A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myeloproliferative Neoplasms)

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Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Primary Objectives:- To evaluate splenic response rate by imaging after 24 weeks of treatment in Cohorts 1B and 2B (i.e., in non-TD cohorts)- To evaluate the rate of conversion from…

Ethical review	Approved WMO
Status	Completed
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52821

Source
ToetsingOnline

Brief title
Manifest

Condition

- Haematological disorders NEC

Synonym
Myeloproliferative Neoplasms (bone marrow cancer)

Research involving
Human

Sponsors and support

Primary sponsor: Constellation Pharmaceuticals
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: CPI-0610, Myeloproliferative Neoplasms, Phase 2, Ruxolitinib

Outcome measures

Primary outcome

Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Primary

Endpoints:

- The splenic response rate is defined as the proportion of patients who

achieve a >= 35% reduction from baseline spleen size by imaging (magnetic

resonance imaging

[MRI] or computed tomography [CT]) after 24 weeks of treatment (Cycle 9, Day 1)

- The conversion rate is defined as the proportion of patients who convert from

TD to TI, where TD is defined as receiving an average of >= 2 RBC transfusions

per month during the 12 weeks prior to enrollment and TI is defined as absence

of RBC transfusions over any consecutive 12 week period

Phase 2 (MF Expansion - JAKi Naïve Arm 3) Primary Endpoint:

- The splenic response rate is defined as the proportion of patients who

achieve a >= 35% reduction from baseline spleen size by imaging (MRI or CT)

after 24 weeks of treatment (Cycle 9, Day 1)

Phase 2 (ET Expansion Arm 4)

The proportion of patients who meet the criteria for a CHR, as assessed by modified ELN criteria (5)

• Normalization of platelet count (<= 400 × 10 ^ 9/L)

• WBC count within normal range (<= 10 × 10 ^ 9/L)

• Laboratory results confirmed after 1 cycle (after 3 weeks)

• Normal spleen size (by palpation or imaging)

Secondary outcome

Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Secondary Endpoints:

- PROs will be evaluated using the Myelofibrosis Symptom Assessment Form Version 4.0 (MFSAF v4.0) and the Patient Global Impression of Change (PGIC). Changes from baseline in the TSS from the MFSAF v4.0 and PGIC will be described. The proportion of patients who achieve a >=50% reduction in TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported.

- Time to conversion is defined as the time from the first dose of CPI-0610 until the first day of TI

- The duration of TI is defined as the time from the first onset date of TI to the earliest onset date of loss of TI

- The early anemic response rate is defined as the proportion of patients who achieve a hemoglobin (Hgb) increase of >=1g/dL from baseline over any

consecutive 8 week period in the absence of RBC transfusions

- The anemic response rate is defined as the proportion of patients who enroll as TI and achieve >= 1.5 g/dL Hgb increase from baseline over any consecutive 12 week period in the absence of RBC transfusions

- The overall splenic response rate is the proportion of patients who achieve a >= 35% reduction from baseline spleen size by imaging (MRI or CT); The reduction in spleen size from baseline by imaging (MRI or CT) after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be evaluated.

- Duration of the spleen response is defined as the time when splenic response criteria are first met (a >= 35% reduction from baseline spleen size) until the time at which an increase of >= 25% in spleen volume by imaging compared to baseline is documented

- Rate of response categories (such as complete response/remission (CR), partial response/remission (PR), clinical improvement (CI), stable disease (SD), progressive disease (PD) and relapse) after 24 weeks of treatment and every 6 months thereafter based on the revised 2013 IWG-MRT response criteria

- Time to >=50% reduction in TSS is defined as the time from the first dose of CPI-0610 until the first day of >=50% reduction in TSS from the MFSAF

- This composite response rate is defined as the proportion of patients who achieve a >= 35% reduction from baseline spleen size by imaging (MRI or CT) AND who achieve a >=50% reduction in TSS from the MFSAF after 24 weeks of treatment (Cycle 9, Day 1)

- The rate is defined as the average number of RBC units per patient-month. The rate is defined as the proportion of patients who become TD

