2. SYNOPSIS

Name of Sponsor/Company: Gilead/Sierra	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		

Title of Study: 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

Investigators: Gangat, N (Site 09148), Verstovsek, S (Site 05576), Gotlib, J (Site 05577), Oh, S (Site 07034), Gerds, A (Site 09887), Talpaz, M (Site 12354), Wadleigh, M (Site 08154), Palmer, J (Site 14482), Goel, S (Site 09084), Mesa, R (Site 07018), Miller, C (Site 08956), Rivera, C (Site 08157), Deininger, M (Site 08153), Fleishchman, A (Site 11574), Heaney, M (Site 08808), Gupta, V (Site 08155), Sirhan, S (Site 08156), Roberts, A (Site 08159)

Study center(s): 15 sites in the United States (US), 2 sites in Canada and 1 site in Australia

Publications (reference): None to date

Studied period (years):	**Phase of development:**
Date first subject screened: 30 April 2014 Date last subject last visit: 06 December 2018	Phase 2

Objectives:

The primary objective of this extension study was to determine the long-term safety and tolerability of momelotinib (MMB) in 4 cohorts of subjects:

- Cohort 1: Subjects who were receiving MMB capsules in Study CCL09101E for primary myelofibrosis (PMF), post-polycythemia vera (PV) myelofibrosis (MF), and post-essential thrombocythemia (ET) MF without documented progressive disease.
- Cohort 2: Subjects who were receiving MMB capsules in Study YM387-II-02 for PMF, post-PV/ET MF without documented progressive disease.
- Cohort 3: Subjects who were receiving MMB tablets in Study GS-US-354-0101 for PV or ET who completed 24 weeks of treatment and whose disease had not progressed on study. Per Amendment 3, Cohort 3 was closed, and all enrolled subjects were discontinued from Study GS-US-352-1154 due to limited efficacy of MMB in the treatment of PV and ET on GS-US-354-0101.
- Cohort 4: Subjects who were receiving MMB tablets in Study GS-US-352-1672 for PMF, post-PV MF, and post-ET MF, who completed 24 weeks of treatment in Study GS-US-352-1672 and responded to treatment while on study, per the investigator's discretion.

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

Methodology:

This study was designed as an open-label extension trial for subjects with PMF, post-PV MF, post-ET MF, PV or ET who had both tolerated MMB and achieved stable disease or better while enrolled in one of four parent MMB clinical studies. The study consolidated ongoing patient access to MMB following the closure of 4 different parent studies and allowed ongoing data collection during extended treatment.

This extension study was conducted using the MMB tablet presentation, following confirmation of comparable oral bioavailability to the Phase 2 investigational capsule presentation in a clinical pharmacokinetic study (GS-US-352-0102).

The term "cohort" is used in this report to refer to any of the 4 groups of subjects who enrolled to GS-US-352-1154 after completion of the relevant parent studies or to any of the 4 respective parent study populations, irrespective of whether or not they entered this GS-US-352-1154 extension study.

The Phase 2 parent MMB clinical studies included:

CCL09101/CCL09101E (Cohort 1) – a Phase 2, open-label study (CCL09101) and the initial extension study (CCL09101E) in subjects with PMF or post-PV or post-ET MF. The core Study CCL09101 consisted of a dose-escalation phase and a dose-confirmation phase. Subjects who had completed 9 cycles (1 cycle = 28 days) of MMB treatment on the core study, CCL09101, enrolled in the initial extension study, CCL09101E, and continued MMB at the same daily dose level that they tolerated and from which they derived a clinical benefit in the core study. The capsule presentation of MMB was administered in both the CCL09101 core and CCL09101E extension studies.

YM387-II-02 (Cohort 2) – a Phase 1/2, open-label study in subjects with PMF or post-PV or post-ET MF. The study consisted of a dose-escalation and a dose-confirmation phase with MMB administered twice daily. Subjects who tolerated MMB after the initial 6 treatment cycles (1 cycle = 28 days) were allowed to continue MMB treatment in the maintenance phase of the study. The capsule presentation of MMB was administered in this study.

GS-US-354-0101 (Cohort 3) – a Phase 2, open-label study in subjects with PV or ET. Of note, this cohort was closed and the 13 enrolled subjects were discontinued from Study GS-US-352-1154 due to limited efficacy of MMB for the PV and ET indications in the final analysis of the parent Study GS-US-354-0101. The tablet presentation of MMB was administered in this study.

GS-US-352-1672 (Cohort 4) – a Phase 2, open-label, translational biology study in transfusion-dependent subjects with PMF, post-PV or post-ET MF. Subjects received MMB for 24 weeks on study. The tablet presentation of MMB was administered in this study.

Procedures performed at a regular follow-up visit in the subject's parent MMB study could be used to fulfill screening criteria and to establish any new medical history for this extension study. Study visits consisting of clinical, laboratory and disease assessments occurred every 3 months for as long as subjects remained on active MMB therapy. Cohorts 1 and 2 also had study visits at Months 1 and 2. Subjects were followed for safety and disease status for 30 days after the last dose of study drug. All treatment-emergent adverse events (AEs) and laboratory abnormalities present at the end of study were to be followed until resolution or the event was determined to be irreversible by the investigator.

An interim clinical study report (CSR) (dated 24 October 2016) was completed for this study (GS-US-352-1154) which provided safety and efficacy results for Cohorts 1 and 2 (parent studies CCL09101/CCL09101E and YM387-II-02, respectively), through to a data cutoff date of 23 June 2016. This final CSR supplants the interim GS-US-352-1154 CSR.

Data presented by cohort in this CSR provide the most mature, complete and final safety and efficacy results for the CCL09101, YM387-II-02 and GS-US-352-1672 studies in subjects with MF. These final efficacy analyses provide an extended window beyond that reported in the parent study CSRs documenting both new responses and the durability of responses in all subjects.

