the treatment of MPN-associated MF. A descriptive summary for non-ruxolitinib treated subjects will be provided.

Additional details will be outlined in the SAP.

9.7.2 Secondary Efficacy Endpoints

9.7.2.1 Key Secondary Efficacy Endpoint

The key secondary endpoint, defined as the proportion of subjects who become RBC-transfusion free over any consecutive 16-week period starting during the Blinded Core Treatment Period (or the time from randomization up to and including Week 24), will be tested in the same manner as the primary efficacy endpoint. Examples of any consecutive 16-week period are from Day 1 to 112, Day 2 to 113, Day 3 to 114, etc. The [redacted] procedure will be used to control type I error. The key secondary endpoint will be tested only when the primary endpoint reaches statistical significance in the ITT population.

Full details will be included in the SAP.

9.7.2.2 Additional Secondary Efficacy Endpoints

Other secondary endpoints will be summarized descriptively, unless otherwise specified, and will be based on the ITT population.

Duration of RBC-TI 12 will be summarized only for subjects who achieved RBC-TI 12 response. It is defined as the maximum duration of an RBC-TI 12 response, calculated from the start of a response (ie, RBC-TI 12) through end of treatment or at the time of crossover (if applicable).

Reduction in transfusion burden is defined as the proportion of subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units from baseline over any consecutive 12-week period. It will be calculated from randomization through and including Week 24.

Duration of reduction in transfusion burden is defined as the maximum duration of when subjects reduce their transfusion burden by ≥ 50% and by ≥ 4 units from baseline over any consecutive 12-week period. It will be calculated from the start of the response up through end of treatment or at the time of crossover (if applicable).

RBC-TI ≥ 12 weeks in treatment period (RBC-TI 12/TP) is defined as the proportion of subjects who become RBC-transfusion free over any consecutive 12-week period, calculated from the time of randomization up to the end of treatment or at the time of crossover (if applicable). Examples of any consecutive 12-week period are from Day 1 to 84, Day 2 to 85, Day 3 to 86, etc.

RBC-TI ≥ 16 weeks in treatment period (RBC-TI 16/TP) is defined as the proportion of subjects who become RBC-transfusion free over any consecutive 16-week period, calculated from the time of randomization up to the end of treatment or at the time of crossover (if applicable). Examples of any consecutive 16-week period are from Day 1 to 112, Day 2 to 113, Day 3 to 114, etc.

Change in RBC transfusion burden is defined as the mean change in transfusion burden (RBC units) from baseline. It will be calculated from randomization up to and including Week 24. This analysis will be conducted in subjects that remain on study (in the Treatment Phase or the Long-term Follow-up Period) at the time of Study Day 169.

Cumulative duration RBC-transfusion independence is defined as the cumulative response duration for subjects achieving multiple episodes of RBC-TI 12, calculated from randomization up through end of treatment or at the time of crossover (if applicable).

Mean Hgb increase ≥ 1 g/dL is defined as the proportion of subjects achieving a mean Hgb increase ≥ 1 g/dL from baseline over any consecutive 12-week period in absence of RBC transfusions, calculated from any consecutive "rolling" 12-week period starting from randomization up to and including Week 24, as well as randomization up to end of treatment or at the time of crossover (if applicable).

Change in serum ferritin from baseline is calculated from randomization up to and including Week 24, as well as randomization up to end of treatment. This analysis will be conducted in subjects that remain on study (in the Treatment Phase or the Long-term Follow-up Period) at the time of Study Day 169.

Full details will be included in the SAP.

9.8 Safety Analysis

All safety analyses will be performed on the safety population. Full details will be included in the SAP. Planned data presentations and analyses include the following:

- Adverse events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events will be summarized by system organ class and preferred term. Treatment-emergent adverse events (TEAEs) leading to death or to discontinuation from treatment, TEAEs classified as National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) all grades or Grade 3/4 TEAEs, related to investigational product, and serious TEAEs will be summarized separately.
- Clinical laboratory results will be summarized descriptively by treatment group. Clinically significant hematologic and nonhematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE (version 5.0). Cross tabulations will be provided to summarize frequencies of abnormalities. Additionally, frequency of ADA will also be reported.
- Spleen assessment data and vital sign measurements, including body weight, will be listed for each subject at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by treatment group.

Graphical displays will be provided where useful to assist in the interpretation of results.

9.9 Timing of Analyses

9.9.1 Interim Analysis for Futility

An interim analysis (IA) to assess futility will be performed on the primary endpoint in the ITT population when approximately [redacted] randomized subjects have completed the Day 169 Response Assessment or have discontinued IP prior to the end of Week 24 ([redacted] information fraction).

A conditional power approach is used for the futility analysis; if the interim analysis shows less than [redacted] conditional power, the trial may stop for futility. An external DMC will review the unblinded interim data and provide a futility recommendation.

9.9.2 Interim Analysis for Superiority

An IA to test for superiority will be performed on the primary and key secondary endpoints in the ITT population when approximately [redacted] randomized subjects have been followed for 40 weeks to accommodate the start of the key secondary endpoint [redacted] information fraction).

The study is expected to be fully enrolled by the time these [redacted] subjects complete their 40 weeks of follow-up. If enrollment is slower than expected, the interim analysis may be delayed and the information fraction for the calculation of the superiority boundary will be updated to accommodate the actual number of subjects with full 40-week follow-up at the time of the analysis.

[redacted] If the analysis occurs at exactly [redacted] information fraction, this corresponds to a [redacted] that is spent for this analysis. At exactly [redacted] information fraction, the corresponding [redacted] is [redacted] corresponding to a one-sided [redacted]

An external DMC will review the unblinded interim data and will inform the Sponsor whether the superiority boundary has been crossed for the primary endpoint and if so, the key secondary endpoint.

9.9.3 Final Analysis

The final analysis will be performed when all subjects have reached their primary and key secondary endpoints or have discontinued IP earlier. More specifically, the final analysis will be performed when all subjects have completed 40 weeks of assessments (Week 24 plus 16 weeks of efficacy follow-up for the maturity of the key secondary endpoint), including subjects who discontinued IP early but continue to remain on study.