- AUC(0-t), AUC(0-inf), AUCtau,ss, Tmax, Cmax, Ctrough,T1/2, Vd/F, CL/F

AUC(0-t), AUC(0-inf), AUCtau,ss, Tmax, Cmax, Ctrough,T1/2, Vd/F, CL/F

Phase 2 (MF Expansion-JAKi Naïve) Secondary Endpoints:

- PROs will be evaluated using the MFSAF v4.0 and the PGIC. Changes from baseline in the TSS from the MFSAF and PGIC will be described. The proportion of patients who achieve a >=50% reduction in TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported.
- The splenic response rate is defined as the proportion of patients who achieve a >= 35% reduction from baseline spleen size by imaging (MRI or CT) after 12 weeks of treatment (Cycle 5, Day 1)
- This composite response rate is defined as the proportion of patients who achieve a >= 35% reduction from baseline spleen size by imaging (MRI or CT) AND who achieve a >=50% reduction in TSS from the MFSAF after 24 weeks of treatment (Cycle 9, Day 1)
- Conversion rate is defined as the proportion of patients who convert from TD to TI
- Time to conversion is defined as the time from the first dose of CPI-0610 until the first day of TI in patients with TD as baseline
- The duration of TI is defined as the time from the first onset date of TI to the earliest onset date of loss of TI in patients with TD as baseline
- The anemic response rate is defined as the proportion of patients who enroll as TI and achieve >= 1.5 g/dL Hgb increase from baseline over any consecutive 12 week period in the absence of RBC transfusions

- Time to anemic response in patients who enroll as TI is defined as the time from the first dose of CPI-0610 until the first day of >= 1.5 g/dL Hgb increase from baseline

- The duration of anemic response in patients who enroll as TI is defined as the time from the first day of >= 1.5 g/dL Hgb increase from baseline until the first day the Hgb drops below 1.5 g/dL from baseline.

- The rate of conversion is defined as the proportion of patients who require an average of >= 2 units of RBC transfusions per month over a 12 week period.

- The early anemic response rate is defined as the proportion of patients who achieve a Hgb increase of >=1g/dL from baseline over any consecutive 8 week period in the absence of RBC transfusions

- The overall splenic response rate is the proportion of patients who achieve a >= 35% reduction from baseline spleen size by imaging (MRI or CT); duration of the spleen response is defined as the time when splenic response criteria are first met (a >= 35% reduction from baseline spleen size) until the time at which an increase of >= 25% in spleen volume by imaging compared to baseline is documented

- Rate of response categories (such as CR, PR, CI, SD, PD and relapse) after 24 weeks of treatment and every 6 months thereafter based on the revised 2013 IWG-MRT response criteria

- Time to >=50% reduction in TSS is defined as the time from the first dose of CPI-0610 until the first day of >=50% reduction in TSS from the MFSAF

- The rate is defined as the average number of RBC units per patient-month

- AUC(0-t), AUC(0-inf), AUCtau,ss, Tmax, Cmax, Ctrough,T1/2, Vd/F, CL/F

AUC(0-t), AUC(0-inf), AUCtau,ss, Tmax, Cmax, Ctrough,T1/2, Vd/F, CL/F

Phase 2 (ET expansion Arm 4)

- The proportion of patients with >= 50% reduction from baseline in the MPN-SAF total score.

PGIC will also be summarized.

- The proportion of patients who meet the following criteria for a partial hematological response:

• Platelets 400-600 × 10^9/L

• WBC within normal range (<= 10 × 10^9/L)

• Laboratory results confirmed after 1 cycle (after 3weeks)

- The proportion of patients with either a complete or partial hematological response at any time point and duration of response

- The time from the first onset date of response to the earliest onset date of loss of response, as measured by:

• Hematologic response

• Symptom improvement

- The proportion of patients with hemorrhagic or TE events

- The incidence of AEs and SAEs and changes from baseline in vital signs, and laboratory values

- tmax, Ctrough, AUClast, AUC0-8,ss, Cmax,ss, tmax,ss of CPI-0610

- The rate of transformation defined as the proportion of patients who convert to MF or AML during the study

- Assessment of post-treatment transcriptional changes in the pharmacodynamic

effects of CPI-0610 in the blood and bone marrow from baseline and changes in signaling pathway activity assessed by measuring levels of mRNA and/or protein.