Number of subjects (planned and analyzed):

Planned: Based on the number of subjects in Cohorts 1, 2, 3 and 4, a maximum of 105 subjects could be enrolled in Study GS-US-352-1154. No formal hypothesis testing was planned for this study.

Analyzed: A total of 268 subjects were enrolled to one of the 3 relevant parent studies (Studies CCL09101, YM387-II-02 and GS-US-352-1672) and included in the Study GS-US-352-1154 analyses, of which 265 were efficacy-evaluable. A total of 74 subjects were enrolled to Cohorts 1, 2 and 4 of Study GS-US-352-1154 and analyzed for safety and efficacy.

Data from Cohort 3 subjects were not analyzed in this report, nor were data from any of the 39 subjects from the GS-US-354-0101 parent study in subjects with PV or ET. Cohort 3 listings containing subject information, drug compliance, and safety data are provided separately in this final CSR. In addition, a safety summary of Cohort 3 subjects who enrolled to Study GS-US-352-1154 is provided in Section 12.3.4 of this CSR.

Diagnosis and main criteria for inclusion in GS-US-352-1154:

Four cohorts of subjects with myeloproliferative neoplasms who tolerated MMB and whose disease had not progressed on a parent study.

Test product, dose and mode of administration, batch number:

This extension study was conducted using the MMB tablet presentation batches listed below, following confirmation of equivalent exposure to the Phase 2 investigational capsule presentations in a clinical pharmacokinetic study (GS-US-352-0102). The conversion from capsule to tablet doses is detailed in Section 9.4.5 of this CSR.

MMB 100 mg, 150 mg, or 200 mg tablets were self-administered orally once daily.

Lot Numbers. (100 mg): DT1302D1, DT1401D1, DT1401D1-A, DT1402D1, DT1402D1-A, DT1403D1, DT1601D1

Lot Numbers. (150 mg): DT1302E1, DT1401E1, DT1402E1, DT1402E1-A, DT1403E1, DT1601E1

Lot Numbers. (200 mg): DT1302F1, DT1302F1-A, DT1401F1, DT1402F1, DT1402F1-A, DT1403F1, DT1601F1

Duration of treatment: Subjects could continue MMB therapy for approximately 48 months from entry into this extension study or until study termination.

Reference therapy, dose and mode of administration, batch number: No reference therapy was included in this study.

Criteria for evaluation in Study GS-US-352-1154:

Efficacy: Assessments included follow-up for survival, progression and leukemic transformation. Liver and spleen size were assessed by palpation during physical examination (radiographic confirmation was not required). Other assessments included records of transfusions, hemoglobin levels and Eastern Cooperative Oncology Group (ECOG) performance status. In addition, bone marrow aspirate/biopsy was performed at Months 24 and 48. Patient-reported outcome assessment included patient global impression of change (PGIC) at every study visit.

Treatment response including splenic response and best overall response was assessed using the 2006 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) consensus criteria for treatment responses in myelofibrosis with myeloid metaplasia (Statistical Analysis Plan [SAP], Appendix 4).

Safety: Assessments included characterization of the type, incidence, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.03), timing, seriousness, and relationship to treatment of AEs, and laboratory parameters. Other safety

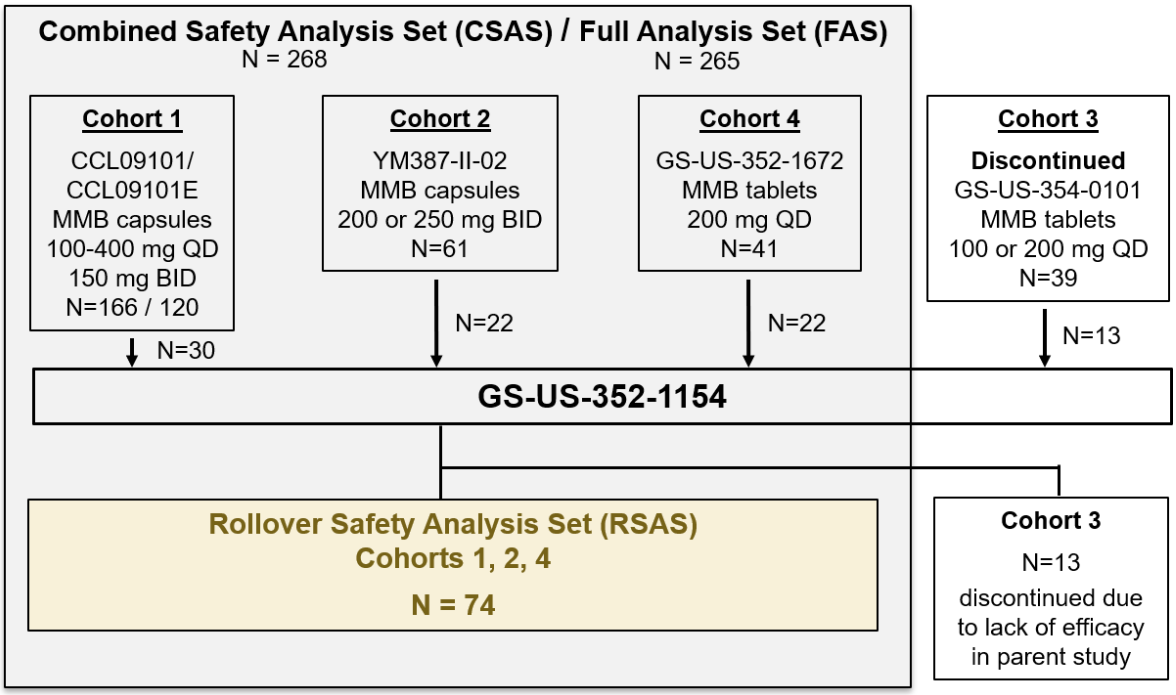
assessments included physical examination and symptom assessments, ophthalmic examination, vital signs, 12-lead electrocardiogram (ECG), and collection of prior and concomitant medications.

