Title of Trial: Phase II Trial with Safety Run-In of MEK Inhibitor MSC1936369B in Subjects with Poor Prognosis Acute Myeloid Leukemia and Other Hematological Malignancies

Investigational Product: Pimasertib

Trial No.: EMR 2000066-002

Study Centers: The trial was planned to be conducted at 9 clinical sites in Europe and the US; 7 sites (4 sites in France and 3 sites in the US) enrolled subjects for the safety run-in phase.

Trial Initiation Date: Sep 2009

Trial Completion Date: Dec 2012 (database-cut-off)

Development Phase: Phase 2

Publication (reference): Ravandi F et al., Blood (ASH Annual Meeting Abstracts) 2011, 118: Abstract 1554

Study Objectives:

The primary objective was to determine the maximum tolerated dose (MTD) for each treatment regimen of pimasertib in subjects with advanced hematological malignancies.

Secondary objectives included preliminary findings on the safety profile, pharmacokinetics (PK), and anti-leukemic activity.

Additional trial objectives included evaluation of pharmacogenetics (PGx) involved in absorption, disposition, metabolism, and elimination, pharmacodynamics and potential genetic variations, gene expression profiles, soluble markers in serum, and specific cytogenetics of blasts in relation to response.

Methodology: This trial was based on a 2-part design. Completion of the safety run-in part of different regimens of pimasertib in subjects with advanced hematological malignancies was to be followed by the open label, 2-regimen phase II part using an optimal 3-stage Chen design.

The safety run-in part was an open-label, dose-escalation, multi-center trial, following a dose escalation “3 + 3” cohort design where 3 to 6 subjects were enrolled at each dose level (DL).

The pimasertib dose was to be escalated on the basis of the dose-limiting toxicity (DLT) assessments. Dose-limiting toxicities were monitored centrally, and the decision to escalate to the next DL was to be made by a safety monitoring committee (SMC).

A decision was made to end the trial after completion of the safety run-in part and not to continue to the phase II part. The basis for this decision was due to an estimated low probability of observing clinical benefit based on limited anti-leukemic effects observed in the safety run-in part.

This report summarizes the findings of the safety run-in phase.

Number of Subjects (Planned and Analyzed):

Eighty (80) subjects with refractory hematological malignancies and no effective standard therapies available were treated and analyzed.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Female and male subjects aged ≥ 18 years with hematological malignancies pathologically confirmed according to World Health Organization (WHO) classification, who either had a second or subsequent relapse after standard therapy with no further established treatment options being available, were refractory to available therapies or were newly-diagnosed older subjects (≥ 75 years of age), who were not candidates for intensive chemotherapy.

Study Treatment: At each DL, subjects received pimasertib (also known as MSC1936369B) twice daily (BID) orally

- on Days 1 to 5, 8 to 12, 15 to 19, and 22 to 26 of a 28-day cycle (R1),
- on Days 1 to 21 of a 28-day cycle (R2)
- or Days 1 to 28 continuously for a 28-day cycle (Regimen 3).

The starting dose of pimasertib was 8 mg BID.

Duration of Treatment: Each subject's involvement in this trial was to be at least 10 weeks for his or her participation in the first treatment cycle. This included a screening period up to 14 days before the first dose, a treatment cycle of 28 days, and a 28 ± 3 days post-treatment follow up. Beyond Cycle 1, subjects were allowed to continue the trial treatment until progressive disease (PD), treatment delay for more than 2 weeks, intolerable toxicity, investigator / subject decision or intercurrent illness or changes in subject condition that rendered the subject ineligible for further treatment.

Reference Therapy, Dose and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Anti-leukemic activity:

Anti-leukemic activity of pimasertib was assessed through a combination of physical examinations, hematology laboratory assessments, bone marrow aspirate, and biopsy examinations as well as additional laboratory and radiological assessments as appropriate according to International Working Group Response Criteria, modified to include stable disease for acute myloid leukemia, acute lymphocytic leukemia, myelodysplastic syndrome

and advanced myeloproliferative diseases and to the European Blood and Marrow Transplant Group Criteria (modified) for multiple myeloma. The Best Overall Response per subject was derived using all on-trial per-timepoint anti-leukemic activity assessments. The best overall response categories considered of clinical importance in this trial were: morphologic complete remission (CR), followed by complete remission with incomplete blood count recovery (CRi), partial remission (PR), stable disease (SD), and PD.