To accommodate the superiority IA and maintain a one-sided alpha of 0.025 across the study, a reduced alpha will be used to determine the efficacy boundary at the time of final analysis based on the [redacted] The alpha-level and efficacy boundary at the time of final analysis will reflect the alpha that was spent at the superiority IA. If the IA occurred at exactly [redacted] information fraction, the final analysis will declare superiority if $Z >$ [redacted] corresponding to a one-sided p [redacted]

Additional follow-up analyses will be performed when subjects complete the Long-term Follow-up Period.

Full details will be included in the SAP.

9.10 Other Topics

9.10.1 Pharmacokinetic Analysis

Population PK analysis may be performed for luspatercept using nonlinear mixed effect modeling. Concentration data obtained from this study and other studies may be combined to develop a population PK model that describes the PK exposure data and the associated variability. Subject-specific factors (demographics, baseline characteristics, markers for organ function, anti-luspatercept antibodies, etc.) may be explored as covariates for their potential to influence luspatercept PK parameters. Empiric individual Bayesian estimates of PK parameters will be generated using the final population PK model. With these individual parameter estimates, appropriate measures of luspatercept exposure (area under the curve [AUC], maximum plasma concentration of drug [C_{max}], or other exposure metrics of interest) will be computed for each subject. The relationship between serum luspatercept exposure and selected efficacy endpoints and AEs of interest may be explored as appropriate.

9.10.2 Patient-reported Outcome Measures

The objective of the PRO measurements (MF-SAF v4.0, FACT-An, PGI-TS, RBC transfusion-related experience measures, Global Treatment Satisfaction, and EQ-5D-5L) is to explore the effect of luspatercept in patients with MPN-associated MF on health-related quality of life, health utility scores, anemia-related symptoms, and satisfaction with RBC transfusions and overall treatment experience.

9.10.3 Healthcare Resource Utilization

The objective of collecting healthcare resource utilization data is to characterize the medical resource utilization among subjects treated with luspatercept as compared to subjects receiving placebo treatment. Healthcare resource utilization data will be collected. Analyses on healthcare resource utilization will be conducted and descriptive statistics will be provided as outlined in the SAP.

9.10.4 Biomarker Analysis

The relationship between biomarkers and clinical outcomes will be explored. No formal statistical analysis of biomarker data will be performed. The full statistical analysis will be described in a separate biomarker study report.

9.10.5 Subgroup Analysis

Appropriate subgroup analyses by stratification factors and other baseline characteristics for clinical activity may be conducted as exploratory analyses.

Full details will be included in the SAP.

9.10.6 Sensitivity Analysis

Sensitivity analyses and supplemental estimands will be further described in the SAP.

9.10.7 Data Monitoring Committee

An external, independent, unblinded DMC will be comprised of experts in MPN-associated MF not involved in the ACE-536-MF-002 protocol, an independent Reporting Statistician, and may include additional ad hoc members. During the DMC meetings, representatives of the Sponsor may attend the blinded part of the DMC meetings but will not have access to unblinded data.

During the course of the study, the DMC will review the unblinded safety data regularly as well as safety and efficacy data in accordance with the guidelines for the preplanned analyses and the procedure pertaining to monitoring for transformation to blast phase as outlined in the DMC charter. An independent third party (Statistical Data Analysis Center) will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the DMC members for each scheduled meeting.

The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter, which will be endorsed by the DMC prior to the first data review meeting.

Operational details for the DMC will also be detailed in the DMC charter.

9.10.8 Steering Committee

A steering committee (SC) will be established by charter for this study and be comprised of Study Investigators, Sponsor representatives, and may include additional ad hoc members. The SC will review blinded data and will serve in an advisory capacity to the Sponsor. The SC may advise and recommend to the Sponsor the following (but not limited to):

- Changes to the protocol or conduct of the study based upon emerging clinical or scientific data from this and/or other studies.
- Procedures to ensure the safety of subjects and integrity of study data.
- Procedures to meet the overall goals and objectives of the study.

The SC responsibilities, authorities, and procedures will be detailed in the SC charter, which will be endorsed by the SC prior to the first data review meeting.

Operational details for the SC will also be detailed in a separate SC charter.

Note: The SC is separate from the DMC.

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.4), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (See Section 7.4 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the eCRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the eCRF. The overdose itself should not be reported as an AE. In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for luspatercept overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, spleen assessment findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 42 days after the last dose of IP as well as those SAEs made known to the Investigator at any time that are suspected of being related to IP.

All AEs (serious/non-serious) will be recorded on the CRF and in the subject's source documents. Refer to Section 10.6 for instructions on how to report SAEs to Drug Safety.

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2 Severity/Intensity

For each AE, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0; APPENDIX L);

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Adverse events (AEs) that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

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

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3 Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4 Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.2.5 Action Taken

The Investigator will report the action taken with IP as a result of each AE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

The Investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3 Adverse Events of Special Interest

10.3.1 Other Malignancies/Premalignancies

The occurrence of a new malignancy or premalignant lesion will be monitored as an event of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the development of any new malignancy or premalignant lesion as a serious adverse event, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF up to and including at least 5 years following the date of first dose of IP or 3 years post last dose of IP of the Posttreatment Follow-up Period, whichever occurs later.

Events of new malignancy and premalignant lesions (excluding benign tumors or benign neoplasia) are to be reported within 24 hours of the Investigator's knowledge of the event to Celgene Drug Safety and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation of the diagnosed malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, computed tomography [CT] scans, etc.).

Malignancies or cancerous tumors are lesions capable of invading into adjacent tissues and may be capable of spreading to distant tissues. A benign tumor has none of those properties.

Malignancy or cancer is characterized by anaplasia, invasiveness, and metastasis. For MPN-associated MF studies, these also include transformation to blast phase, myeloproliferation (eg, clinically significant increases in blasts), etc.

Premalignant or precancerous lesions refer to a state of disordered morphology of cells that is associated with an increased risk of cancer. If left untreated, these conditions may lead to cancer. Such conditions are usually either dysplasia or benign neoplasia (and the dividing line between those is sometimes blurry). Sometimes the term "precancer" is used to describe carcinoma in situ, which is a noninvasive cancer that has not progressed to an aggressive, invasive stage. Not all carcinoma in situ will progress to invasive disease.

Premalignant lesions are morphologically atypical tissue which appears abnormal under microscopic examination and in which cancer is more likely to occur than in its apparently normal counterpart.

10.3.2 Thromboembolic Events

The occurrence of a thromboembolic event will be monitored as an event of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report the occurrence of thromboembolic events as an SAE, regardless of casual relationship to IP, occurring at any time for the duration of the study.