Statistical Methods:

Analysis Sets: The analysis sets used in this study include the following:

- The Combined Safety Analysis Set (CSAS) included all enrolled subjects in Studies CCL09101/CCL09101E, YM387-II-02, and GS-US-352-1672 who received at least 1 dose of MMB (N = 268). This population was used for selected safety analysis.
- The Full Analysis Set (FAS) included all enrolled subjects in Studies CCL09101/CCL09101E, YM387-II-02 and GS-US-352-1672 who received at least 1 dose of MMB and had at least 1 postbaseline efficacy evaluation (N = 265). This population forms the basis of the main efficacy analyses contained in this report.
- The Rollover Safety Analysis Set (RSAS) included only the 74 subjects in Study GS-US-352-1154 who rolled over from CCL09101/CCL09101E (Cohort 1), YM387-II-02 (Cohort 2) or GS-US-352-1672 (Cohort 4). Data are presented through to 30 days after the last dose date of study drug for each subject. This population forms the basis of the main safety analyses and selected efficacy analyses contained in this report.

Safety data from Cohort 3 are provided separately in this final CSR.



Efficacy:

The focus of the efficacy analyses in this final CSR is mainly on the 265 efficacy-evaluable MF subjects who originally enrolled into one of the 3 analyzed parent studies using data captured from entry into the original parent study, inclusive of any additional efficacy data captured during participation in this extension study. For most efficacy endpoints, results are presented for the overall populations and by cohort for both the FAS and the RSAS.

Secondary and exploratory efficacy endpoints were overall survival (OS), progression-free survival (PFS), leukemia-free survival (LFS), splenic response rate, duration of splenic response, anemia

response rate, duration of anemia response, transfusion independence (TI) response rate and duration of TI response, best overall response per physician assessments, rate of red blood cell (RBC) transfusions, change in hemoglobin level over time, and change in patient global impression of change (PGIC) to assess symptomatology.

Efficacy endpoints were analyzed using the same methods as reported in the parent studies unless otherwise specified.

The secondary or exploratory endpoints were analyzed as follows:

Survival: Survival endpoints, including OS, PFS and LFS, were analyzed using the Kaplan-Meier (KM) method. By design, in both the parent studies and in this extension study, subjects were followed up only until completion of the safety follow-up assessment(s) performed approximately 30 days after the last dose of MMB.

- Overall survival (OS) – defined as the interval from first dosing date of MMB in the parent study to death from any cause.
- Progression-free survival (PFS) – defined as the interval from the first dose of MMB on the parent study until the first documentation of definitive progressive disease as defined in 2006 IWG-MRT or death due to any cause.
- Leukemia-free survival (LFS) – 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 a relevant AE as specified in the SAP or death from any cause.

Surviving subjects who were free of the event(s) of interest (death, progression or leukemic transformation) and subjects who had discontinued MMB and lost to follow-up were censored at the last time that the subject was known to be alive, alive and progression-free, or alive and leukemia-free on study, for analyses of OS, PFS, and LFS, respectively. Subjects were 'known to be alive' based on all the in-person visit dates captured in the datasets, ie, bone marrow biopsy, central lab collection, CT scan, physical exam, drug administration in clinic, concomitant medication and therapy start date, ECG, safety follow-up, hospitalization and pregnancy testing.

The survival data presented for each endpoint (OS, PFS, and LFS) include the number of subjects with the event or who were censored; the median, first and third quartile (Q1 and Q3) durations of survival (with 95% confidence interval [CI]) and KM survival curves.

Splenic response and duration of splenic response: Spleen size was measured during Study GS-US-352-1154 by physical examination (palpation) by the investigator, and clinical improvement based on splenic response was defined according to the 2006 IWG-MRT criteria as (i) a reduction of 50% or more in palpable spleen length for a spleen that was palpable at least 10 cm below the left costal margin (LCM) at baseline, or (ii) a spleen that was palpable at ≥ 5 cm and < 10 cm below the LCM at baseline becoming not palpable for at least 56 days. Splenic response rate, defined as the proportion of subjects who achieved clinical improvement, was presented with corresponding 2-sided 90% exact CIs using the binomial distribution.

For subjects who achieved a splenic response by palpation, the duration of splenic response in days was defined as the interval from the first onset of splenic response that lasted ≥ 56 days (in the parent study or this extension study) to the onset date of loss of splenic response. Loss of response was defined as the reduction of splenomegaly by $< 50\%$ among responders (with splenomegaly ≥ 10 cm below the LCM at baseline) that lasts ≥ 56 days, or the recurrence of > 0 cm splenomegaly among responders (with splenomegaly > 5 and < 10 cm below the LCM at baseline) that lasts ≥ 56 days. Duration of splenic response for responders was summarized using descriptive statistics (n, mean, standard deviation [StD], median, min, and max) and the KM method (medians, Q1, Q3, ranges, corresponding 90% CIs, and KM plot).

Spleen assessment in the Cohort 4 parent study (GS-US-352-1672) was performed by magnetic resonance imaging (MRI) and splenic response was defined as a ≥ 35% reduction in spleen volume at Week 24. Duration of spleen response was not evaluated in the Cohort 4 parent study.

Anemia response and duration of anemia response: Anemia response was a composite endpoint of TI response for those subjects who were transfusion-dependent (TD) at baseline and hemoglobin response for those who were hemoglobin response-evaluable, defined as those with a hemoglobin level of < 10 g/dL but were not TD (Study CCL09101) or were transfusion-independent (Study YM387-II-02) at baseline.

Anemia response-evaluable subjects were defined as subjects who either were TD or had a hemoglobin level of < 10 g/dL but were not TD (CCL09101/CCL09101E) or were transfusion-independent (YM387-II-02) at baseline.

