STATISTICAL ANALYSIS PLAN

Study Title:	Open-label Study to Assess the Long-term Safety and Efficacy of Momelotinib in Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia
Name of Test Drug:	Momelotinib (MMB)
Study Number:	GS-US-352-1154
Protocol Version:	Amendment 4
Protocol Date:	06 November 2017
Analysis Type:	Final Analysis
Analysis Plan Version:	Final
Analysis Plan Date:	26Apr2019
Analysis Plan Author:	Brian Pierce

CONFIDENTIAL AND PROPRIETARY INFORMATION

LIST OF ABBREVIATIONS

BMI	Body mass index
BPM	Beats per minute
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
DAVG	Difference between time-weighted average post-baseline and baseline
DMC	Data monitoring committee
ECG	Electrocardiogram
FR	Federal Register
HLT	High level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intent to treat
IVRS/IWRS	Interactive voice/web response system
LLT	Lower level term
MedDRA	Medical dictionary for regulatory activities
PT	Preferred term
SAP	Statistical analysis plan
SOC	System organ class
TFLs	Tables, figures, and listings
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-352-1154 (also referred to Rollover Study in this document). This SAP is based on the study protocol amendment dated 06 November 2017 and the electronic case report form (eCRF). Any changes made after the finalization of the SAP will be documented in the CSR.

As subjects in GS-US-352-1154 study were rolled-over from different previous studies, this statistical analysis plan (SAP) describes the statistical analysis for data collected in both the current and previous studies:

Cohort 1: CCL09101, CCL09101E, GS-US-352-1154

Cohort 2: YM387-II-02, GS-US-352-1154

Cohort 3: GS-US-354-0101, GS-US-352-1154

Cohort 4: GS-US-352-1672, GS-US-352-1154

This SAP also describes analyses for GS-US-352-1154 study only.

1.1. Study Objectives

The primary objective of this study is to determine the long-term safety and tolerability of MMB in 4 cohorts of subjects:

- Cohort 1: Subjects who are currently receiving MMB capsules in the CCL09101E study for PMF and post-PV/ET MF without documented progressive disease.
- Cohort 2: Subjects who are currently receiving MMB capsules in the YM387-II-02 study for PMF and post-PV/ETMF without documented progressive disease.
- Cohort 3 was closed and all enrolled subjects were discontinued from this study due to limited efficacy of MMB in the treatment of PV and ET on GS-US-354-0101.
- Cohort 4: Subjects who are currently receiving MMB tablets in the GS-US-352-1672 study for PMF and post-PV/ET MF, who completed 24 weeks of treatment and have responded to treatment, per investigators discretion.

The secondary objective of this study is to determine the long-term efficacy of MMB in these 4 cohorts of subjects.

1.2. Study Design

This is an open-label study for subjects with MF, post-PV/ET MF, PV or ET, who have tolerated MMB and their corresponding disease has not progressed per 2006 IWG-MRT criteria for MF or 2013 IWG-ELN and IWG-MRT criteria for PV/ET while enrolled in the parent study. After screening, subjects in Cohorts 1 and 2 will discontinue the MMB capsule and initiate the tablet form of MMB. Subjects in Cohort 4 will discontinue MMB tablets from the parent study and initiate MMB tablets in this study at the same dose they were receiving in the parent study. Subjects in Cohort 3 enrolled to this study under the original protocol and protocol amendments 1 and 2, where they discontinued MMB tablets from the parent study and initiated MMB tablets in this study. On 20 March 2015 parent study GS-US-354-0101 was terminated due to limited efficacy. All subjects in Cohort 3 were discontinued from GS-US-352-1154.

MMB dose adjustments may be made in this study. Subjects may participate in this study for approximately 4 years or until study termination.

Schedule of Assessments

Procedures performed at a regular follow-up visit on subject"s previous MMB study may be used to fulfill screening criteria and to establish any new medical history on this study. At Day 1, the starting dose of MMB tablets will be determined per the criteria in protocol Section 5.3. All subjects will self-administer MMB tablets. Subjects who have not undergone a bone marrow aspirate/biopsy within 12 months prior to Day 1 of this study will undergo a bone marrow biopsy. The bone marrow aspirate/biopsy will be repeated every 24 months and/or at the time of study withdrawal. Study visits consisting of clinical, laboratory, and disease assessments will be completed every 3 months. Cohorts 1 and 2 will have 2 additional visits at Months 1 and 2. All study required laboratory assessments will be performed by Central laboratory and ECG assessments will be performed and interpreted by local departments. Following treatment, subjects will be followed for safety and disease status for a period of 30 days. Subjects who continue treatment with MMB in the extended access program following the end of this study are not required to complete the 30-day post-treatment follow-up assessments.