Post-treatment changes from baseline in bone marrow fibrosis and hematopoietic cell populations.

Post-treatment changes from baseline in the ratio of mutant to wild type JAK2, CALR, and other ET-relevant alleles.

Post-treatment changes from baseline in circulating concentrations of cytokines.

- Assessment of genomic and transcriptomic features associated with response

- Percent change from baseline in spleen volume

Study description

Background summary

MF is a clonal myeloproliferative disease. It shares many of the characteristics of the other myeloproliferative diseases (essential thrombocythemia and polycythemia vera), but is characterized by more exaggerated abnormalities in megakaryocytes and by a more aggressive disease course with complications from cytopenias and transformation to acute leukemia. The megakaryocytes of patients with MF are hyperplastic, and this hyperplasia accounts for the thrombocytosis that may be seen early in the natural history of the disease. The hyperplastic megakaryocytes are also functionally abnormal. They release abnormal amounts of TGF-beta into the bone marrow, and TGF-beta stimulates the proliferation of fibroblasts in the bone marrow. The deposition of collagen in the bone marrow by fibroblasts leads to the fibrosis that is a hallmark of this disease and that impairs normal hematopoiesis. The hyperplastic megakaryocytes also release a diverse array of cytokines that account for many of the constitutional symptoms of the disease. Many cytokines signal through the JAK-STAT pathway, which explains why JAK inhibitors have activity in this disease. In addition, approximately 50% of patients with MF have activating mutations in JAK2. Regardless of the JAK2 mutational status of patients, it is thought that patients with MF have deregulated JAK-STAT signaling, which is why they respond to JAKi therapy regardless of their mutational status. Irrespective of the presence of mutations, the JAK/STAT pathway has been implicated in the inflammatory state of MF and other myeloproliferative diseases. More recently, the elevated pro inflammatory

cytokines present in MF have also been linked to the NF-*B pathway. The resultant inflammation in MF has several downstream ramifications, including bone marrow fibrosis, constitutional symptoms and extramedullary hemopoiesis (EMH). The fibrosis and EMH are several of the key factors leading to anemia, one of the signature features of MF. In fact, at the time of diagnosis, approximately 40% of patients have anemia (defined as a hemoglobin [Hgb] <10g/dL), and about 25% of patients require red blood cell (RBC) transfusions. As myelofibrosis progresses, virtually all patients end up developing anemia. While JAK inhibition is useful in the management of patients with MF, its efficacy is limited. The only JAKi currently approved for use in patients with MF is ruxolitinib. In Phase 3 trials a greater than 50% improvement in symptom scores was seen in 46% of patients treated with ruxolitinib compared to 5% of patients treated with placebo. And a 35% or greater reduction in spleen volume occurred in 29% to 42% of patients compared to 1-5% of patients treated with placebo or best available therapy. While ruxolitinib was effective in relieving constitutional symptoms and spleen size, there was little evidence to suggest that it modified the underlying disease, with infrequent histomorphologic changes in the marrow or reduction in mutated JAK2 allele burden. Unfortunately, anemia and thrombocytopenia occur frequently with ruxolitinib, and reach Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 levels in 45% and 13% of patients, respectively. In general, anemia is of concern for any patient. Maintenance of sufficient oxygen in the presence of anemia requires a compensatory increase in cardiac output, stressing the cardiovascular system. In MF in particular, anemia is associated with a poorer prognosis and a lesser quality of life. Chronic transfusions can lead to a variety of complications, but of more concern in MF, TD in this setting is an indicator of endstage disease, and an independent prognostic factor for survival. Hence there remains a need for better treatments for MF, particularly in patients with anemia. In regards to the anemia associated with ruxolitinib, this side effect is related to ruxolitinib*s mechanism of action. The hormone responsible for endogenous RBC production is erythropoietin, which, when bound to its receptor, activates JAK2, eventually leading to the production of RBCs. Ruxolitinib treatment can therefore worsen anemia via inhibition of JAK2. There is a typical pattern of anemia associated with ruxolitinib therapy as highlighted in data from the Phase 3 trial of ruxolitinib versus placebo in JAKi naïve patients with MF (COMFORT-1). In this study, the mean Hgb in ruxolitinib treated patients decreased from baseline over time, reaching a nadir after 2-3 months of treatment prior to recovery to a new steady state after 6 months of treatment. While the new steady state level was stable, it was lower than that at baseline (the proportion of ruxolitinib patients requiring at least 1 transfusion followed a similar pattern). Mean Hgb levels in the placebo group remained stable throughout the study. In a separate Phase 3 randomized trial of ruxolitinib versus an investigational JAKi in JAKi naïve patients (SIMPLIFY-1), the mean percent change in Hgb over the first 6 months of treatment was -6.5% in the ruxolitinib group. The rate of patients randomized to ruxolitinib who were RBC transfusion dependent (TD) in this study increased over the first 6 months of treatment (24.7% to 40.1%), when TD was