Transfusion dependence was defined as receiving at least 2 units of RBC within 30 days prior to Cycle 1 Day 1 for Cohorts 1 and 2 (Studies CCL09101/CCL09101E and YM387-II-02, respectively), and as receiving at least 4 units of RBC in the 8 weeks prior to the first dose of MMB for Cohort 4 (Study GS-US-352-1672).

Transfusion independence responders were subjects who were TD at the parent study baseline and had a ≥ 12-week TI response at any time from the first dose of MMB in the parent study until the end of this extension study.

Hemoglobin responders were those who were hemoglobin response evaluable at baseline and experienced a ≥ 2 g/dL increase in hemoglobin level from baseline for ≥ 12 weeks. Hemoglobin response was not assessed in subjects who were TD at baseline due to the confounding nature of transfusions on the measurement of hemoglobin.

Anemia response rate, TI response rate and hemoglobin response rate were presented with corresponding 2 sided 90% exact CIs using the binomial distribution for evaluable subjects for each endpoint. Results are presented by cohort and for the overall FAS and similarly for the RSAS.

Duration of TI response was defined as the interval from the first onset date of TI response (in the parent study or Study GS-US-352-1154) to the earliest date of loss of response. The first onset date of TI response was defined as the first day of the 12-week period without a transfusion. Loss of TI response was defined as when subjects received any RBC transfusion after achieving a transfusion response. Data from responders who retained the response were censored at the last assessment date.

Duration of anemia response was defined as the interval from the first onset date of anemia response (in the parent study or Study GS-US-352-1154) to the earliest date of loss anemia response defined as the administration of any RBC transfusion after achieving a TI response or hemoglobin response. Duration of anemia response for responders was summarized using descriptive statistics (n, mean, StD, median, min, and max) and using the KM method (medians, Q1, Q3, ranges, corresponding 90% CIs, and KM plot).

Other Efficacy Endpoints:

The best overall response per physician assessments (defined according to the 2006 IWG-MRT criteria) was presented with corresponding 2 sided 90% exact CIs using the binomial distribution. Best overall response was categorized as follows: complete remission, partial remission, clinical improvement, stable disease, or progressive disease.

The change in hemoglobin level over time from baseline (in the parent study) was summarized using descriptive statistics.

The rate of RBC transfusion was calculated as the total number of RBC units transfused across all subjects divided by the total period of MMB exposure for each subject. The rate of RBC transfusion, defined as the average number of RBC units per subject-month, was presented for each cohort.

PGIC results, self-reported by subjects in comparison to their perceived symptom burden at entry to Study GS-US-352-1154, were summarized for all postdose visits for the proportions of subjects with each outcome.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. All summarized AEs were treatment-emergent. Treatment-emergent AEs were defined as AEs with onset dates on or after the start of study drug in the parent study and no later than 30 days after permanent discontinuation of study drug, or any AEs leading to premature discontinuation of study drug. Pre-existing events that increased in severity or changed in nature during, or as a consequence of, participation in the clinical study were also considered AEs.

New-onset AEs were defined as any event with an onset date on or after the start date of study drug in Study GS-US-352-1154 and no later than 30 days after permanent discontinuation of study drug, or any AEs leading to premature discontinuation of study drug in Study GS-US-352-1154. New-onset AEs also included pre-existing events that increased in severity or otherwise changed in nature after the start of GS-US-352-1154.

The safety and tolerability analyses in this final CSR are mainly focused on the RSAS and include analyses of safety data for these 74 subjects captured from entry into the original parent study until discontinuation from GS-US-352-1154. To more closely characterize long-term safety, results for these 74 subjects with MF are presented for this overall duration as well as for new-onset events that occurred during the extension study.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by MedDRA system organ class and preferred term) were provided for the CSAS as well as for the RSAS. Adverse events were also summarized by severity grade, investigator assessment of relationship to study drug, seriousness, discontinuations due to AEs, dose modifications or interruptions due to AEs, and AEs leading to death. In addition, Grade 3 or above clinical laboratory abnormalities were summarized for selected hematology and chemistry parameters using descriptive analyses.

Results are also presented by starting dose at entry into this GS-US-352-1154 extension study noting however, that this starting dose reflects MMB tolerability and dose modification within the preceding parent studies.

Exposure-adjusted incidence rates for events of interest were calculated for the CSAS.

RESULTS AND CONCLUSIONS:

Subject Disposition, Demographics, and Baseline Characteristics: A total of 268 subjects with MF were enrolled and received at least 1 dose of study drug in one of the parent studies (ie, CSAS). Of these 268 subjects, 265 had at least 1 postbaseline efficacy assessment (ie, FAS).

Of the 268 subjects with MF treated with study drug in one of the parent studies, 74 subjects (27.6%) entered this extension study (ie, RSAS). The 74 subjects initiated MMB dosing at the following MMB dose levels upon entry to this extension study: 100 mg: 12 subjects; 150 mg: 10 subjects; 200 mg: 52 subjects.

GS-US-352-1154: Number of Subjects in Analysis Sets by Cohort

Analysis Set	Cohort 1 CCL09101/ CCL09101E	Cohort 2 YM387-II-02	Cohort 4 GS-US-352-1672	Overall
Combined Safety Analysis Set (CSAS)	166	61	41	268
Full Analysis Set (FAS)	165	60	40	265
Rollover Safety Analysis Set (RSAS)	30	22	22	74

The median age of the 265 subjects in the FAS was 69.0 years (baseline of parent study). More than half of the subjects were male (60.4%), and most were white (89.8%). About half of the subjects (53.2%) were TD and 55.1% had not received MF treatment prior to parent study entry.