	Screening/ enrollment	Months 1&2 (Cohorts 1 & 2 only)	3 M	6 M	9 M	12 M	15 M	18 M	21 M	24 M	27 M	30 M	33 M	36 M	39 M	42 M	45 M	48 M+/Q3 Months/ ESDD	Post-treatment Follow up[h]
Informed Consent	X																		
General and Safety Assessments																			
Medication History	X																		
Physical Examination and Symptoms Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination					X		X			X				X				X[a]	
Response Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease Assessments																			
PGIC	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusion Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																			
Bone Marrow Aspirate/Biopsy	X[b]									X								X[g]	
Serum / Urine Pregnancy Test[c]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thiamine status	X	X[f]	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC and Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product																			
MMB Accountability and Dispensing	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	

a EOT/Early Withdrawal if not done within the previous 6 months
b Bone Marrow biopsy at screening if not performed within 12 months of Day 1.
c For women of childbearing age only. Serum or urine testing at screening only. Urine pregnancy test for other visits.
d Dispensing only
e Accountability only at ESDD visit or final study visit
f Thiamine levels may be repeated if sample was not able to be analyzed during Screening/Enrollment Visit
g Bone marrow biopsy to be performed at month 48 only, not required for Q3 Months visits or ESDD visit
h Subjects who continue treatment with MMB in the extended access program following the end of the study are not required to complete the 30 day post-treatment follow-up assessments.

Randomization	Study is Open-Label and set in approximately 35 centers in North America, Europe and Australia.
Study Duration	Subjects will continue on MMB for a duration of approximately 4 years from the start of this study or until study termination.

1.3. Sample Size and Power

Planned Sample Size	Based on the number of previously enrolled subjects in Cohorts 1,2, and 3 including the number of expected subjects in Cohort 4, up to 105 subjects may be enrolled: Cohort 1: 30 subjects enrolled Cohort 2: 22 subjects enrolled Cohort 3: 13 subjects enrolled Cohort 4: 40 subjects expected
Power Statement	No formal hypothesis testing is planned for this study.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

An interim analysis was conducted using data collected by 23 June 2016 to support an intended MMB marketing application. Cohorts 1 and 2 were included in the interim analysis. Due to the limited efficacy, the parent study GS-US-354-0101 was terminated on 20 March 2015. All subjects who enrolled to GS US 352-1154 study from GS US 354-0101 (Cohort 3) were discontinued. Due to the small number of subjects and the limited exposure to MMB, subjects in Cohort 3 were not included in the interim analysis. No subject enrolled in Cohort 4 by data cutoff date for the interim analysis.

2.2. Final Analysis

After all subjects have either discontinued or completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed. Final analysis will include all subjects with MF who enrolled to GS-US-352-1154 study from CCL09101, CCL09101E (Cohort 1), YM387-II-02 (Cohort 2), and GS-US-352-1672 (Cohort 4).

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

For efficacy analysis and other analyses based on combined data from parent studies and GS-US-352-1154, the analysis results will be presented by cohort. Analyses based on GS-US-352-1154 study data only are conducted by the initial dose level received in this study regardless of any dose modification occurring during the study.

By-subject listings will be presented for all subjects in the Rollover Safety Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The dose level to which subjects were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

Only subjects with MF (Cohort 1, 2, and 4) will be included in the safety and efficacy analysis for this study. Cohort 3 subjects were discontinued from GS-US-352-1154 study due to limited efficacy in the parent study. All data from Cohort 3 will be listed separately.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded, will be summarized by dose level.

3.1.1. Full Analysis Set

The Full Analysis Set includes all enrolled subjects in studies CCL09101, YM387-II-02, and GS US 352 1672 who received at least one dose of MMB and had at least one post-baseline efficacy assessment. The FAS will be used for all Secondary and Exploratory Efficacy assessments.

3.1.2. Combined Safety Analysis Set

The Combined Safety Analysis Set includes all enrolled subjects in studies CCL09101, YM387-II-02, and GS US 352 1672 who received at least one dose of MMB. Select safety assessments will be analyzed using the Combined Safety Analysis Set.

3.1.3. Rollover Safety Analysis Set

The Rollover Safety Analysis Set includes all subjects who are enrolled in GS-US-352-1154 study excluding subjects enrolled in Cohort 3. Only subjects with MF are included in the Rollover Safety Analysis Set which is equivalent to Full Analysis Set (FAS) defined in the protocol as all subjects who are enrolled to the study in Cohorts 1, 2, and 4. This analysis set will be used for demographic and baseline characteristics, study treatment administration and compliance, and safety analyses.