10.4 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.5 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.5.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 12 weeks of the subject's last dose of IP, are considered immediately reportable events. Investigational product (IP) is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.5.2 Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Males will be advised to use a latex condom during any sexual contact with FCBP prior to study entry and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy.

10.6 Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 42 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the eCRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is recorded within the eCRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the eCRF as well.

In addition, any report of transformation to blast phase or AML, regardless of causality, will be reported as an expedited safety report to the regulatory authorities, if requested.

10.7 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to luspatercept based on the Investigator Brochure.

In the United States, expedited reports sent to the FDA by the Sponsor based on the reasonable possibility threshold are known as "IND safety reports" and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be causally related to luspatercept by the Sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population, as detailed in the IB will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information *(in Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators)*:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity;
- Other important safety information and periodic reports according to the local regulations.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC (See Section 14.3 for record retention information).

10.8 COVID-19 Reporting

The occurrence of a COVID-19 event will be monitored as part of the assessment of AEs throughout the course of the study. Investigators are to report the occurrence of COVID-19 events, regardless of casual relationship to IP, occurring at any time for the duration of treatment up to 42 days after last dose.

11 DISCONTINUATIONS

11.1 Treatment Discontinuation

Subjects will have an End of Treatment (EOT) Visit at the time of IP discontinuation (refer to Section 6.4). All subjects who received at least one dose of IP will be followed for at least 5 years following the date of first dose of IP or 3 years post last dose of IP, whichever occurs later.

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Meeting applicable treatment discontinuation criteria found in Section 7.3, Table 5
- Withdrawal by subject
- Death
- Lost to follow up
- Pregnancy
- Protocol deviation impacting subject safety and data integrity
- Study terminated by Sponsor
- Failure of JAK2 inhibitor treatment or switching to a different JAK2 inhibitor treatment
- Requiring a medication/procedure on the prohibited medication/procedure list (refer to Section 8.2 for more information)
- Other (to be specified on the eCRF and in the protocol)
  - Clinical benefit criteria (refer to Section 6.2.2 for more information)

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects discontinued from IP for any reason will have EOT evaluations at the time of discontinuation, outlined in Section 6.4. Subsequently, subjects would then move into the Posttreatment Follow-up Period, consisting of a 42-Day Follow-up Period and Long-term Follow-up Period (refer to Section 6.5).

11.2 Study Discontinuation

Subjects who discontinue from treatment for any reason will be followed via telephone contact by the site for collection of data on survival, cause(s) of death, transformation to blast phase, and posttreatment therapies for MPN-associated MF during the 42-Day Follow-up Period. During the Long-term Follow-up Period time points, collection of data on posttreatment therapies for MPN-associated MF, survival, cause(s) of death, and transformation to blast phase will occur every 3 months after the 42-Day Follow-up Period for at least 3 years after the last dose of IP or 5 years post first dose (whichever occurs later), or until death, lost to follow up, or withdrawal of consent from the study.

Every attempt should be made to contact subjects during follow up unless subjects discontinue from the study. Every attempt should be made to collect all data on discontinued subjects.

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Withdrawal by subject
- Death
- Lost to follow up
- Study terminated by Sponsor
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12 EMERGENCY PROCEDURES

12.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2 Emergency Identification of Investigational Products

Except for the subject unblinding to determine crossover eligibility, the blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblinded dose information.

13 REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, IPs, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4 Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5 Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

13.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7 Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8 Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

The Sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed, and the availability of a roll-over protocol exists into which any subjects that remain on study may be consented to continue receiving access to luspatercept if they are deriving clinical benefit or be monitored for long-term safety. Such a protocol would be written for a compound that would not yet be commercially available.

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;

- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14 DATA HANDLING AND RECORDKEEPING

14.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2 Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3 Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made into the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3 Investigational Medicinal Product Quality Issues

Issues that call into question IP safety, purity, potency, quality, and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all Sponsor-supplied IP suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labeling, and IP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated, and a response will be provided back to the investigational site.

16 PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18 APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ActRIIB	Activin receptor type IIB
ADA	Antidrug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
AnS	Anemia subscale score
ASCT	Allogenic stem cell transplantation
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BM	Bone marrow
BMP6, BMP9	Bone morphogenetic protein 6, bone morphogenetic protein 9
BSC	Best supportive care
CALR	Calreticulin
CI	Confidence interval
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
DIPSS	Dynamic International Prognostic Scoring System
DMC	Data Monitoring Committee
EC	Ethics Committee
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
EEA	European Economic Area
ELN	European LeukemiaNet
EMA	European Medicines Agency
EMH	Extramedullary hematopoiesis
EOT	End of treatment
EPO	Erythropoietin
EQ-5D-5L	EuroQol Group 5 Dimensions – 5 Levels
ESA	Erythropoiesis stimulating agent
ET	Essential thrombocythemia
EWB	Emotional Well-being
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FACT-G	Functional Assessment of Cancer Therapy – General
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FS	Fatigue-related symptoms
FWB	Functional Well-being
GDF11	Growth differentiation factor 11
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
HCV-RNA	Hepatitis C virus RNA
HepB	Hepatitis B
HepC	Hepatitis C
Hgb	Hemoglobin
HI-E	Hematologic improvement – erythroid response
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICT	Iron chelation therapy
IL	Interleukin

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
IP	Investigational product
IPSS-R	International Prognostic Scoring System – Revised
IRB	Institutional Review Board
IRT	Integrated response technology
ITT	Intent-to-treat
IWG-MRT	International Working Group – Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
JAK2	Janus kinase 2
MDRD	Modification of diet in renal disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MF-SAF	Myelofibrosis Symptom Assessment Form
mITT	Modified Intent-to-treat
MPL	Thrombopoietin receptor
MPN	Myeloproliferative neoplasm
NCI	National Cancer Institute
PGI-TS	Patient Global Impression of Transfusion Satisfaction
PIN	Personal identification number
PK	Pharmacokinetics
PMF	Primary myelofibrosis
Post-ET MF	Post-essential thrombocythemia myelofibrosis
Post-PV MF	Post-polycythemia vera myelofibrosis
PRO	Patient-reported outcomes
PV	Polycythemia vera
PWB	Physical Well-being
RBC	Red blood cell count
RBC-TI	Red blood cell – transfusion independence
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SC	Steering committee
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
STAT	Signal transducers and activators of transcription
SUSAR	Suspected unexpected serious adverse reaction
SWB	Social Well-being
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
TOI	Trial output index
TP	Treatment period
TSQM	Treatment Satisfaction Questionnaire: Medication
ULN	Upper limit of normal
WBC	White blood cell count
WHO	World Health Organization

APPENDIX B IWG-MRT: INTERNATIONAL WORKING GROUP – MYELOPROLIFERATIVE NEOPLASMS RESEARCH AND TREATMENT (IWG-MRT)

Proposed nomenclature by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)

de novo presenting disease	
	Primary myelofibrosis (PMF)
Myelofibrosis transformation from prior polycythemia vera	
	(PV) or essential thrombocythemia (ET)
	Post PV myelofibrosis (post-PV MF)
	Post ET myelofibrosis (post-ET MF)
Transformation to acute leukemia	
	Primary myelofibrosis in blast phase (PMF-BP)
	Post PV/ET MF in blast phase

Source: Mesa, 2007.