The main differences in subject characteristics across the 3 parent studies are in the proportion of subjects who were TD at entry into the parent study (highest in GS-US-352-1672, by design, at 100% and just under 50% for the other 2 parent studies) and in the proportion of subjects who had received prior MF treatment (ranging from 20.0% in GS-US-352-1672 to 73.3% in YM387-II-02).

The median age of the 74 subjects who enrolled into the GS-US-352-1154 extension study (the RSAS) was 66.5 years (baseline of parent study). About half of the subjects were male (51.4%), and most were white (86.5%). About half of the subjects (48.6%) were TD and most (71.6%) had not had prior MF treatment at baseline in the parent study. Compared to the 265 subjects in the FAS, the 74 subjects who entered this extension study were, at the time of entry to the parent studies, slightly younger (median age 66.5 vs 69.0 years), and fewer were male (51.4% vs 60.4%), transfusion-dependent (48.6% vs 53.2%) or had received prior MF treatment (28.4% vs 44.9%).

In the RSAS, 15 subjects (20.3%) completed Month 48 or later visits, as measured from the start of entry into this extension study, while the remaining subjects discontinued from the study, including six who rolled over to a subsequent extension study prior to Month 48. The most common reasons subjects discontinued study drug during participation in the GS-US-352-1154 extension study were investigator decision (20.3%) and disease progression (17.6%). A total of 19 subjects from this extension study were transitioned into a subsequent extended access study, SRA-MMB-4365.

Efficacy Results:

Survival Analyses

The single-arm nature of the study designs, the limited follow-up time of 30 days following the last dose of study drug, the small number of deaths reported given the absence of long-term survival follow-up, the high level of censoring, and the differences in study populations and parent study designs preclude definitive conclusions being drawn for the survival analyses. Thus, the overall survival, progression-free survival and leukemia-free survival data are descriptive only.

Overall Survival

In the FAS, 49 of 265 subjects (18.5%) were known to have died, including 21.2% of subjects in Cohort 1 (Studies CCL09101/CCL09101E), 13.3% of subjects in Cohort 2 (Study YM387-II-02), and 15.0% of subjects in Cohort 4 (Study GS-US-352-1672).

In the RSAS, 8 of 74 subjects (10.8%) were known to have died during GS-US-352-1154 participation, including 10.0% of subjects in Cohort 1, 9.1% of subjects in Cohort 2, and 13.6% of subjects in Cohort 4.

The causes of death in the RSAS were consistent with known principal causes of death in subjects with MF, including infection, thrombo-hemorrhagic events, heart failure and leukemic transformation.

The median KM estimate of OS was not reached in the FAS or RSAS analyses.

Progression-free Survival

In the FAS, disease progression (as defined by 2006 IWG-MRT) or death were reported for 89 of 265 subjects (33.6%), including 36.4% of subjects in Cohort 1, 33.3% of subjects in Cohort 2, and 22.5% of subjects in Cohort 4.

Progression-free survival for the RSAS was not analyzed.

The median KM estimate of PFS for the FAS overall was 54.9 months, ranging from 23.1 months for Cohort 4 to 44.1 months for Cohort 1 and 63.7 months for Cohort 2.

Leukemia-free Survival

In the FAS, leukemic transformation or death were reported for 56 of 265 subjects (21.1%), including 23.6% of subjects in Cohort 1, 16.7% of subjects in Cohort 2, and 17.5% of subjects in Cohort 4. Overall, 13 subjects had leukemic transformation events.

In the RSAS, leukemic transformation or death were reported for 10 of 74 subjects (13.5%), including 10.0% of subjects in Cohort 1, 13.6% of subjects in Cohort 2, and 18.2% of subjects in Cohort 4.

The median KM estimate of LFS was not reached in the FAS or RSAS analyses.

Splenic Response Rate and Duration of Response

In the FAS, 102 of 229 subjects (44.5%) with baseline splenomegaly (> 5 cm) achieved a splenic response consistent with clinical improvement of splenomegaly based on 2006 IWG-MRT criteria.

In the RSAS, 45 of 63 subjects (71.4%) with baseline splenomegaly (> 5 cm) achieved a splenic response. Two new splenic responses, achieved at the Month 1 and Month 6 visits respectively, were reported during subject participation in Study GS-US-352-1154. In addition, 1 subject in Cohort 1 who achieved a splenic response in the parent study had a complete resolution of palpable splenomegaly at the Month 3 visit while on Study GS-US-352-1154.

MMB was also effective at maintaining splenic response.

In the FAS, the overall median duration of splenic response was 364 days by descriptive statistics and 2557 days by KM estimate. In the RSAS, the overall median duration of splenic response was 990 days by descriptive statistics and 2557 days by KM estimate.

The longer duration by KM estimate was expected as this method of durability determination treats censored observations as carrying the same distributional properties as the uncensored observations.

Spleen response rate and duration of response by cohort are presented below.

	Cohort 1 CCL09101/ CCL09101E/ GS-US-352-1154	**Cohort 2 YM387-II-02/ GS-US-352-1154**	**Cohort 4 GS-US-352-1672/ GS-US-352-1154**	**Overall**
Spleen Response Rate, n/N (%)				
FAS	60/147 (40.8%)	36/50 (72.0%)	6/32 (18.8%)	102/229 (44.5%)
RSAS	20/25 (80.0%)	19/21 (90.5%)	6/17 (35.3%)	45/63 (71.4%)
Median Duration of Response by Descriptive Statistics, Responders Only (Days)				
FAS	466.5	253.0	447.5	364.0
RSAS	1704.5	736.0	447.5	990.0
Median Duration of Response by KM method, Responders Only (Days)				
FAS	2557.0	990.0	NR	2557.0
RSAS	2654.0	990.0	NR	2557.0

FAS = Full Analysis Set; NR = not reached; RSAS = Rollover Safety Analysis Set
Note: Spleen response rate is presented as n/N (%), where n = number of responders, N = number of evaluable subjects, % = proportion of n/N.