3.2. Subject Groups

For analyses based on the combined data from parent studies and GS-US-352-1154, subjects will be grouped according to the cohort and median average daily dose defined in Section 4.3.2.1. For analyses based on the GS-US-352-1154 data only, subjects will be grouped according to the initial dose level assigned in this study.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subsets

There are no prespecified subject subgroupings for efficacy and safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study visit window may be due to:

1. a visit occurring in the window but data were not collected or were unusable, or
2. a visit not occurring in the window, or
3. a subject permanently discontinuing from study before reaching the window.

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in Sections 4.3.1, 4.3.2 and 7.1.5.2.

The handling of missing or incomplete dates for adverse event onset date is described in Section 7.1.5.3.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the first dosing date of study drug will be used for analyses and presentation in listings. The baseline value used in efficacy analysis or other analyses based on combined data will be the baseline defined in the parent study. For analyses based on GS-US-352-1154 study data only, the baseline value will be the baseline defined in the study.

The following censoring convention will be applied for time-to-event endpoints:

- Duration of response: Data from subjects who remain a responder will be censored at the date of last visit.

- Progression-free survival: Data from surviving, non-progressing subjects will be censored at the last adequate response assessment date prior to the initiation of myelofibrosis treatment other than MMB or the last time that lack of definitive progression was objectively documented.

- Overall survival: Data from subjects who remained alive while on study will be censored at the date of last contact.

By-subject listings will be sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within subject. The dose level to which subjects were originally assigned will be used in the listings.

3.8. Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For post-dose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, for the analysis of the combined data, study day 1 is the day of first dose of study drug in parent study. For the analysis of GS-US-352-1154 study only, study day 1 is the day of first dose of study drug in GS-US-352-1154 study.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug in parent study and GS-US-352-1154 study may be included in the calculation of the baseline value for parent study and GS-US-352-1154 study, respectively.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade.
- For subjects who prematurely discontinued from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination Visit"
- For subjects who prematurely discontinued the study/treatment, end of study or early study drug discontinuation (ESDD) visit data will be included to derive last visit in study and best overall response.
- Data collected on a follow-up visit will be summarized as a separate visit and labeled "Follow-up Visit."
- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries but will be included in the listings.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, non-missing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline values for combined data and GS-US-352-1154 study data will be the last non-missing value on or prior to the first dosing date or on first dosing date and prior to dosing of study drug in parent study and GS-US-352-1154 study, respectively unless specified differently. If multiple measurements occur on the same day, the last non-missing value prior to first dosing date of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

If multiple valid, non-missing, categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- The last available record on or prior to first dosing date of study drug in parent study and GS-US-352-1154 study will be selected as baseline values for combined data and GS-US-352-1154 study data, respectively. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings).
- For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

A summary of subject enrollment will be provided by dose level per investigator within a country and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column. Subjects will be considered enrolled once enrolled in IXRS.

4.2. Disposition of Subjects

A summary of subject disposition will be provided by dose level and cohort. This summary will present the number of subjects enrolled and the number of subjects in each of the categories listed below:

- Rollover Safety Analysis Set
- Completed Month 48 or later of study treatment
- Discontinued study drug with reasons for discontinuation of study drug
- Completed Month 48 or later
- Discontinued the study with reasons for discontinuation of study

Subjects who completed Month 48 visit or later will be considered study/drug completers. A by-subject listing of study/drug completion information including the reason for premature study withdrawal/study drug termination will be provided by subject identification (ID) number in ascending order to support the above summary tables.

The denominator for the percentages of subjects in each category will be the number of subjects in the Rollover Safety analysis set.

4.3. Extent of Exposure

Extent of exposure to study drug during GS-US-352-1154 study will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.3.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug in GS-US-352-1154 study will be defined as last dosing date minus first dosing date in this study plus 1, regardless of any temporary

interruptions in study drug administration, and will be expressed in months using up to 1 decimal place (eg, 4.5 months). If the last study drug dosing date is missing:

- If the study drug is permanently withdrawn, the latest date among the study drug end date will be used.
- If the study drug completion status is unknown the date of death will be used for analysis.
- If the stop date is partial then the stop date will be imputed with the earliest of the last day of the month (if only day is missing) or the last month of the year (if day and month are missing), or the death date if applicable.

The total duration of exposure to study drug in GS-US-352-1154 study will be summarized using descriptive statistics by dose level for the Rollover Safety Analysis Set.

The total duration of exposure to study drug during parent and GS-US-352-1154 studies will also be summarized using descriptive statistics, which is defined as last dosing date in this study minus first dosing date in parent study plus 1, regardless of any temporary interruptions in study drug administration. Summaries will be presented by cohort and median average daily dose for the Rollover Safety Analysis Set.

The number and percentage of subjects who had dose increase and/or dose reduction will be provided in terms of frequency count (n) and percentage (%). Reasons for dose increase/reduction will be summarized.