Pharmacokinetics:

Concentration-time profiles for pimasertib were obtained based on plasma samples. Pharmacokinetic parameters were calculated using standard non-compartmental analyses.

Pharmacodynamics:

Blood samples were collected for assessing ERK phosphorylation.

Safety:

Safety was assessed by adverse events (AEs), deaths, clinical laboratory abnormalities, electrocardiograms, echocardiograms / multi-gated acquisition (MUGA) data, vital signs, and ophthalmologic assessments.

In this trial, DLT assessments were part of the overall safety assessments of the trial drug. DLTs were toxicities pre-defined in the protocol as any treatment delay > 2 weeks due to treatment-related adverse effects and any Grade ≥ 3 non-hematological toxicity excluding Grade 4 asymptomatic increases in liver function tests (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) reversible within 7 days in subjects with liver involvement, and Grade 3 asymptomatic increases in liver function tests reversible within 7 days for subject without liver involvement, Grade 3 vomiting unless encountered and persistent for more than 3 days despite adequate and optimal therapy, and Grade 3 diarrhea unless encountered and persistent for more than 3 days despite adequate and optimal anti diarrhea therapy at any DL and judged to be possibly or probably related to the trial treatment by the investigator and / or the sponsor.

Statistical Methods:

The data are summarized descriptively.

Results:

Subject Disposition:

A total of 116 subjects were screened, but 35 of the 116 subjects did not enter the trial because of screening failure. A total of 81 subjects were enrolled and 80 subjects were treated in this trial: 33 subjects in Regimen 1 (R1: 8-75 mg BID), 32 subjects in Regimen 2 (R2: 8-90 mg BID), and 15 subjects in Regimen 3 (R3: 60-75 mg BID). Thirty three subjects were enrolled in R2 but only 32 were dosed. Of the 80 treated subjects, 79 (98.8%) subjects were off

treatment at the time of this report; 1 subject in R2 was still on treatment after 141 weeks as of 20 Dec 2012 (database cut-off).

Demographics and Baseline Characteristics:

The proportion of male subjects (63.8%) participating in the trial was greater than the proportion of female subjects (36.3%). The mean age was similar across the 3 regimens: 60.7 years (R1), 59.3 years (R2), and 59.5 years (R3). The age range was 22 to 80 years, age distribution of 18 to <60 years comprised 32 subjects; 60 to <75 years, 35 subjects; and ≥ 75 years, 13 subjects. Most subjects were white (75.0%). The remaining subjects were African American/ black (10.0%), other ethnic origin (8.8%), and Asian (6.3%). The mean body mass index (BMI) was similar across the 3 regimens; 26.50 kg/m2, 25.75 kg/m2, and 24.74 kg/m2. The majority, 44 subjects (55.0%), had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 at screening. All other subjects had an ECOG PS of 0: 17 subjects (21.3%) or 2: 19 subjects (23.8%). Two subjects had a diagnosis of acute lymphoblastic leukemia (ALL), 66 subjects a diagnosis of acute myeloid leukemia (AML), 3 subjects a diagnosis of myeloproliferative disorders (MPD), 6 subjects a diagnosis of myelodysplastic syndrome (MDS), and 3 subjects a diagnosis of multiple myeloma (MM).

Determination of Maximum Tolerated Dose:

The primary objective to establish the MTD for each regimen was met only for Regimen 3 (continuous treatment). The 60 mg BID continuous dose was deemed tolerable by the SMC and this dose level was considered the MTD of pimasertib when administered to patients with leukemia. A MTD was not established in the R1 and R2. At the highest administered dose level (R1: 75 mg BID; R2: 90 mg BID) most subjects were not evaluable for dose limiting toxicity due to disease progression or disease complications.

Anti-leukemic Activity Results:

Thirty nine of 80 subjects across the 3 regimens had SD as their best overall tumor response with pimasertib treatment: One out of 2 subjects with a diagnosis of ALL, 34/66 subjects with a diagnosis of AML, 2/3 subjects with a diagnosis of MPD, 0/6 subjects with a diagnosis of MDS, and 2/3 subjects with a diagnosis of MM. One subject in R3, 60 mg BID dose cohort, with a diagnosis of ALL at screening, had CRi for 4.3 weeks and 1 subject in R1, 30 mg BID dose cohort, with a diagnosis of MDS at screening, had PR as the best overall response.