Anemia Response Rate and Duration of Response

Anemia response, a composite endpoint of TI response and hemoglobin response, depending on a subject's status at baseline, was prioritized in this CSR based on the previously developed SAP.

However, as transfusion dependence is strongly associated with poor prognosis in MF, the achievement of a TI response is considered the most clinically relevant method of assessing MMB's anemia benefit.

In the FAS, 90 of the 191 subjects (47.1%) who were evaluable for anemia response at baseline (as defined in Section 9.7.1.8.3), were anemia responders, defined as subjects with a TI response or a hemoglobin response, depending on the subject's baseline transfusion status and hemoglobin level.

In the RSAS, 35 of the 52 subjects (67.3%) who were evaluable for anemia response at baseline were anemia responders. Seven new anemia responses were reported during subject participation in Study GS-US-352-1154.

MMB was also effective at maintaining anemia response.

In the FAS, the overall median duration of anemia response was 238 days using descriptive statistics and the KM estimate was 358 days. In the RSAS, the overall median duration of anemia response was 358 days by descriptive statistics and the KM estimate was 421 days.

Anemia response and duration of anemia response by cohort are presented below.

	Cohort 1 CCL09101/ CCL09101E/ GS-US-352-1154	**Cohort 2 YM387-II-02/ GS-US-352-1154**	**Cohort 4 GS-US-352-1672/ GS-US-352-1154**	**Overall**
Anemia Response Rate[a], n/N (%)				
FAS	61/111 (55.0%)	12/40 (30.0%)	17/40 (42.5%)	90/191 (47.1%)
RSAS	13/18 (72.2%)	6/12 (50.0%)	16/22 (72.7%)	35/52 (67.3%)
Transfusion Independence Response Rate[b], n/N (%)				
FAS	49/72 (68.1%)	11/29 (37.9%)	17/40 (42.5%)	77/141 (54.6%)
RSAS	7/7 (100.0%)	5/7 (71.4%)	16/22 (72.7%)	28/36 (77.8%)
Hemoglobin Response Rate[c], n/N (%)				
FAS	12/39 (30.8%)	1/11 (9.1%)	n/a[d]	13/50 (26.0%)
RSAS	6/11 (54.5%)	1/5 (20.0%)	n/a[d]	7/16 (43.8%)
Median Duration of Anemia Response by Descriptive Statistics, Responders Only (Days)				
FAS	254.0	134.5	205.0	237.5
RSAS	995.0	120.0	281.5	358.0
Median Duration of Anemia Response by KM Method, Responders Only (Days)				
FAS	413.0	134.5	358.0	358.0
RSAS	1806.0	120.0	358.0	421.0

FAS = Full Analysis Set; KM = Kaplan-Meier; RSAS = Rollover Safety Analysis Set; TD = transfusion-dependent

Note: Response rates are presented as n/N (%), where n = number of responders, N = number of evaluable subjects, % = proportion of n/N

[a]Denominator consists of both TD subjects and subjects with Hgb < 10 g/dL at baseline who were not TD (Study CCL09101) or who were transfusion-independent (Study YM387-II-02) (ie, hemoglobin response-evaluable).

[b]Transfusion responders are defined as subjects who were TD at baseline having ≥ 12 weeks TI response.

[c]Hemoglobin responders are defined as subjects who were hemoglobin response-evaluable having ≥ 2 g/dL increase in Hgb from baseline for ≥ 12 weeks.

[d]GS-US-352-1672 subjects were not classified by hemoglobin level at baseline and were not evaluated for hemoglobin response given that all subjects were transfusion-dependent at study entry. The number of hemoglobin responders (n) and the number of subjects with Hgb < 10 g/dL at baseline (N) were noted as 0 in the statistical output table.

Transfusion Independence Response and Duration of Response

In the FAS, 77 of the 141 (54.6%) subjects who were TD at baseline became TI responders. In the RSAS, 28 of the 36 subjects (77.8%) who were TD at baseline became TI responders. Five of the 7 new anemia responses were new TI responses that occurred during subject participation in Study GS-US-352-1154.

MMB was effective at maintaining a TI response.

In the FAS, the overall median duration of TI response was 185 days by descriptive statistics and the KM estimate was 235 days. In the RSAS, the overall median duration of TI response by descriptive statistics was 194 days and the KM estimate was 205 days.

	Cohort 1 CCL09101/ CCL09101E/ GS-US-352-1154	**Cohort 2 YM387-II-02/ GS-US-352-1154**	**Cohort 4 GS-US-352-1672/ GS-US-352-1154**	**Overall**
Median Duration of TI Response by Descriptive Statistics, Responders Only (Days)				
FAS	198.0	126.0	205.0	185.0
RSAS	357.0	114.0	281.5	193.5
Median Duration of TI Response by KM Method, Responders Only (Days)				
FAS	240.0	126.0	358.0	235.0
RSAS	357.0	114.0	358.0	205.0

FAS = Full Analysis Set; KM = Kaplan-Meier; RSAS = Rollover Safety Analysis Set; TI = transfusion independence
Note: Number of responders in FAS = 141 and in RSAS = 36.

Hemoglobin Response Rate

In the FAS, 13 of 50 subjects (26.0%) in Cohorts 1 and 2 who had hemoglobin levels < 10 g/dL but were not TD (CCL09101/CCL09101E) or were transfusion-independent (YM387-II-02) at baseline were hemoglobin responders, defined as subjects with a ≥ 2 g/dL increase from baseline for ≥ 12 weeks.

In the RSAS, 7 of 16 subjects (43.8%) who had a hemoglobin level of < 10 g/dL but were not TD (CCL09101/CCL09101E) or were transfusion-independent (YM387-II-02) at baseline were hemoglobin responders. Two of the 7 new anemia responses were hemoglobin responses that occurred during subject participation in Study GS-US-352-1154.