4.3.2. Adherence with Study Drug Regimen

The total number of tablets administered will be summarized using descriptive statistics (n, mean, StD, median, min-max) by dose level for GS-US-352-1154 study. The total number of tablets administered during parent and GS-US-352-1154 studies will also be summarized using descriptive statistics (n, mean, StD, median, min-max) by cohort and median average daily dose.

The presumed total number of tablets administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Tablets Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

If a bottle is not returned or returned with unknown number of tablets, it is assumed that subject did not consume any tablet from this bottle.

4.3.2.1. Average Daily Dose

The average daily dose in mg will be calculated using the following formula:

$$\text{Average Daily Dose (mg)} = \frac{\sum(\text{Daily Dose in mg})}{\text{Total Number of Days on Study Drug}}$$

where Total Number of Days on Study Drug = Last Dosing Date – First Dosing Date + 1

For each cohort, the median value will be calculated for average daily dose. Summaries of combined data from parent studies and GS-US-352-1154 will be grouped by cohort and median average daily dose (<=median value, > median value) and Total.

4.3.2.2. On-Treatment Adherence

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject‟s actual on-treatment period based on the study drug regimen. Investigator-prescribed interruption, reductions and escalations as specified in the protocol will be taken into account.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}}\right) \text{x } 100$$

Descriptive statistics for the level of on-treatment adherence, total number of tablets received and average daily dose will be provided by dose level for the Rollover Safety Analysis Set.

A by-subject listing of study drug administration will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.4. Protocol Deviations

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, non-adherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by dose level for the Rollover Safety Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE DATA

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by dose level and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. Age and sex are collected in GS-US-352-1154 study and other demographic data were collected in the parent study. The summary of demographic data will be provided for the Rollover Safety Analysis Set.

A by-subject demographic listing will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics collected in the parent study include body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2), and Eastern Cooperative Oncology Group (ECOG) performance status, transfusion dependence status (Yes, No) at baseline and prior treatment for PV/ET/PMF. These baseline characteristics will be summarized by dose level and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Rollover Safety Analysis Set.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history from the parent study will not be reported in the electronic case report form (eCRFs) thus will not be listed for this study. Any ongoing AE from the parent study at the time of enrollment in this study will be considered medical history on this study and will be listed.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary objective of this study is safety. There is no primary efficacy endpoint.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints are all efficacy-related endpoints. All analyses/summaries of efficacy endpoints will be performed excluding Cohort 3 subjects. The secondary efficacy endpoints are:

- Overall survival (OS) - defined as the interval from first dosing date of study drug in parent study to death from any cause. Subjects who are lost to follow-up or survived until the end of the study will be censored at the last date that they were known to be alive.

- Progression-free survival (PFS) - defined as the interval from the first dose of MMB on the previous study until the first documentation of definitive progressive disease as defined in Appendix 4 or death due to any cause, ie., PFS(months) = (date of censoring or date of earliest of Progressive Disease or death – first dose date + 1) / 30.125. Subjects who are free of Progression will be censored at the last assessment date.

- Leukemia free survival: defined as the interval from the first dose of MMB on the parent study until the first documented leukemic transformation defined by the occurrence of an AE listed in Appendix 1 or death from any cause, ie., LFS(months) = (date of censoring or date of earliest of leukemic transformation or death – first dose date + 1) / 30.125. Subjects who are free of leukemia transformation will be censored at the last assessment date. Leukemic transformation was documented in the AE eCRF page.

- Rate of RBC transfusion: defined as the average number of RBC units excluding cases due to overt bleeding per subject month from the first dose of MMB on the parent study.

- Duration of splenic response: defined as the interval from the first onset of splenic response (in the parent study or this study) to the earliest date of loss of splenic response. Splenic response is defined according to the 2006 IWG-MRT criteria as a reduction of 50% or more in palpable splenomegaly of a spleen that was ≥ 10 cm below the LCM at baseline or a spleen that was palpable at > 5 cm and < 10 cm below the LCM at baseline becoming not palpable for at least 56 days.

- Duration of anemia response: defined as the interval from the first onset date of anemia response (in the parent study or GS-US-352-1154 study) to the earliest date of loss anemia response. Anemia evaluable subjects were defined as subjects who were transfusion dependent at baseline or who were not transfusion dependent (defined for Studies CCL09101 and GS-US-352-1672) or were transfusion independent (defined for Study YM387-II-02) but with a hemoglobin level < 10 g/dL at baseline. Transfusion dependent was defined as receiving at least 2 units of RBCs within 30 days prior to Cycle 1 Day 1. Anemia response was a composite endpoint of transfusion independence response and hemoglobin response. Transfusion responders were defined as subjects who had a ≥ 12-week transfusion independence response and who were transfusion dependent at baseline. Hemoglobin responders were defined as having ≥ 2 g/dL increase from baseline for ≥ 12 weeks and who were not transfusion dependent/transfusion independent at baseline. Loss of anemia response was defined as having > 0 units of RBC transfusion after achieving a transfusion independence response or hemoglobin response. If a subject had a transfusion date but the number of units received was not recorded, the subject was assumed to have loss of response.