defined as >= 4 RBC transfusions or Hgb <8g/dL in the prior 8 weeks. Similarly, the rate of those who were RBC transfusion independent (TI) decreased over that same timeframe (70% to 49.3%) when TI was defined as 0 RBC transfusions and Hgb >= 8g/dL in the prior 12 weeks.

ET is characterized by excessive clonal platelet production resulting from inordinate platelet production rather than from prolonged platelet survival in peripheral blood . The term *essential* refers to an innate problem of hematopoiesis in the bone marrow. This contrasts with *secondary thrombocytosis,* which is a high platelet count in reaction to another issue in the patient*s body (eg, splenectomy) (18). Platelet kinetic data suggest that megakaryocyte proliferation occurs autonomously of circulating thrombopoietin (TPO) levels in ET. The simultaneous normal or slightly elevated plasma TPO concentrations and lower MPL (TPO receptor) expression in platelets and megakaryocytes result in a net overall normal clearance of TPO. Because TPO levels do not influence megakaryocyte proliferation in ET, therapeutic agents that directly affect megakaryocytes may be useful treat this disease.
In ET, similar to MF, driver mutations deregulate the normally occurring endomitosis that generates polyploidy in megakaryocytes, resulting in mild-to-moderate megakaryocyte hyperplasia with hyperploid nuclei. Recent preclinical models and clinical studies have shown that NF-*B pathway activation in both mutant and nonmutant hematopoietic cells drive expression of pro-inflammatory cytokines that typify the MPNs. The resulting continuously activated leukocytes and platelets release greatly elevated inflammatory cytokines that perpetuate inflammation in the MPN microenvironment, engendering MPN-associated symptoms.
BET proteins are transcriptional regulators that control key oncogenic pathways, including NF-*B and TGF-β signaling, important drivers of inflammation and fibrosis, respectively, in MF. CPI-0610 has the potential through its multiple mechanisms of action to reduce abnormal megakaryocytes, the major contributor to the pathogenesis of ET, through its inhibitory effects: (I) megakaryocyte differentiation and proliferation; (II) the inflammatory cytokine expression and release via the NF-*B signaling pathway (CPI-0610 treatment may diminish the quantity of platelets and the pro-inflammatory cytokines that are released from megakaryocytes); and (III) targeting genes of TGF-ß signaling, especially secretion of collagen by fibroblasts (CPI-0610 may diminish bone marrow fibrosis by BET inhibition of pro-fibrotic pathways).
Although not approved for the treatmen

Study objective

Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Primary Objectives:
- To evaluate splenic response rate by imaging after 24 weeks of treatment in Cohorts 1B and 2B (i.e., in non-TD cohorts)
- To evaluate the rate of conversion from red blood cell (RBC) TD to RBC

transfusion independence (TI) in Cohorts 1A and 2A (i.e., in TD cohorts)

Phase 2 (MF Expansion- JAKi Naïve Arm 1 and Add-on to JAKi Arm 2) Primary Objective:
- To evaluate splenic response rate by imaging after 24 weeks of treatment

Phase 2 (ET Expansion Arm 4) Primary Objective:
-To evaluate the complete hematological response rate