Rate of RBC Transfusion

Subjects in the RSAS (N = 74) had a lower RBC transfusion rate during their participation in Study GS-US-352-1154 than during the corresponding parent study period (median RBC transfusion rates of 0.00 units/month vs 0.08 units/month).

Other Benefits

Best Overall Response

Per investigator's assessment of best overall response (based on 2006 IWG-MRT criteria), 141 of 265 subjects (53.2%) in the FAS achieved clinical improvement or better, including 4 subjects (1.5%)

with partial remission, and 96 subjects (36.2%) with stable disease. One new partial remission was achieved during subject participation in Study GS-US-352-1154 with the subject showing complete resolution of splenomegaly at the Month 3 visit.

Change in PGIC Over Time

Overall, 57 of 74 subjects (77.0%) reported improvement in PGIC at any post-Screening time point during their participation in Study GS-US-352-1154, including 83.3% of subjects in Cohort 1, 81.8% of subjects in Cohort 2 and 63.6% of subjects in Cohort 4. Among the 49 subjects (66.2%) who reported "very much improved" or "much improved" at any time on study, approximately 60% of subjects had improvement that lasted for > 12 months and approximately 40% of subjects had improvement that lasted for > 24 months. Overall, about one-third of the subjects showed deterioration in PGIC before study discontinuation.

Bone Marrow Fibrosis

Bone marrow results were available from parent study baseline and Month 24 and/or Month 48 for 23 of the 74 subjects (31.1%) in the RSAS. Six of these 23 subjects (26.1%) showed improvement including one subject who achieved an improvement of bone marrow fibrosis from Grade 2 at baseline to Grade 0 at Month 24. The improvement was also supported by cellularity and blast analyses. Other ≥ 1 grade improvements in bone marrow fibrosis included 3 subjects with 1 grade improvement at Month 24 and 2 subjects with 1 grade improvement at Month 48. In this same sample, 4 subjects had a 1 grade worsening. The small number of subjects with 1 grade or more change and the considerable amount of missing data preclude any definitive conclusions being drawn.

Safety Results:

The MMB safety and tolerability analyses detailed here focus mainly on the RSAS, which is comprised of the 74 subjects with MF who rolled over from Cohorts 1, 2 and 4 into the GS-US-352-1154 extension study. Key safety conclusions are based principally on an examination of new-onset AEs occurring during participation in the extension study.

Exposure

The overall median duration of exposure to MMB in the GS-US-352-1154 subjects (N = 74) since the first dose of MMB in the parent study was 1666 days (range: 177 to 2999 days), or approximately 4.6 years; with 3 subjects remaining on MMB treatment for > 8 years, 11 subjects for > 7 years, and 20 subjects for > 6 years.

The overall median duration of exposure to MMB in Study GS-US-352-1154 was 509 days (range: 1 to 1623), or approximately 1.4 years, consistent with the shorter observation on average, in the extension study.

For comparison, the median duration of exposure to MMB for the 265 subjects in the FAS was 424 days (range: 1 to 2999), or approximately 1.2 years.

Adverse Events

A total of 73 subjects (98.6%) in the RSAS experienced at least 1 AE since their first dose of MMB in the parent study. The most commonly reported AEs were diarrhea (55.4%), fatigue (47.3%), nausea (44.6%), peripheral sensory neuropathy (41.9%), and dyspnea (40.5%). The most commonly reported ≥ Grade 3 AEs were thrombocytopenia (27.0%), anemia (21.6%), and neutropenia (18.9%). These hematological abnormalities were the most commonly reported ≥ Grade 3 treatment-related AEs.

New-onset Adverse Events

A total of 72 subjects (97.3%) in the RSAS experienced a new-onset AE, defined as an AE with an onset date on or after the first dose of MMB in Study GS-US-352-1154. The most commonly reported new-onset AEs were fatigue (29.7%), anemia (24.3%), dyspnea (23.0%), diarrhea (21.6%), and nausea (20.3%). The majority (~ 83%) of the AEs were Grade 1 or 2. Anemia (14.9%), thrombocytopenia (8.1%), cardiac failure congestive, abdominal pain, pneumonia, and platelet count

decreased (5.4% each) were the most common ≥ Grade 3 AE reported. No general trend of dose-related increase or decrease in new-onset AE incidence was observed across the 3 assigned dose levels of MMB in Study GS-US-352-1154.

The incidence and type of new-onset AEs in RSAS subjects occurring within this extension study was compared with the incidence and type of AEs noted in the same subjects during parent study participation alone and in the overall dosing period. In general, the incidence of common AEs was lower for subjects in the RSAS during the extension study period than during their participation in the preceding parent studies, except for those AEs associated with advanced stage of MF such as anemia, dyspnea or fatigue. No evidence of cumulative toxicities or new safety signals upon long-term exposure to MMB treatment was noted.

New-onset AEs of peripheral neuropathy Standardized MedDRA Query (narrow terms) were reported for 14.9% of subjects during their participation in Study GS-US-352-1154. All of the events were Grade 1 or 2. All of the subjects with new-onset events appeared to have potential risk factors for peripheral neuropathy before Study GS-US-352-1154 entry.

New-onset AEs of cataract occurred in 8.1% of subjects in Study GS-US-352-1154. All but one of these events were Grade 1 or 2, with one nonserious Grade 3 event reported. The incidence of cataract observed in this extension study is consistent with the prevalence of cataract for the older age group in this subject population.

No serious opportunistic infections were reported during subject participation in this extension study. New-onset malignant neoplasms were reported for 10.8% of subjects in this study, including 3 subjects each with acute myeloid leukemia and skin cancers. The incidences of infections and malignancies are commensurate with the subject population.

Adverse events leading to death were reported for 10.8% in this study. None was considered related to MMB.