- Transfusion Response Rate is defined as becoming not transfusion dependent for ≥ 12 weeks at any time from the first dose of MMB on the previous study until end of this study.

- Overall Response Rate: Treatment response is assessed using the 2006 IWG-MRT criteria for treatment response in myelofibrosis. Best overall response is determined in the following order: complete remission, partial remission, clinical improvement, stable disease, or progressive disease. Overall response rate is defined as the proportion of subjects who achieve complete remission or partial remission.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

Analysis/summaries for secondary efficacy endpoints will be performed using the Full Analysis Set by cohort, unless otherwise specified.

6.2.2.1. Overall Survival

Incomplete death dates will be imputed by the following algorithm:

- If day is missing but the month and year are available, then the imputed day will be the midpoint of the month or the last assessment date + 1, whichever is later.

- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the latest month that the subject was known to be alive if they have the same year, whichever is later.

OS will be analyzed using the Kaplan-Meier method. Surviving subjects will be censored at the last time that the subject is known to be alive on study (including all the in-person visit

dates captured in the datasets, ie, BM biopsy, central lab collection, CT scan, physical exam, drug administration in clinic, concomitant medication and therapy start date, ECG, safety follow up, hospitalization, pregnancy testing). The number of subjects who died, censored, Median with 90% CI, Q1, Q3, and Kaplan-Meier survival curves will be presented.

6.2.2.2. Progression-free Survival

Progression-free survival (PFS) will be analyzed using the Kaplan-Meier method. The number of subjects who died and/or having progressive disease, censored, Median with 90% CI, Q1, Q3, and Kaplan-Meier survival curves will be presented.

6.2.2.3. Leukemia-free Survival

Leukemia-free survival (LFS) will be analyzed using the Kaplan-Meier method. The number of subjects who died and/or having leukemia, censored, Median with 90% CI, Q1, Q3, and Kaplan-Meier survival curves will be presented.

6.2.2.4. Rate of RBC transfusion

Rate of RBC transfusion will be calculated as the total number of RBC units across all subjects divided by the total exposure time among these subjects in a dose level. Descriptive statistic of rate of RBC transfusion will be presented. Transfusions due to clinically overt bleeding will be excluded from this analysis.

6.2.2.5. Duration of Splenic/Anemia Responses

Duration of splenic response and anemia response will be summarized by descriptive statistics. They will be also analyzed using Kaplan-Meier method. The number of subjects who had event, censored, Median with 90% CI, Q1, Q3, and Kaplan-Meier survival curves will be presented. Data from responders who keep the response will be censored at the last assessment date. Anemia response rate, hemoglobin response rate, transfusion independence response rate, and splenic response rate are presented.

6.2.2.6. Transfusion Response Rate

Transfusion response rate will be presented by cohort and the numbers and percentages of subjects who have not reached transfusion dependence for ≥ 12 weeks.

6.2.2.7. Overall Response Rate per Physician Assessment

The overall response rate will be presented by cohort and the numbers and percentages of subjects who have best overall response as CR, PR, CI, SD, and PD will also be provided.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

Exploratory endpoints are:

- Change in hemoglobin level over time
- Patient global impression of change (PGIC)

6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

The change in hemoglobin level over time from baseline (parent study) will be summarized using descriptive statistics along with number of subjects with at least 1g, 1.5g, and 2g change in hemoglobin over the course of the study.

Summary of Patient global impression of change (PGIC) comparing responses in consecutive visits will be done on all post-dose visits.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events except for anemia are graded by the investigator according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Anemia (hemoglobin) is graded using CTCAE Version 3.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (lift-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. For CCL09101, CCL09101E, YM0387-II-02 studies, relationship recorded as „Possibly", „Probably" and „Definitely" will be deemed as related, „Not Related" and „Unlikely" as unrelated. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance & Epidemiology Department, previously Drug Safety and Public Health Department, before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Newly Onset Adverse Events

- Newly onset adverse events are defined as any with an onset date on or after the start date of study drug in the GS-US-352-1154 study and no later than 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug in the GS-US-352-1154 study.

7.1.5.3. Incomplete Dates

When the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.
- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date if they have the same year, whichever is later.