APPENDIX C 2016 WORLD HEALTH ORGANIZATION (WHO) DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS (PMF)

2016 WHO diagnostic criteria for prePMF and overt PMF

PrePMF[a]	Overt PMF[b]
Major criteria	
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis > Grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis	1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis Grades 2 or 3*
2. Not meeting the WHO criteria for BCR-ABL1$^+$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms	2. Not meeting WHO criteria for ET, PV, BCR-ABL1$^+$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker[c], or absence of minor reactive BM reticulin fibrosis[d]	3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker[c], or absence of reactive myelofibrosis[d]
Minor criteria	
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:	Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition	a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥ 11 x 10^9/L	b. Leukocytosis ≥ 11 x 10^9/L
c. Palpable splenomegaly	c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range	d. LDH increased to above upper normal limit of institutional reference range
	e. Leukoerythroblastosis

BM = bone marrow; CALR = calreticulin; CML = chronic myeloid leukemia; ET = essential thrombocythemia; JAK2 = Janus kinase 2; LDH = lactate dehydrogenase; MPL = thrombopoietin receptor; PMF = primary myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

* More than 25% above mean normal predicted value.

[a] Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion.

[b] Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion.

[c] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

[d] Minor (Grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

*In Grades MF-2 or MF-3 an additional trichrome stain is recommended.

Source: Arber, 2016.

APPENDIX D PROPOSED CRITERIA FOR THE DIAGNOSIS OF POST-POLYCYTHEMIA VERA AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS

International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) recommended criteria for post-PV MF and post-ET MF

Criteria for post-polycythemia vera myelofibrosis	Criteria for post-essential thrombocythemia myelofibrosis
Required criteria:	
1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria	1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria
2. Bone marrow fibrosis Grade 2–3 (on 0–3 scale)[3] or Grade 3–4 (on 0–4 scale) [a]	2. Bone marrow fibrosis Grade 2–3 (on 0–3 scale)[3] or Grade 3–4 (on 0–4 scale) [a]
Additional criteria (two are required):	
1. Anemia[b] or sustained loss of requirement of either phlebotomy (in absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis	1. Anemia[b] and a ≥ 2 $mgml^{-1}$ decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture	2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly	3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)	4. Increased LDH (above reference level)
	5. Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)

LDH = lactate dehydrogenase; WHO = World Health Organization.

[a] Grade 2–3 according to the European classification:[3] diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification:[4] diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

[b] Below the reference range for appropriate age, sex, gender and altitude considerations.

Source: Barosi, 2008.

APPENDIX E DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)

DIPSS Risk Score

Prognostic variables	Value		
	0	**1**	**2**
Age, years	≤ 65	> 65	
White blood cell count, x 10^9/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Yes/No	No	Yes	

The risk category is obtained adding up the values of each prognostic variable.

Risk categories are defined as:

- low: 0;
- intermediate-1: 1 or 2;
- intermediate-2: 3 or 4;
- and high: 5 or 6.

Source: Passamonti, 2010.

APPENDIX F EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

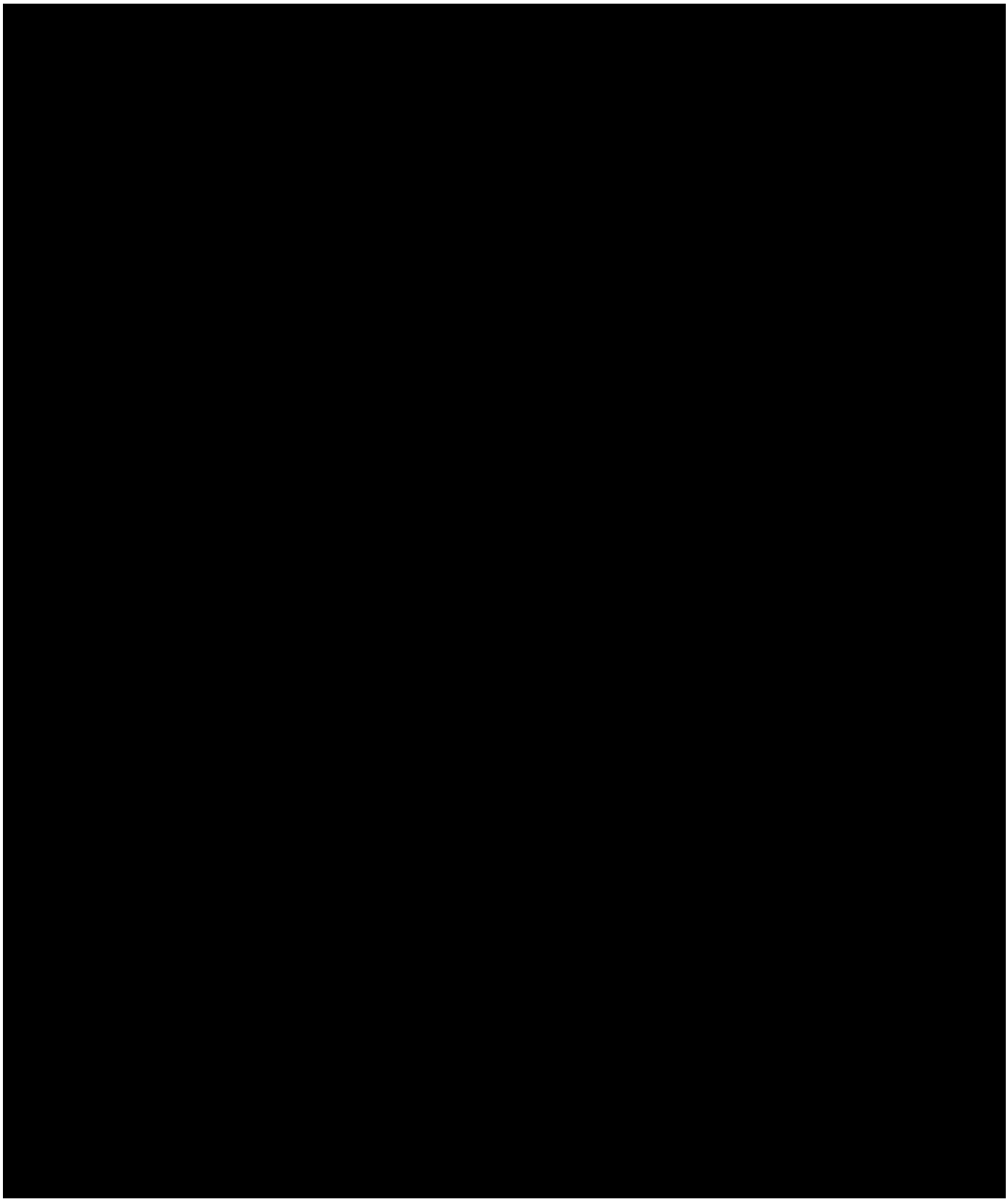
The ECOG scale is used to assess a subject's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the subject.