Study design

This is a Phase 1/2, multicenter, open-label, dose escalation study (Phase 1) of CPI-0610 in patients with acute leukemia, MDS, MDS/MPN or MF and expansion study (Phase 2) of CPI-0610 in patients with MF previously or currently treated with a JAKi as a single agent (Arm 1: Prior JAKi Monotherapy Arm) and in combination with ruxolitinib (Arm 2: Add-on to JAKi Combination Arm), in patients with MF who are JAKi naïve in combination with ruxolitinib (Arm 3: JAKi Naïve Combination Arm), and in high-risk patients with ET who are resistant or intolerant to HU (Arm 4: ET Monotherapy Arm). In both phases of the study, CPI-0610 will be administered PO QD for 14 days followed by a 7-day break, with cycles of treatment repeated every 21 days. This dosing regimen was originally chosen based on the aims of achieving continuous inhibition of the expression MYC and other genes (like BCL-2) for approximately 2 weeks, since preclinical studies suggest that longer exposure times are associated with greater antitumor activity. The 7-day break from treatment built into each cycle of treatment acknowledges the possible need for recovery from on-target normal tissue toxicity when pharmacologically active doses of CPI-0610 are given.

NOTE: Phase 1 is complete.

Intervention

Phase 2 (MF expansion):

The expansion arm doses for myelofibrosis (MF) patients previously treated (or ineligible to receive treatment with) or currently treated with a JAK inhibitor (Prior JAKi) or currently treated with JAK inhibitor (Add-on to JAKi) are:
- Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with CPI-0610 alone): CPI-0610 at initial dose of 125 mg once daily (QD) for 14 days followed by a 7-day break (upward titration allowed; 1 cycle = 21 days)
- Arm 2: Add-on to JAKi Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib): CPI-0610 at initial dose of 125 mg QD for 14 days followed by a 7-day break (upward titration allowed); ruxolitinib at dose patient is taking at the time of screening (1 cycle = 21 days)

NOTE: There are 2 cohorts within Arm 1: Cohort 1A (transfusion dependent [TD]) and Cohort 1B (non-TD) and 2 cohorts within Arm 2: Cohort 2A (TD) and Cohort 2B (non-TD).

The expansion arm doses for myelofibrosis (MF) patients who have not previously been treated with a JAKi (JAKi Naïve):
- Arm 3: JAKi Naïve Combination Arm (MF patients treated with CPI-0610 in combination with
ruxolitinib): CPI-0610 at initial dose of 125 mg QD for 14 days followed by a 7-day break (upward titration allowed); ruxolitinib at initial dose dependent on applicable approved package insert with upward titration allowed (1 cycle = 21 days).

Phase 2 (ET-expansion)
- Arm 4: ET patients treated with CPI-0610 alone: CPI-0610 at initial dose of 125 mg once daily (QD) for 14 days followed by a 7-day break (upward titration allowed; 1 cycle = 21 days)

Study burden and risks

What participation involves

Your study doctor will determine how long your participation in this study will last, based on how you respond to the study drug and your tolerability of the treatment.

Screening
We will first evaluate whether you may participate. The procedures during screening will be;
- Confirmation of your eligibility to participate in this study.
- You will be asked questions about your health, medications, medical and myelofibrosis / essential thrombocytemia history and therapy.
- You will be asked questions about your ability to do activities of daily living and your transfusion history. A transfusion history is a history of blood transfusions in your medical record before entry on the study. A blood transfusion is a process in which blood is injected into the body of a person who is badly injured or ill.
- A physical examination will be performed.
- An electrocardiogram (ECG) will be performed.
- Blood samples will be taken for biomarker (explanation below) testing.
- A pregnancy test will be done, if you are a woman of childbearing potential.
- A tuberculosis test (per applicable local regulations) will be administered for Arm 3 patients only.
- A CT (or MRI) scan will be performed to measure spleen.
- A bone marrow biopsy will be taken for biomarker testing (the bone marrow biopsy sample will be accepted as the screening sample if obtained within 3 months of the start of the study. Therefore, in these cases it is not necessary

to take a new bone marrow biopsy during screening).
- Myelofibrosis Symptom Assessment form or Neoplasm Symptom Assessment Form.

Some screening tests and procedures are part of your regular medical care and may be done even if you do not join the study. If you have had some of these tests or procedures recently, they may not have to be repeated. This will be reviewed with you by your study doctor.