Incomplete AE stop date will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 31Dec or 30 days after the last dose of study drug if they have the same year, whichever is earlier.
- If day is missing but the month and year are available, then the imputed day will be the last day of the month or 30 days after the last dose of study drug if they have the same month and year, whichever is earlier.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Rollover Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and dose level. For other AEs described below, summaries will be provided by SOC, PT, and dose level:

- TEAEs
- TEAEs of Grade 3 or higher
- Drug-related TEAEs
- Drug-related TEAEs of Grade 3 or higher
- TE SAEs
- TE drug-related SAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death
- TEAEs leading to change in dose or temporary interruption of study drug
- AE of interest for
    - Peripheral Neuropathy Standardized MedDRA Queries (SMQ) (narrow and broad terms; defined as AEs listed in Appendix 2. Peripheral Neuropathy SMQ AEs)
    - Peripheral Neuropathy SMQ (narrow and broad terms) leading to study drug discontinuation
    - Cataract MedDRA Search Terms (MST) (defined as AEs listed in Appendix 3. Cataract MST AEs)
- Newly Onset AE for
    - Peripheral Neuropathy Standardized MedDRA Queries (SMQ) (narrow and broad terms; defined as AEs listed in Appendix 2. Peripheral Neuropathy SMQ AEs)

- Cataract MedDRA Search Terms (MST) (defined as AEs listed in Appendix 3. Cataract MST AEs)

A brief, high-level summary of AEs described above will be provided by dose level and by the number and percentage of subjects who experienced the above AEs. The number and percentage of subjects who experienced at least 1 TEAE will be summarized by SOC, PT, maximum severity, and dose level.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable) and then by PT in descending order of total frequency within each SOC for the overall column. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in a given subject during the study.

For TEAE during parent and GS-US-352-1154 studies described below, summaries will be provided by cohort and median average daily dose:

- Overall summary of AEs
- TEAEs by SOC, PT
- TE SAEs by SOC, PT
- TEAEs by SOC, PT, and maximum severity

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- AEs with Severity of Grade 3 or Higher
- SAEs
- Deaths
- AEs leading to death
- AEs leading to discontinuation of study drug
- AEs leading to change in dose or temporary interruption of study drug
- AE of interest for
  - Peripheral Neuropathy SMQ (narrow and broad terms)

— Peripheral Neuropathy SMQ (narrow and broad terms) leading to study drug discontinuation

— Cataract MST

7.1.6.2. Summaries of Exposure-Adjusted AE Incidence

Exposure-adjusted TEAEs during parent and GS-US-352-1154 studies will be provided. The number of subjects with a TEAE, total person years, incidence rate per person year and 95% confidence intervals will be presented by PT, cohort and median average daily dose. Total person year (exposure at risk) is the sum of (AE onset date minus first dosing date in parent study plus 1) divided by 365.25. Incidence rate per person year is calculated as the number of subjects with a TEAE divided by total person year. The following summaries will be provided:

- TEAEs by PT
- TEAEs of Grade 3 or higher by PT
- TE SAEs by PT

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be based on observed data and will be reported using SI units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities for the Rollover Safety Analysis Set and Combined Safety Analysis Set.

A by-subject listing for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a CTCAE version 4.03 severity grade of 1 or higher will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by dose level for Hgb, Platelets, ANC, Uric Acid, Creatinine and Thiamine as follows:

- Baseline values
- Values at each postbaseline visit
- Postbaseline maximum value
- Postbaseline minimum value
- Change and percentage change from baseline at each postbaseline visit
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value

The baseline laboratory values for combined data and GS-US-352-1154 study data will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug in parent study and this study, respectively. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

CTCAE Version 4.03 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis except for anemia (hemoglobin) which will be graded using the CTCAE Version 3.0. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and dose level; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded Treatment-emergent laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dosing date.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by dose level for body weight as follows:

- Baseline value
- Values at each postbaseline visit
- Postbaseline maximum value
- Postbaseline minimum value
- Change from baseline at each postbaseline visit
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

A by-subject listing of body weight and other vital sign parameters will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first dose of study drug in the parent study.

Prior medications will be listed for the Rollover Safety Analysis Set.

7.4.2. Concomitant Medications

Concomitant medications are defined as any medications meeting the following criteria:

Starting on or after the first dose of study drug in the parent study up to 30 days post the last dose

Starting before and continuing after the first dose of study drug in the parent study up to 30 days post the last dose

The incomplete dates handling method used for AE summaries will be used for concomitant medication summaries (Section 7.1.5.3).

Concomitant medications will be summarized by preferred name using the number and percentage of subjects for each dose level and overall. A subject reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of subjects who received that medication. Medication may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC Drug class and then by preferred term in order of descending overall frequency within each ATC Drug class. For drugs with the same frequency, sorting will be done alphabetically.

Concomitant medications will be summarized and listed for the Rollover Safety Analysis Set.