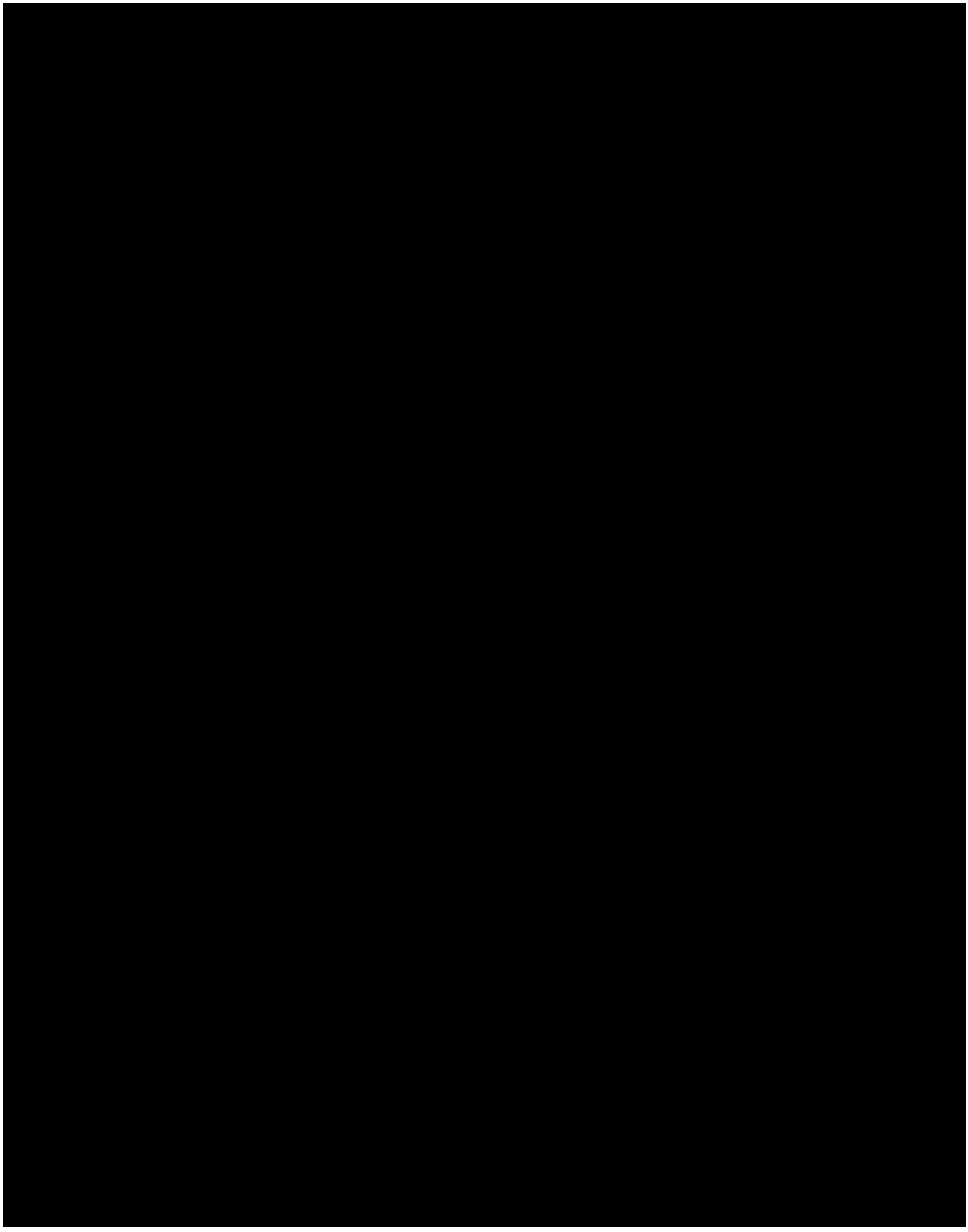
Eastern Cooperative Oncology Group (ECOG) Performance Status	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