New-onset serious AEs (SAEs) were reported for 50.0% of subjects in this study, which is similar to the incidence rate in the parent studies. Adverse events leading to study drug discontinuation were reported for 13.5% of subjects and AEs leading to dose modification/interruptions occurred in 27% of subjects.

Other Safety Data

New-onset Grade 4 laboratory abnormalities were decreased neutrophil count and decreased lymphocyte count (1 subject each, 1.4%). The most common new-onset Grade 3 laboratory abnormalities were decreased platelet count (4 subjects, 5.4%), decreased white blood cell and increased international normalized ratio (3 subjects each, 4.1%).

No clinically significant effects of MMB on vital signs were reported in Study GS-US-352-1154.

CONCLUSIONS:

The primary objective of this extension study was to determine the long-term safety and tolerability of MMB in subjects originally enrolled to 4 therapeutic open-label Phase 2 MMB parent studies.

The secondary objective of this study was to further characterize the long-term efficacy of MMB in these cohorts of subjects based on data from this extension study and from the preceding parent studies.

The key value of this dataset is the large number of subjects who received MMB for an extended duration, which provides insights into the durability of efficacy and long-term safety. Despite some differences in study design, dose, formulation, duration of dosing, and timing of enrollment for the 3 relevant parent studies, the subject characteristics were generally similar. Nonetheless, integrated data or data presented by cohort or dose level must be interpreted with caution.

Nearly 28% of subjects (74 of 268 subjects) enrolled to one of the three Phase 2 parent studies achieved sufficient clinical benefit with MMB to enter the GS-US-352-1154 extension study. The

cumulative median duration of exposure to MMB in the GS-US-352-1154 subjects since the first dose of MMB in the parent study was 1666 days (~4.6 years), with 3 subjects treated for > 8 years, 11 subjects for > 7 years, and 20 subjects for > 6 years. The median duration of additional MMB exposure for the 74 subjects in Study GS-US-352-1154 was 509 days (~1.4 years). Following the conclusion of this study, 19 of the 74 subjects transitioned to a further extended access study (SRA-MMB-4365) to continue additional MMB treatment.

The data presented in this final CSR confirm that MMB is effective at inducing and maintaining substantive spleen and anemia responses and other benefits in subjects with MF consistent with its differentiated mechanism of action. The compound is also well tolerated without evidence of cumulative toxicity, as summarized by the following conclusions:

- MMB was well tolerated with extended duration of daily dosing of MMB for approximately 4.6 years for the 74 subjects who enrolled in Study GS-US-352-1154, with some of these subjects remaining on therapy for more than 8 years since their first dose in their parent study.
- The safety profile of MMB in these 74 subjects with MF was consistent with that observed in previous MMB studies in subjects with MF. No new safety concerns emerged.
- Substantial spleen, anemia and other disease benefits were observed in the Full Analysis Set (N = 265) inclusive of all data from the efficacy-evaluable subjects enrolled in the 3 cohorts. MMB efficacy was particularly robust in the long-term responders who participated in this extension study as demonstrated by the Rollover Safety Analysis Set (N = 74) analyses.
- In the FAS, 102 of 229 subjects (44.5%) with baseline splenomegaly achieved a splenic response, assessed by palpation. In the RSAS, 45 of 63 subjects (71.4%) with baseline splenomegaly achieved a splenic response, including 2 subjects with new splenic responses during participation in Study GS-US-352-1154.
- MMB was effective at maintaining splenic responses, with a median duration of response in the FAS of 364 days by descriptive statistics and 2557 days by KM estimate. In the RSAS, the overall median duration of splenic response was 990 days by descriptive statistics and 2557 days by KM estimate.
- The anemia response rate in the FAS was robust and durable.
  - In the FAS, 90 of the 191 subjects (47.1%) evaluable subjects achieved an anemia response, with a median duration of anemia response of 238 days by descriptive statistics and 358 days by KM estimate.
  - Impressively, 77 of the 141 subjects (54.6%) who were TD at baseline achieved at least 12 weeks of TI response with an overall median duration of 185 days by descriptive statistics and 235 days by KM estimate.
- The anemia response rate was even more robust and durable in the RSAS.
- Anemia response was achieved in 35 of the 52 subjects (67.3%) who were anemic or transfusion-dependent at baseline. The median duration of anemia response for these subjects was 358 days by descriptive statistics and 421 days by KM estimate.
  - Continued long-term exposure to MMB was able to elicit 7 additional anemia responses, 5 of which were TI responses, during the extension period.
  - A TI response was achieved in 28 of the 36 subjects (77.8%) who were transfusion-dependent at baseline, with a median duration of response of 194 days by descriptive statistics and 205 days by KM estimate.
  - A hemoglobin response was observed in 7 of 16 subjects (43.8%) who were evaluable for hemoglobin response at baseline.

  - The RBC transfusion rate was lower for subjects during their participation in Study GS-US-352-1154 compared to their participation in the parent study, suggesting that long-term exposure to MMB can further reduce transfusion burden.

- The median KM estimate of OS and LFS was not reached in any of the populations, while the median KM estimate of PFS was 54.9 months overall for the 265 subjects enrolled in the 3 cohorts, noting that the descriptive analyses of OS, PFS and LFS are limited by the high rate of censoring and the single-arm nature of the study design.
- Overall, 57 of 74 subjects (77.0%) reported improvement in the PGIC metric of symptom burden at any post-Screening time point during their participation in Study GS-US-352-1154, suggesting that MMB elicited a marked symptomatic benefit during prolonged administration.
- Clinical improvement or better was documented as the best overall response by investigators in 141 of 265 subjects (53.2%).
- Improvements in the grade of bone marrow fibrosis was documented in 6 of the 23 subjects (26.1%) with serial samples; however, the considerable amount of missing data preclude definitive conclusions being drawn.

Date of the report: 30 April 2020