Pharmacokinetic Results:

Pimasertib was rapidly absorbed in all 3 regimens following single or multiple dosing, exhibited dose proportionality within the dose range of 24 mg to 75 mg, and showed linear PK over the dose ranges tested. Inter-individual variability of pimasertib exposure (maximum plasma concentrations [C_{max}] and area under the curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification [AUC_{0-t}]) following single administration across all doses in the 3 regimens as assessed by the coefficient of variation (CV) ranged between 20% and 80%. Pimasertib C_{max} as well as pimasertib exposure (AUC_{0-t}) increased with rising doses in all 3 regimens; however, dose normalized C_{max} as well

as AUC_{0-t} were considerably lower at doses of 8 mg to 24 mg BID. Median apparent half-life ranged from 2.9 hours to 7.5 hours across Regimens 1, 2, and 3 following administration of the first dose without obvious dose-dependent changes.

Following multiple dosing inter-individual variability of pimasertib exposure (C_{max} and AUC_{0-t}) ranged between 24% and 86% in the 3 regimens. Mean total body clearance from plasma following oral administration (CL/f) of pimasertib following multiple dosing (41 L/h to 114 L/h) was similar compared to single dosing (44 L/h to 119 L/h) indicating the absence of a timedependent effect on clearance. No dose-related changes were observed with apparent oral clearance at steady state (CL_{ss}/f). No obvious dose-dependent changes of the apparent pimasertib half-life (2.9-7.5 h) were observed. Peak-to-trough fluctuations (PTF) observed following BID dosing were ranging from 55% to 239%. The accumulation ratios ranged from 0.84 – 2.84 for C_{max} ($R_{acc}(C_{max})$) and from 0.87 – 2.08 for AUC ($R_{acc(AUC)}$).

Pharmacodynamic Results:

Phospho-ERK (pERK) inhibition was measured as a proximal marker for MEK activity in peripheral blood monocyte cells and blasts. Administration of doses higher than 60 mg BID with 2 and 7 days interruption in R1 and R2 is unlikely to improve the Pd profile of pimasertib when compared to 60 mg BID continuously R3. Sustained inhibition of this biomarker was achieved already at doses lower than 60 mg. However, pERK activity recovered during the washout period of R1 and R2.

Safety Results:

The Safety analysis (SAF) set consisted of 80 treated subjects (33, 32, and 15 subjects in Regimens 1, 2, and 3, respectively). The median length of exposure to pimasertib overall was 3.7, 4.6, and 4.0 weeks in R1 and R2, and R3, respectively. Approximately half of the subjects completed > 4 weeks of treatment. The overall median treatment compliance for all dosages combined was ≥ 95%.

All subjects reported at least 1 treatment-emergent AE (TEAE). The most frequently reported TEAEs (in ≥ 20% subjects) were diarrhea, skin rash, asthenia/fatigue, pyrexia/hyperthermia, nausea, edema peripheral, AST increased, febrile neutropenia, pneumonia, visual disturbances, serous retinal detachment, and vomiting.

Grade ≥ 3 TEAEs were observed on average in 4 out of 5 subjects. These were mostly including events due to underlying disease (such as febrile neutropenia, pneumonia, sepsis, and elevated liver enzymes). Similarly, serious TEAEs were reported in 80% of all subjects who in most cases suffered from pneumonia and febrile neutropenia. Most serious AEs (SAEs) were considered unrelated to trial drug.

The most common treatment-related TEAEs (in > 10% subjects) were diarrhea, nausea, rash, peripheral edema, fatigue/asthenia, and retinal detachment. In 4 subjects, Grade 3 diarrhea was considered treatment related and was reported in 3 out of these 4 subjects also as serious TEAE.

Ocular AEs of special interest (AESIs) were reported in 36% of subjects. Retinal detachment in 8 subjects and macular degeneration in 2 subjects (MedDRA Reported Term: Serous retinal detachment) were generally reversible after temporary treatment interruption, though 3 subjects discontinued after experiencing retinal detachment. In 2 of these subjects outcome of serous retinal detachment (SRD) was reported as resolved and in 1 subject as ongoing. One subject experienced retinal vein occlusion.

Twenty eight subjects died on the trial. For 10 subjects, the cause of death was other than disease progression or disease complication. In these cases fatal outcome followed disease related complications such as pneumonia, sepsis, or hemorrhagic shock. In 1 subject with pneumonia [fatal], asthenia, and diarrhea) the investigator was of the opinion that trial treatment had possibly contributed to the fatal outcome.