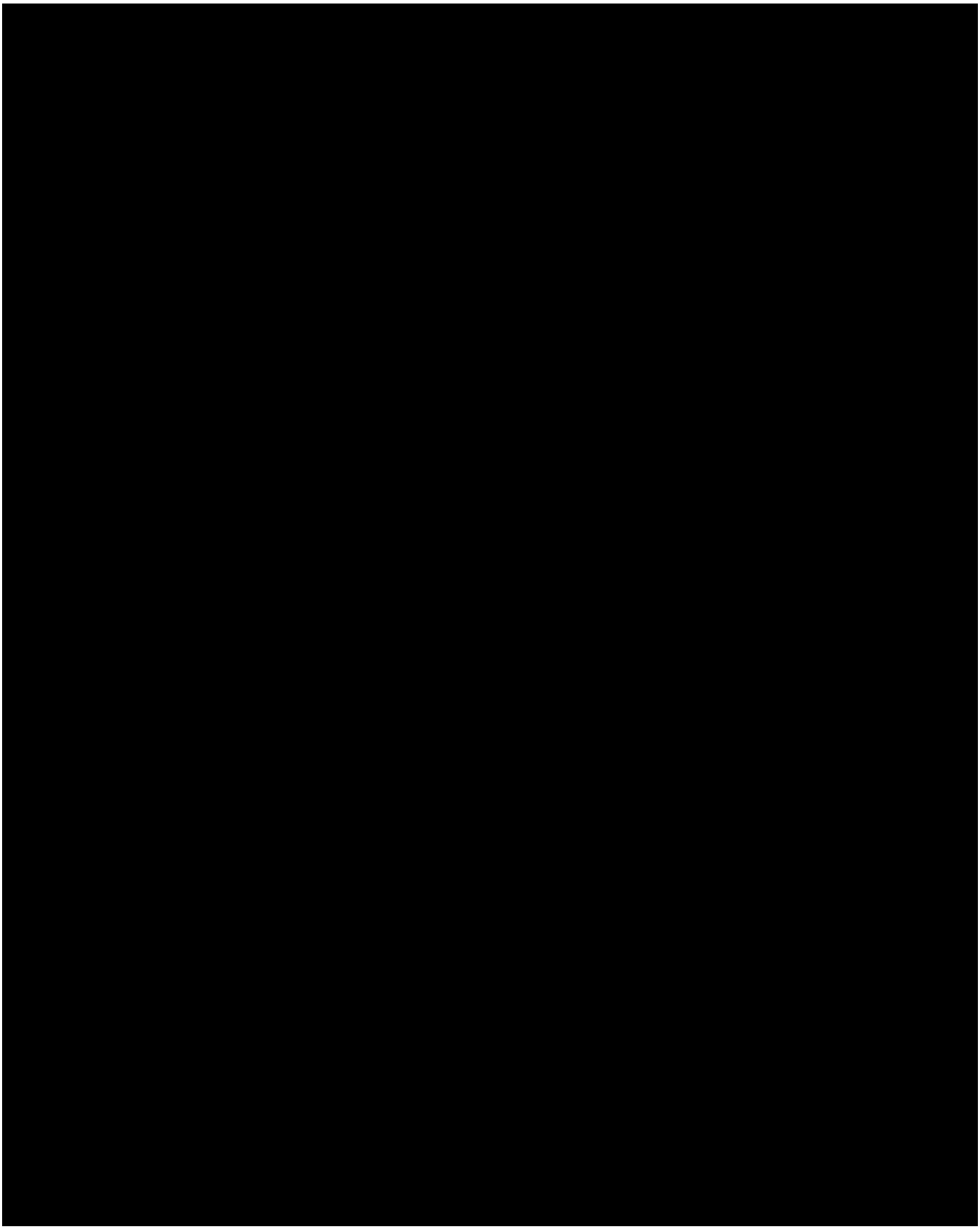
Source: Oken, 1982.

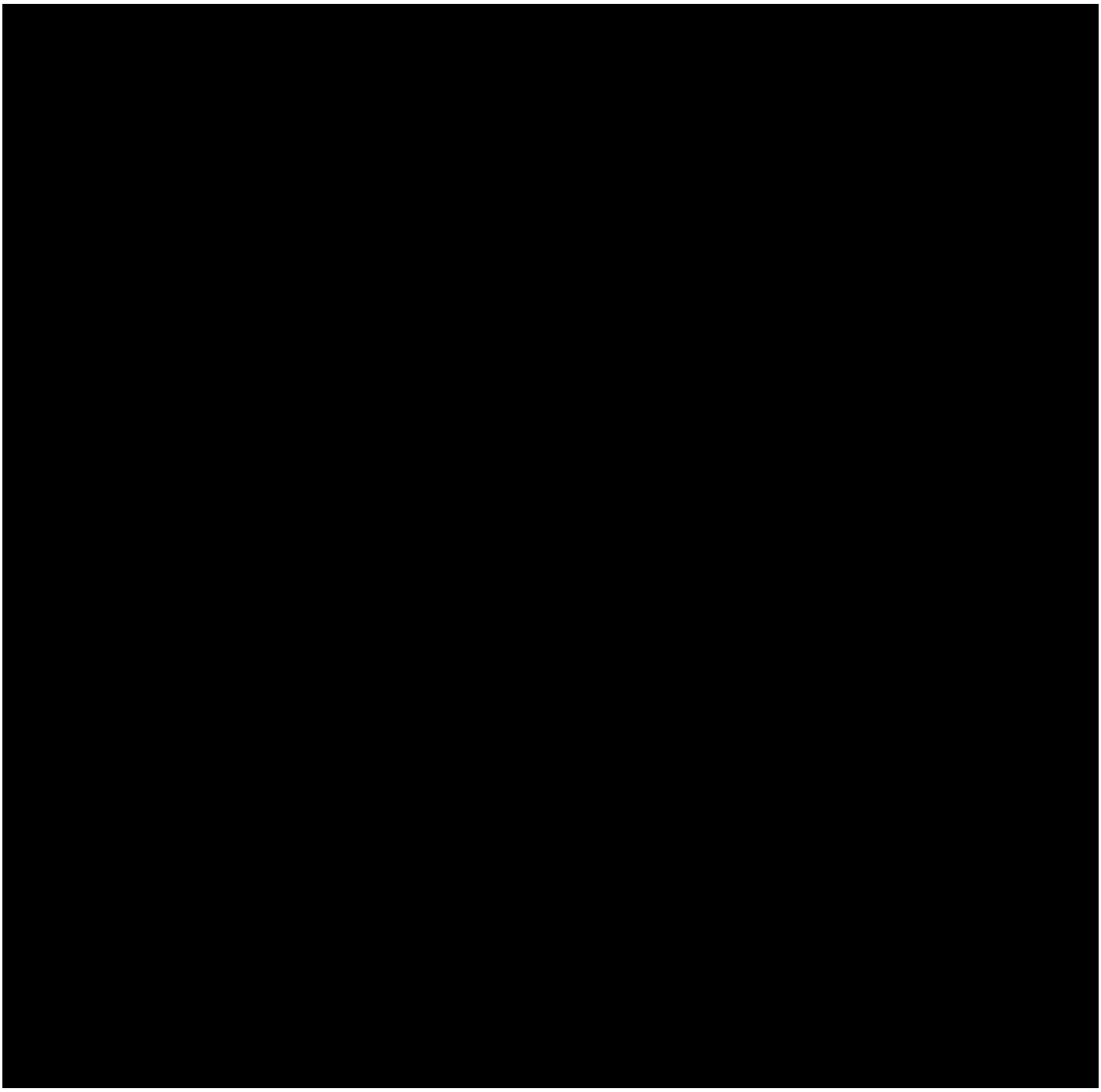
APPENDIX G MYELOFIBROSIS SYMPTOM ASSESSMENT FORM, VERSION 4.0 (MF-SAF V4.0)

