SUPPLEMENTARY APPENDIX

A phase 1/2, open-label study evaluating twice-daily administration of momelotinib in myelofibrosis

Vikas Gupta,[1] Ruben A. Mesa,[2] Michael W.N. Deininger,[3] Candido E. Rivera,[4] Shireen Sirhan,[5] Carrie Baker Brachmann,[6] Helen Collins,[6] Jun Kawashima,[6] Yan Xin[6] and Srdan Verstovsek[7]

[1]Princess Margaret Cancer Centre, University of Toronto, ON, Canada; [2]Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center, Phoenix, AZ, USA; [3]Division of Hematology and Hematologic Malignancies, University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA; [4]Division of Hematology/Oncology, Mayo Clinic Jacksonville, FL, USA; [5]Division of Hematology, Jewish General Hospital, Montreal, QC, Canada; [6]Gilead Sciences, Inc., Foster City, CA, USA and [7]University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Correspondence: vikas.gupta@uhn.on.ca

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Right running head: MOMELOTINIB IN TWICE-DAILY DOSING FOR MYELOFIBROSIS

Vikas Gupta, Ruben A. Mesa, Michael W.N. Deininger, Candido E. Rivera, Shireen Sirhan, Carrie Baker Brachmann, Helen Collins, Jun Kawashima, Yan Xin, and Srdan Verstovsek

Supplemental Methodology Information

Patients and methods

This multicenter, open-label, nonrandomized phase 1/2 study was approved by the institutional research and ethics boards of all of the participating institutions and was conducted in accordance with the principles of the Declaration of Helsinki. The study, registered at clinicaltrials.gov (NCT01423058), was conducted at six sites in the United States and Canada; the first subject enrolled in September 2011 and the study ended in June 2014. Study sites were monitored in accordance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines. A safety review committee (SRC) consisting of principal investigators, an independent medical monitor, and a sponsor representative maintained oversight of all clinical trial activities.

Study design

The study drug, formulated as 50 mg or 150 mg hard-gelatin capsules, was supplied by the sponsor.

The study was conducted in two phases. Part 1 involved a dose-escalation phase to determine the safety and tolerability of twice-daily (BID) momelotinib and to identify dose-limiting toxicities (DLTs) and/or maximum tolerated dose (MTD). Part 2 was conducted as a dose-confirmation phase, which was a cohort expansion at or below the MTD of momelotinib to a minimum dose of 150 mg BID, the choice of which

was determined by the SRC. The Part 1 dose-escalation phase followed a 3 + 3 design, wherein 3 to 6 subjects were to be enrolled per dose cohort until the MTD was reached. The first dosing cohort was 200 mg BID (doses taken approximately 12 hours apart) for a 28-day cycle, with successive cohorts initiated if 2 or fewer DLTs were experienced per 6 subjects in cycle 1. In Part 1, subjects were evaluated weekly for the first cycle, every 2 weeks during cycle 2, then monthly for 4 cycles, for a total of 6 cycles. Higher dosing cohorts (250 mg BID, 300 mg BID, and previous dose + 50 mg BID) were initiated after the SRC reviewed the toxicity and efficacy of the lower dose. In the dose-confirmation phase of the study (Part 2), subjects were to be treated at the MTD or at a lower dose shown to have significant clinical activity, as chosen by the SRC. Subjects were evaluated every 2 weeks during the first treatment cycle and then monthly for 5 cycles, for a total of 6 cycles.

Treatment suspensions

If a subject experienced a DLT or grade ≥3 toxicity, treatment could be suspended for up to 8 weeks and then restarted at a lower dose if the toxicity had reverted to grade ≤1.

Maintenance phase

Subjects enrolled in either phase of the study who achieved at least stable disease or better at the end of cycle 6 and had tolerated the drug well were allowed to continue to receive momelotinib in the maintenance phase and were followed every 12 weeks.

Assessments

The primary safety endpoint was to determine the safety profile and MTD of momelotinib. Safety assessments included characterization of DLTs, treatment-emergent adverse events (TEAEs), adverse event (AE) incidence and severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, v3.0), timing, and relationship to treatment.

The primary efficacy endpoint was the therapeutic response rate as defined by the number of subjects achieving complete remission, partial remission, or clinical improvement as defined by the 2006 International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria.[9] Individual components of the response were also assessed. Palpable spleen and liver size below the costal margin were recorded at baseline and at follow-up assessments. Spleen and liver volume assessments by magnetic resonance imaging (MRI) were performed at baseline, at the end of Weeks 12 and 24, and every 3 months thereafter.

Spleen response by palpation was defined as ≥50% decrease from baseline in palpable spleen length for baseline splenomegaly ≥10 cm that lasted ≥8 weeks, or resolution of palpable splenomegaly for baseline splenomegaly >5 cm and <10 cm that lasted ≥8 weeks. Spleen volume response by MRI was defined as ≥35% reduction in spleen volume from baseline and, for the subgroup who had palpable splenomegaly, >5 cm below the left costal margin at baseline.

Transfusion history for all subjects was recorded at screening for the preceding 6 months and thereafter at each follow-up visit. Red blood cell (RBC) transfusion dependence was defined as transfusion of ≥2 RBC units in the 30 days prior to the first dose of momelotinib. An 8-week anemia response was defined as no RBC transfusions for ≥8 weeks for subjects who were transfusion-dependent, or ≥2 g/dL increase in hemoglobin (Hb) lasting ≥8 weeks for those who were transfusion-independent but had Hb <10 g/dL at baseline. Two post hoc analyses were performed using a 12-week endpoint: one with the same definition of transfusion dependence as the 8-week analysis, and the other using a stricter definition of transfusion dependence at baseline (ie, 6 RBC units within the 12 weeks prior to first dose with at least 1 unit administered in the 28 days prior to the first dose).