7.5. Electrocardiogram Results

Electrocardiogram (ECG) data will be listed only. No summary table will be provided for ECG data.

7.6. Changes From Protocol-Specified Safety Analyses

Any changes to protocol-specified safety analyses after finalization of this document will be outline in the clinical study report.

8. REFERENCES

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guideline for Industry: E3 Structure and Content of Clinical Study Reports *Federal Register.* July 17, 1996 (61 FR 37320).

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: E9 Statistical Principles for Clinical Trials. *Federal Register*. September 16, 1998 (63 FR 49583).

9. SOFTWARE

SAS Software Version 9.2. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

10. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

11. APPENDICES

Appendix 1. Leukemic Transformation MST AEs

Appendix 2. Peripheral Neuropathy SMQ AEs

Appendix 3. Cataract MST AEs

Appendix 4. International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia

Appendix 1. Leukemic Transformation MST AEs

MEDDRA Term Name	MEDDRA Code	MEDDRA Level
Acute megakaryocytic leukaemia	10000860	PT
Acute megakaryocytic leukaemia (in remission)	10057194	PT
Acute monocytic leukaemia	10000871	PT
Acute monocytic leukaemia (in remission)	10000872	PT
Acute myeloid leukaemia	10000880	PT
Acute myeloid leukaemia (in remission)	10000881	PT
Acute myeloid leukaemia recurrent	10059034	PT
Acute myelomonocytic leukaemia	10000890	PT
Acute promyelocytic leukaemia	10001019	PT
Erythraemic myelosis (in remission)	10015246	PT
Erythroleukaemia	10015281	PT
Acute biphenotypic leukaemia	10067399	PT
Acute leukaemia	10000830	PT
Acute leukaemia in remission	10060930	PT
Acute undifferentiated leukaemia	10073479	PT
Blast cell crisis	10053747	PT
Blast crisis in myelogenous leukaemia	10050282	PT
Chloroma	10008583	PT
Chloroma (in remission)	10008584	PT
Eosinophilic leukaemia	10014958	PT
Leukaemia basophilic	10024293	PT
Leukaemia granulocytic	10024299	PT
Leukaemia monocytic	10024305	PT
Monocytic leukaemia in remission	10061295	PT
Myeloid leukaemia	10028549	PT
Myeloid leukaemia in remission	10061301	PT
Aleukaemic leukaemia	10001660	PT
Central nervous system leukaemia	10066231	PT
Leukaemia	10024288	PT
Leukaemia cutis	10053180	PT
Leukaemia in remission	10061220	PT
Leukaemia recurrent	10062489	PT
Leukaemic cardiac infiltration	10077563	PT
Leukaemic infiltration	10069360	PT
Leukaemic infiltration extramedullary	10067117	PT
Leukaemic infiltration gingiva	10067431	PT
Leukaemic infiltration hepatic	10058671	PT
Leukaemic infiltration ovary	10075853	PT
Leukaemic infiltration pulmonary	10052368	PT

Leukaemic infiltration renal	10069359	PT
Leukaemic retinopathy	10059239	PT
Mastocytic leukaemia	10056450	PT
Neonatal leukaemia	10028958	PT

Appendix 2. Peripheral Neuropathy SMQ AEs

Name	Code	Level	Scope
Acute painful neuropathy of rapid glycaemic control	10072909	PT	Narrow
Acute polyneuropathy	10066699	PT	Narrow
Amyotrophy	10002027	PT	Narrow
Autoimmune neuropathy	10070439	PT	Narrow
Axonal neuropathy	10003882	PT	Narrow
Biopsy peripheral nerve abnormal	10004846	PT	Narrow
Decreased vibratory sense	10067502	PT	Narrow
Demyelinating polyneuropathy	10061811	PT	Narrow
Guillain-Barre syndrome	10018767	PT	Narrow
Ischaemic neuropathy	10051307	PT	Narrow
Loss of proprioception	10057332	PT	Narrow
Miller Fisher syndrome	10049567	PT	Narrow
Multifocal motor neuropathy	10065579	PT	Narrow
Myelopathy	10028570	PT	Narrow
Nerve conduction studies abnormal	10029175	PT	Narrow
Neuralgia	10029223	PT	Narrow
Neuritis	10029240	PT	Narrow
Neuronal neuropathy	10071579	PT	Narrow
Neuropathic muscular atrophy	10075469	PT	Narrow
Neuropathy peripheral	10029331	PT	Narrow
Notalgia paraesthetica	10072643	PT	Narrow
Peripheral motor neuropathy	10034580	PT	Narrow
Peripheral nervous system function test abnormal	10034591	PT	Narrow
Peripheral sensorimotor neuropathy	10056673	PT	Narrow
Peripheral sensory neuropathy	10034620	PT	Narrow
Polyneuropathy	10036105	PT	Narrow
Polyneuropathy chronic	10064135	PT	Narrow
Polyneuropathy idiopathic progressive	10036111	PT	Narrow
Radiation neuropathy	10068886	PT	Narrow