What are the biomarkers?
Biomarkers (short for biological marker) are a measurable substance, that can be biological elements (including tissues or cells) or molecules that can be detected and measured in parts of the body like the blood or tissue. They may indicate either normal or diseased processes in the body. The biomarkers will be measured from blood samples and bone marrow biopsies. Please refer to Appendix C of the ICF for more information about biomarkers.

Treatment
There are four different treatment arms;
Arm 1: Subjects who participate in Arm 1 will be treated with the study drug alone. You may be eligible for this arm if you have taken ruxolitinib in the past and you could not continue due to side effects or your myelofibrosis was no longer responding to ruxolitinib.
Arm 2: Subjects who participate in Arm 2 will be treated with the study drug in combination with ruxolitinib. If you are currently taking a stable dose of ruxolitinib, but your myelofibrosis has not responded adequately, you may be eligible for this arm and you will be treated with your current dose of ruxolitinib in combination with the study drug.
Arm 3: Subjects who participate in Arm 3 will also be treated with the study drug and ruxolitinib. If you have never been treated with currently available medication, like ruxolitinib, you may be eligible to be enrolled in this arm.
Arm 4: Subjects who participate in Arm 4 will be treated with the study drug alone. If you have essential thrombocythemia and you have been previously treated with Hydroxyurea but did not respond well or experienced side effects while taking this medication, you may be eligible to be enrolled in this arm.

Your study doctor will inform you, based on your specific condition, as to which arm you are most well-suited for.

Your study doctor will discuss your treatment plan with you and tell you when you should perform or come in for assessments and procedures specific to your treatment plan. Your study drug dose may stay the same or increase throughout the study depending on whether or not you have side effects. If you have side effects, your study doctor may decide to lower the amount of study drug you take. The study doctor may also decide to delay or stop the study drug because of side effects. You may ask your study doctor what dose of study drug you will receive in this study.

The treatment period consists of multiple repeating periods of 21 days, called *cycles*. You will visit the hospital once every cycle to receive the study drug.

Some procedures performed at screening will be repeated during the cycles, additional procedures will be:
- You will be asked to complete the Patient Global Impression of Change form.
- Administration of the study drug (in combination with or without ruxolitinib)
- Patient Medication Diary Review
- Bone marrow biopsy (it is necessary to take a new bone marrow biopsy every 24 weeks after start of the study). Note: Following the bone marrow biopsy after 72 weeks (Cycle 25 Day 1), subsequent biopsies can be considered every 48 weeks (16 cycles) in consultation with the sponsor medical monitor.
-A pregnancy test will be done at the start of each cycle

Visits
The study staff will tell you when to come in for your study visits. You should ask the study staff how long your visits will last. It is not expected that you will need to stay in the hospital during this study unless you have a side effect and the study doctors think staying in the hospital will be safer for you.

Follow-up Contact(s) or Visit(s)
In certain cases, your study doctor or study staff may ask you to return to the clinic after your last study drug dose. This *follow-up* would be done to evaluate your health and disease status. Your study doctor or study staff would explain the exact purposes and follow-up schedule to you.

End of Treatment (EOT) or End of Study (EOS)
The following will take place:
- Bone marrow biopsy (only if biopsy has not been performed within the previous 12 weeks)
- CT (or MRI) scan to measure spleen and liver (only if progressive disease has not been previously documented or, in the absence of documented progressive disease, if imaging has not been done in the previous 3 weeks)
- You will be asked questions about your health and medications (this visit can occur over the phone)
- For patients who discontinue treatment for reasons other than documented disease progression should receive follow-up visits every 12 weeks to document response by imaging, palpation and transfusion requirements until initiation of another anti-cancer therapy or progression.
- Pregnancy test

Please refer to Appendix C of the ICF for a detailed overview of study visits and procedures.