The pattern of DLTs recorded during the dose escalation phase was similar to, but in parts more severe than the AEs described above. There were 2 subjects with cardiac DLTs (congestive cardiac failure and sinus bradycardia).

Electrocardiogram (ECG) monitoring revealed 1 subject (R3, pimasertib 60 mg BID) with a SAE of T wave inversion and QT prolonged which was however considered unrelated to trial drug and due to the subject's underlying condition. Left ventricular ejection fraction (LVEF) decreases of 20% were recorded for 3 subjects in echocardiography/MUGA scans (1 subject with LVEF decrease between 15% to 20% in R1 and 1 subject with LVEF decrease between 20% to 25% in R2). Electrocardiogram and echocardiography/MUGA did not indicate cardiotoxic effects of pimasertib in addition to DLTs described above.

Clinical hematology and blood chemistry results did not raise additional safety concerns. As expected for hematological malignancies subjects did show a number of abnormal hematology and blood chemistry results. CTCAE grades of these abnormal results were in most cases below Grade 3. In 5 subjects Grade 4 electrolyte imbalances were observed under trial treatment.

They were clinically manageable and no action was necessary with regards to trial drug. Pimasertib-associated adverse reactions observed in this trial were mainly characterized by gastrointestinal AEs (diarrhea, nausea, vomiting), skin reactions (rash), and ophthalmologic AEs (serous retinal detachment, retinal vein occlusion).

Conclusions:

This trial assessed the safety and anti-leukemic activity of the MEK-inhibitor pimasertib, orally, as a single agent, using 3 twice daily regimens of administration, in 80 subjects with refractory hematological malignancies of poor prognosis and no effective standard therapies available. The primary objective was to establish the recommended dose, defined as the MTD, with each regimen for further clinical development. The primary objective was met only for Regimen 3 (continuous treatment). The 60 mg BID continuous dose was deemed tolerable by the SMC and this dose level was considered the MTD of pimasertib when administered to patients with leukemia. A MTD was not established in the R1 and R2. At the highest

administered dose level (R1: 75 mg BID; R2: 90 mg BID) most subjects were not evaluable for dose limiting toxicity due to disease progression or disease complications.

Dose escalation in the interrupted regimens R1 and R2 was discontinued by the SMC as R3 was expected to be superior based on improvement of pharmacodynamics (i.e., due to sustained target inhibition over the complete treatment cycles at dose levels lower than 60 mg BID when compared to the recovery of pERK level in PBMCs during scheduled treatment breaks in the interrupted regimens R1 and R2) at a comparable safety profile.

The most frequent TEAEs were diarrhea followed by skin rash, asthenia/fatigue, pyrexia/hyperthermia, nausea, edema peripheral, AST increased, febrile neutropenia, pneumonia, visual disturbances, serous retinal detachment, and vomiting. Grade $\geq$ 3 TEAEs were mainly hematological and related to the underlying malignancy.

Thirty nine of 80 subjects across the 3 regimens had SD as their best overall tumor response with pimasertib treatment. One subject in R3 had CRi for 4.3 weeks and 1 subject in R1 had PR as the best overall response. One subject with stable disease continued on trial treatment after 141 weeks as of 20 Dec 2012 (database cut-off).

Pimasertib was rapidly absorbed, exhibited dose proportionality within the dose range of 24 mg to 75 mg BID, showed linear PK over the dose ranges tested and did not exhibit a time dependent effect. The apparent elimination half-life of around 5.0 hours warrants BID administration to sustain pimasertib plasma levels over the entire dosing interval of 12 hours. These characteristics in combination with the observed inter-individual variability in pimasertib exposure comprise a favorable PK profile.

In conclusion, pimasertib has an acceptable tolerability profile with non-hematological toxicity as DLT. Pimasertib dosed intermittently or continuously was tolerated, with predominantly reversible mild or moderate AEs. The MTD is determined as 60 mg BID when administered continuously per 28-day cycle to subjects with hematological malignancies. As best overall leukemia response in nearly half of the subjects treated with pimasertib as single agent in this trial SD, and in one subject each PR and CRi were observed.

The SMC did not support continuation of the trial into the phase II part due to the lack of clinically relevant anti-leukemia activity of pimasertib as single agent in the safety run-in and therefore by sponsor decision the phase II randomized part of the trial in advanced haematological malignancies was not implemented.