Name	Code	Level	Scope
Sensorimotor disorder	10062162	PT	Narrow
Sensory disturbance	10040026	PT	Narrow
Sensory loss	10040030	PT	Narrow
Small fibre neuropathy	10073928	PT	Narrow
Tick paralysis	10077336	PT	Narrow
Toxic neuropathy	10067722	PT	Narrow
Anti-ganglioside antibody positive	10072516	PT	Broad
Areflexia	10003084	PT	Broad
Autonomic failure syndrome	10056339	PT	Broad
Autonomic neuropathy	10061666	PT	Broad
Burning feet syndrome	10070237	PT	Broad
Burning sensation	10006784	PT	Broad
Decreased nasolabial fold	10076861	PT	Broad
Dysaesthesia	10013886	PT	Broad
Electromyogram abnormal	10014431	PT	Broad
Formication	10017062	PT	Broad
Gait disturbance	10017577	PT	Broad
Genital hypoaesthesia	10068912	PT	Broad
Hereditary motor and sensory neuropathy	10077306	PT	Broad
Hypoaesthesia	10020937	PT	Broad
Hyporeflexia	10021089	PT	Broad
Hypotonia	10021118	PT	Broad
Mononeuritis	10027910	PT	Broad
Mononeuropathy	10062203	PT	Broad
Mononeuropathy multiplex	10027918	PT	Broad
Motor dysfunction	10061296	PT	Broad
Muscle atrophy	10028289	PT	Broad
Muscular weakness	10028372	PT	Broad
Nerve degeneration	10056677	PT	Broad
Neuromuscular pain	10074313	PT	Broad
Neuromuscular toxicity	10062284	PT	Broad
Neuromyopathy	10029323	PT	Broad

Name	Code	Level	Scope
Neuropathy vitamin B6 deficiency	10029332	PT	Broad
Neurotoxicity	10029350	PT	Broad
Paraesthesia	10033775	PT	Broad
Paraesthesia ear	10052433	PT	Broad
Peripheral nerve lesion	10067633	PT	Broad
Peripheral nerve palsy	10058530	PT	Broad
Peripheral nerve paresis	10071663	PT	Broad
Peroneal nerve palsy	10034701	PT	Broad
Phrenic nerve paralysis	10064964	PT	Broad
Skin burning sensation	10054786	PT	Broad
Temperature perception test decreased	10068015	PT	Broad
Tinel's sign	10052492	PT	Broad
Ulnar neuritis	10045380	PT	Broad
Vulvovaginal hypoaesthesia	10075520	PT	Broad

Appendix 3. Cataract MST AEs

MEDDRA Term Name	MEDDRA Code	MEDDRA Level
Atopic cataract	10069649	PT
Cataract	10007739	PT
Cataract congenital	10007747	PT
Cataract cortical	10007748	PT
Cataract diabetic	10007749	PT
Cataract nuclear	10007759	PT
Cataract operation	10063797	PT
Cataract subcapsular	10007764	PT
Cataract traumatic	10007766	PT
Lens discolouration	10070549	PT
Lenticular opacities	10024214	PT
Radiation cataract	10037756	PT
Toxic cataract	10044135	PT
Bioptic surgery	10078003	PT
Cornea verticillata	10077604	PT

Appendix 4. International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia

Complete remission (CR)	I. Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly. II. Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least 100 x 10^9/L, and absolute neutrophil count (ANC) at least 1.0 x 10^9/L. In addition, all 3 blood counts should be no higher than the upper normal limit. [a] III. Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy. IV. Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.[b]
Partial remission (PR)	Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.
Clinical improvement (CI)	Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks): i. A minimum 20-g/L increase in hemoglobin level or becoming transfusion independent (applicable only for subjects with baseline hemoglobin level of less than 100 g/L). ii. Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable. [c]

	iii. A minimum 100% increase in platelet count and an absolute platelet count of at least 50 000 x 10^9/L (applicable only for subjects with baseline platelet count below 50 x 10^9/L). iv. A minimum 100% increase in ANC and an ANC of at least 0.5 x 10^9/L (applicable only for subjects with baseline ANC below 1 x109/L).
Progressive disease (PD)	Requires 1 of the following: [d] i. Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm. ii. Leukemic transformation confirmed by a bone marrow blast count of at least 20%. iii. An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.
Stable disease (SD)	None of the above.
Relapse (Loss of CR, PR, or CI)	Subject with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for even CI.