Myelofibrosis (MF) symptoms were assessed at baseline, at the end of Weeks 2 and 4 of cycle 1, at the end of cycles 2 and 3, and then at the end of every 3 cycles. Symptom response was defined as ≥50% reduction in total symptom score (TSS) using the MF Symptom Assessment Form lasting ≥12 weeks. TSS was defined as the sum of scores of the following constitutional symptoms: worst level of fatigue

during the past 24 hours, early satiety, abdominal pain, abdominal discomfort, night sweats, itching (pruritus), and bone pain.

Pharmacokinetic and pharmacodynamic assessments

In the dose-escalation phase of the study (Part 1), plasma samples for PK analysis were collected on Days 1 and 28 of each subject's first cycle of momelotinib therapy, and pre-dose on Day 29 of cycle 6. In the dose-confirmation phase of the study (Part 2), samples were collected from a subset of subjects (approximately 15) on Days 1 and 28 of cycle 1, and pre-dose on Day 29 of cycles 3 and 6. Sampling for pharmacodynamic (PD) analysis was collected pre-dose on Day 1 of cycle 1, then 6 and 24 (±4) hours post-dose, and at Weeks 8 and 20 for both parts of the study. Plasma levels of cytokines were analyzed by enzyme-linked immunosorbent assay or Meso Scale Discovery (Rockville, MD, United States). *JAK2 V617F* allele burden was determined by polymerase chain reaction of peripheral blood granulocytes for known allele-positive subjects at screening; and subjects that were *JAK2V617F*-positive at screening had follow-up assays performed on Day 29 of cycles 3 and 6, and then every 6 to 12 cycles during maintenance for both parts of the study. Major molecular response (MR) was defined as the absence of mutant allele in previously positive cases.

Statistical methods

Summary statistics were presented for various categorical and continuous variables, as well as two-sided 95% confidence intervals (CIs) on selected parameters.

The safety analysis included all enrolled subjects who had at least one dose of the study drug. For efficacy analysis, a modified intent-to-treat (mITT) approach was used that included all enrolled subjects who received at least 1 dose of study medication and had at least 1 follow-up efficacy evaluation. The mITT analysis set was used for baseline characteristics and all efficacy endpoints. All statistical analyses were performed using SAS® version 9.2 or later (SAS Institute Inc., Cary, NC, United States).

Comparison of post-treatment cytokine data with baseline was carried out using Wilcoxon signed rank tests. A significant change from baseline was declared when ≥20% change from baseline was observed without multiple testing adjustments.

Supplemental Treatment-emergent Adverse Event Data

Table S1. Nonhematologic Treatment-emergent Adverse Events (>10% of total subjects) across all momelotinib dose levels

Preferred term	*Total N=61 n (%)*	*Grades ≥3 N (%)*
Gastrointestinal disorders		
Diarrhea	28 (45.9)	—
Nausea	21 (34.4)	—
Vomiting	16 (26.2)	2 (3.3)
Abdominal pain	15 (24.6)	—
Constipation	7 (11.5)	—
Dyspepsia	7 (11.5)	—
General disorders and administration site conditions		
Fatigue	18 (29.5)	7 (11.5)
Peripheral edema	14 (23.0)	—
Pyrexia	14 (23.0)	3 (4.9)
Infections and infestations		
Pneumonia	12 (19.7)	7 (11.5)
Sinusitis	7 (11.5)	—
Injury, poisoning, and procedural complications		
Contusion	7 (11.5)	—
Investigations		
Alanine aminotransferase increased	17 (27.9)	3 (4.9)
Blood creatinine increased	17 (27.9)	2 (3.3)
Aspartate aminotransferase increased	12 (19.7)	2 (3.3)
Lipase increased	12 (19.7)	5 (8.2)
Amylase increased	8 (13.1)	2 (3.3)
Weight decreased	8 (13.1)	—
Metabolism and nutrition disorders		
Decreased appetite	11 (18.0)	—
Hyperkalemia	10 (16.4)	4 (6.6)

Musculoskeletal and connective tissue disorders	28 (45.9)	—
Arthralgia	9 (14.8)	—
Nervous system disorders		
Dizziness	22 (36.1)	—
Peripheral neuropathy	27 (44.3)	2 (3.3)
Headache	16 (26.2)	—
Dysgeusia	8 (13.1)	—
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	13 (21.3)	2 (3.3)
Cough	9 (14.8)	—
Skin and subcutaneous tissue disorders		
Rash	9 (14.8)	—
Vascular disorders		
Hypotension	15 (24.6)	2 (3.3)

Table S2. Hematologic Treatment-emergent Adverse Events (>10% of total subjects) across all momelotinib dose levels

Preferred term	*Grades 1-2 N (%)*	*Grades ≥3 N (%)*	*Total N=61 n (%)*
Blood and lymphatic system disorders	—	27 (44.3)	33 (54.1)
Thrombocytopenia	—	18 (29.5)	24 (39.3)
Anemia	—	7 (11.5)	11 (18.0)
Neutropenia	—	3 (4.9)	7 (11.5)