APPENDIX H FUNCTIONAL ASSESSMENT OF CANCER TREATMENT – ANEMIA (FACT-AN), VERSION 4

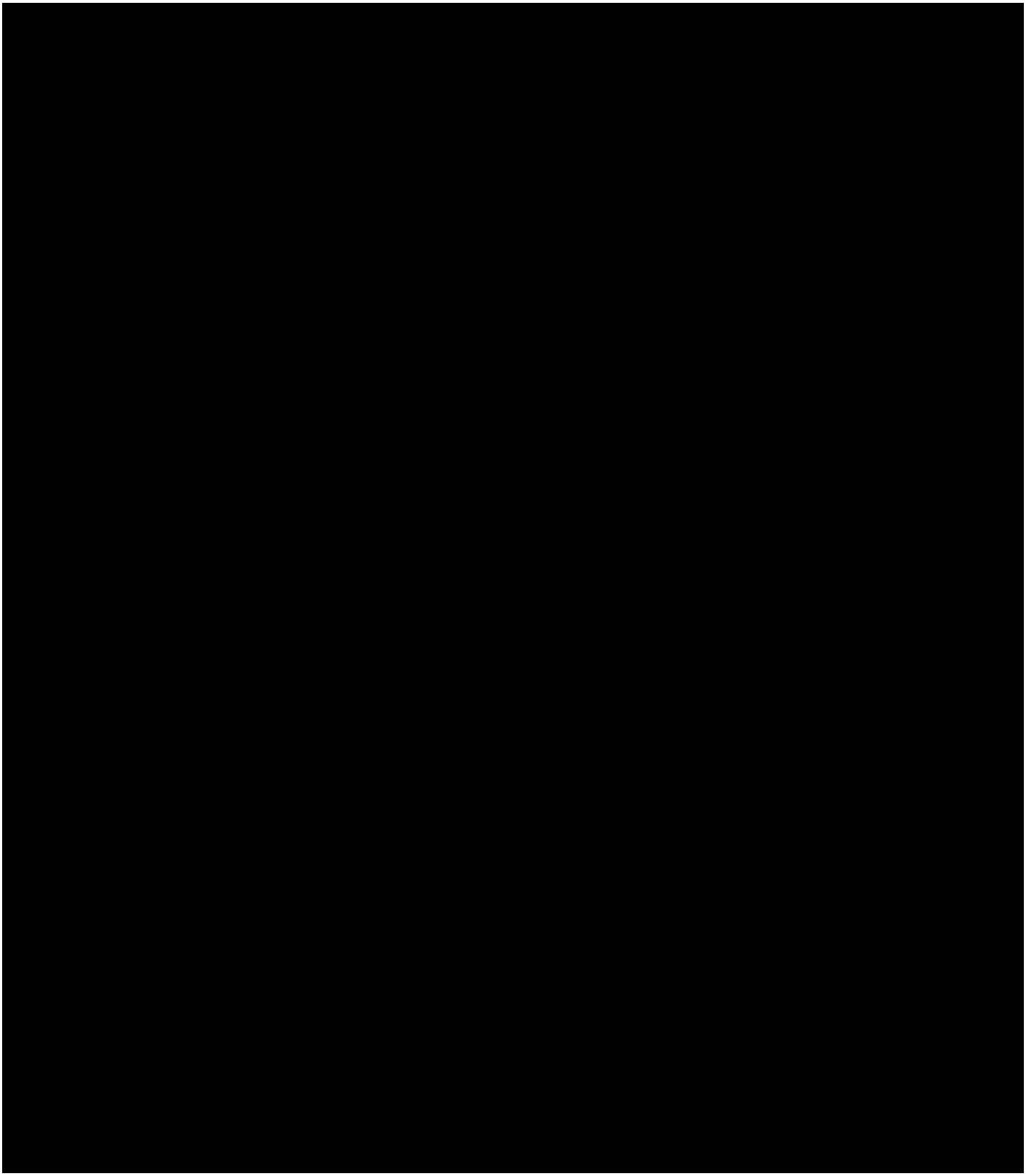






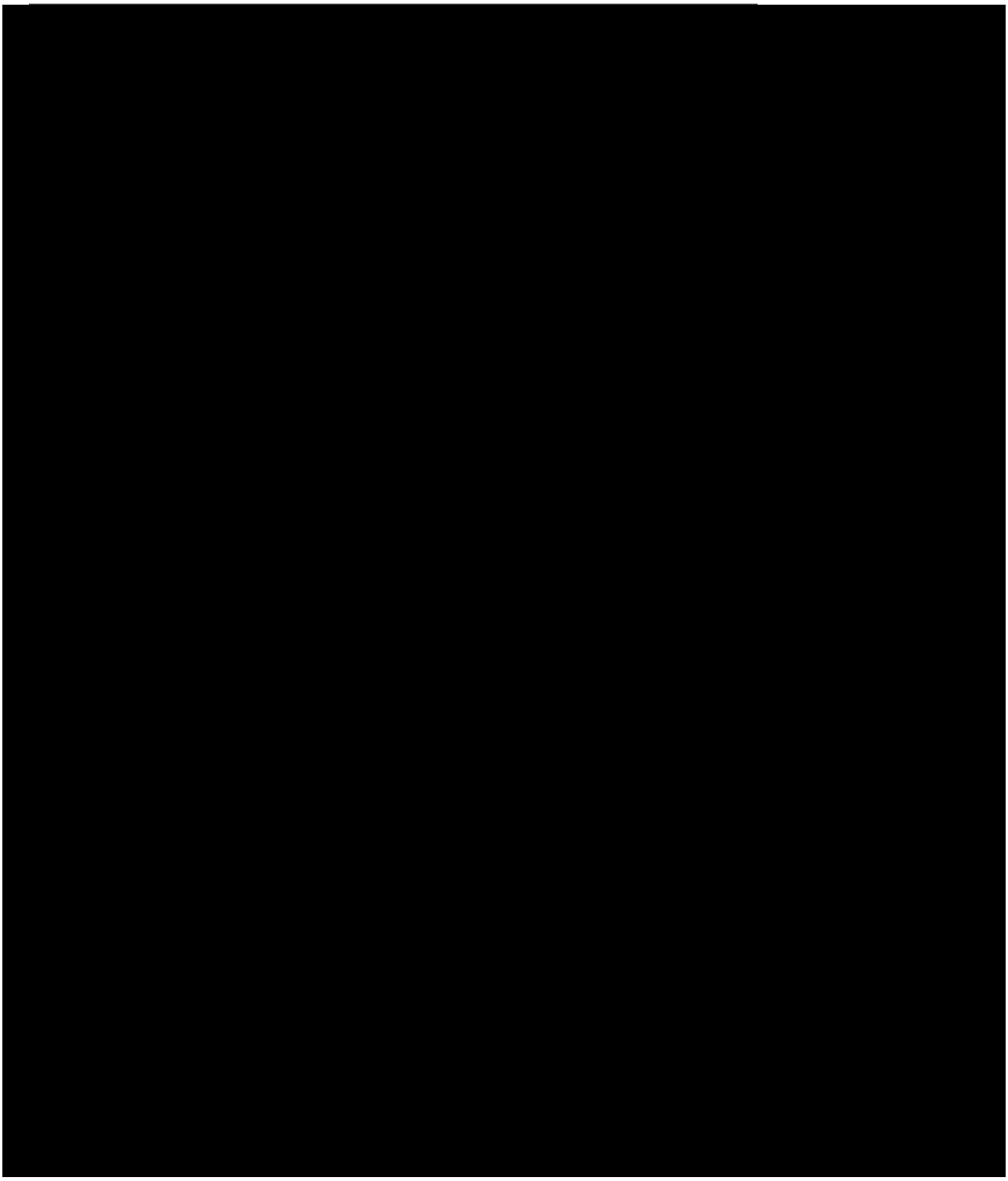


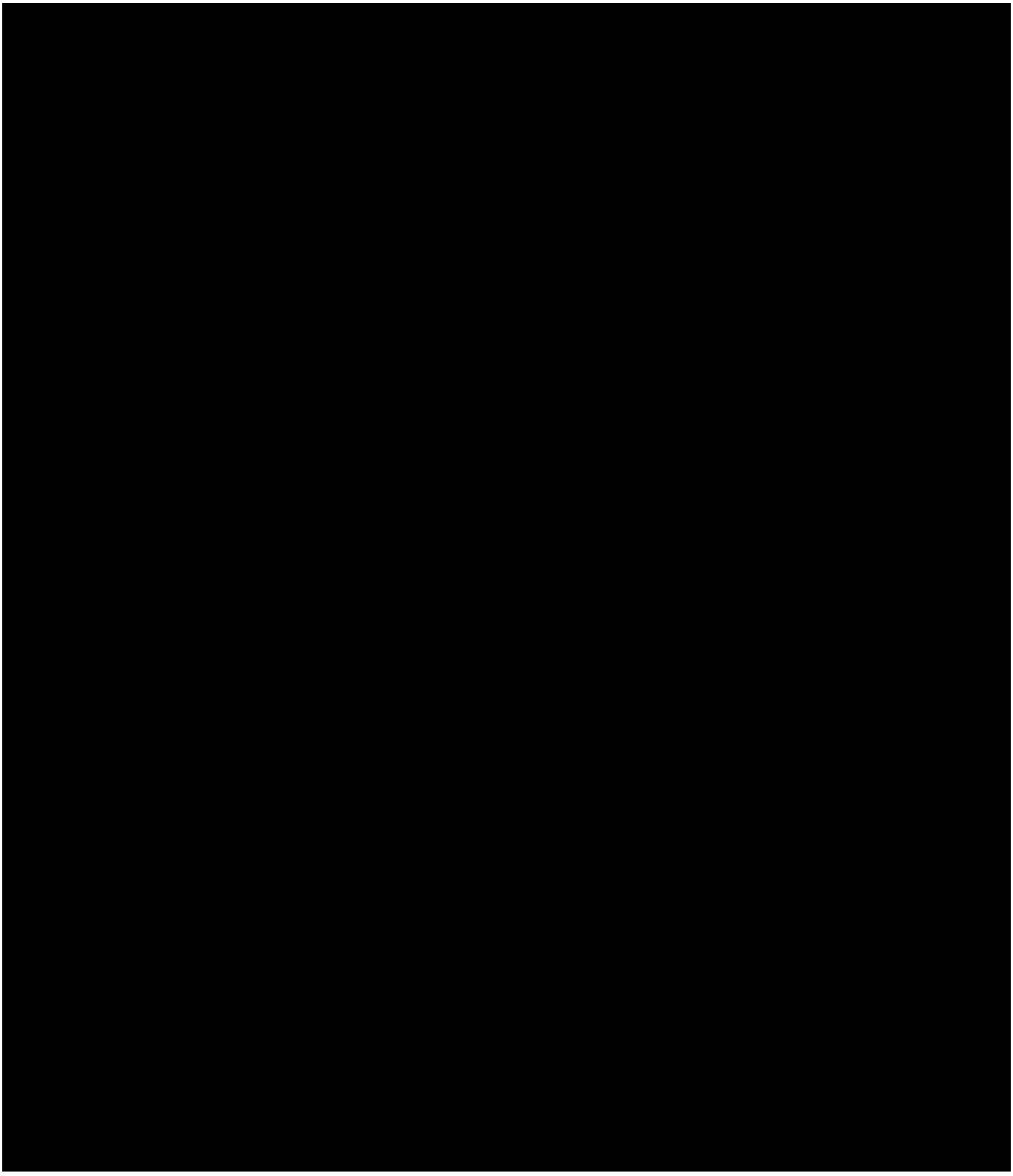
APPENDIX I QUESTIONNAIRES TO ASSESS BURDEN OF RBC TRANSFUSIONS



APPENDIX J GLOBAL TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION (TSQM)

APPENDIX K EQ-5D-5L





APPENDIX L NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE), VERSION 5.0

Currently active minor version of NCI CTCAE, version 5.0:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50