Smart phone with study specific application

During screening visit (or in some cases at a later visit) a smart phone with a study specific application may be provided to you during your participation in the study. If a device is provided to you the investigator or designated site staff will make the smart phone ready for use. When the smartphone is provided to you, you will be instructed by the investigator or designated site staff on how to use the smartphone and application during the study. If you have questions or experiences issues using the device, you can ask the investigator or designated site staff for help. You will be asked to complete all application activities directly within the application and given notification reminders. You will also receive visit reminders on the smartphone. You are advised to go into the smart phone application daily to complete all required activities. You will be asked to complete assigned tasks including Myelofibrosis Symptom Assessment or Neoplasm Symptom Assessment and Patient Global Impression of Change forms. Myelofibrosis Symptom Assessment Neoplasm Symptom Assessment forms will be completed during screening every day for 7 days prior to Day 1 of each cycle. Patient Global Impression of Change form will be completed the day of odd numbered

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Phase 2 (MF Expansion - Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Inclusion criteria

Patients must meet all of the following criteria to be enrolled in this study:,
1. Adult (aged >= 18 years)
2. Patients with confirmed diagnosis of MF who meet all of the following criteria:
a. Dynamic International Prognostic Scoring System (DIPSS) risk category of intermediate-2 or higher.
b. Platelet count >= 75 x 10^9 /L without the assistance of thrombopoietic factors or transfusions
c. ANC >= 1 x 10^9 /L without the assistance of granulocyte growth factors
d. Spleen volume of >= 450 cm^3 by CT or MRI for Cohorts 1B and 2B OR RBC TD transfusions (defined as an average of >= 2 units of RBC transfusions per month [total of >= 6 RBC transfusions over the 12 wks] prior to enrollment) for Cohorts 1A and 2A
e. Peripheral blood blast count < 10%
f. At least 2 symptoms measurable (score >= 1) using the MFSAF v4.0
g. Monotherapy Arm (Arm 1) patients only: Previously treated with a JAKi and be intolerant, resistant, refractory or lost response to the JAKi; have not received the JAKi within 42 weeks prior to start of study drug, or are ineligible to be treated with a JAKi
h. Combination Arm (Arm 2) patients only: Must have received ruxolitinib for at least 6 months and be on a stable ruxolitinib dose for a minimum 8 weeks (prior to start of study drug)
3. ECOG performance status <= 2
4. Serum direct bilirubin <= 1.5 x ULN (upper limit of normal)
5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5 x ULN. The AST and /or ALT may be elevated up to 5 x ULN if the elevation can be reasonably ascribed to liver involvement.
6. Calculated or measured creatinine clearance (CrCl) >= 45 ml/min
7. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy
8. Male and WOBCP and partners of patients with reproductive potential must agree to use highly effective contraceptive methods for 94 days after the last dose of pelabresib for male patients and male partners of female patients and for 184 days after the last dose of study drug for WOCBP and female partners of male patients

9. Patients must give written informed consent to participate in this study before the performance of any study-related procedure,

Phase 2 (MF Expansion - JAKi Naive Arm 3) Inclusion criteria,

Patients must meet all of the following criteria to be enrolled in this study:,
1. Adult (aged >= 18 years)
2. Patients with confirmed diagnosis of MF who meet all of the following criteria:
a. DIPSS risk category of intermediate-2 or higher
b. Platelet count >= 100 x 10^9 /L without the assistance of thrombopoietic factors or transfusions
c. ANC >= 1 x 10^9 /L without the assistance of granulocyte growth factors
d. Spleen volume of >= 450 cm^3 by CT/MRI
e. Peripheral blood blast count <10%
f. At least 2 symptoms measurable (score >= 3) or a total score of >= 10 using the MFSAF v4.0
g. No prior treatment with JAKi allowed
3. ECOG performance status <= 2
4. Life expectancy of >24 weeks
5. Serum direct bilirubin < 2.0 x ULN
6. AST and ALT <= 2.5 x ULN. The AST and /or ALT may be elevated up to 5 x ULN if the elevation can be reasonably ascribed to liver involvement.
7. Calculated or measured CrCl >= 45 ml/min
8. Patients with a history of transfusions must have a documented transfusion record during the 12 weeks prior to the first dose of study drug
9. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy
10. Male and WOCBP and partners of patients with reproductive potential must agree to use highly effective contraceptive methods
11. Patients must give written informed consent to participate in this study before the performance of any study-related procedure

Phase 2 Arm 4 (ET Expansion) Inclusion Criteria
Patients must meet all of the following criteria to be enrolled in this study:
1. Adult (aged >= 18 years)
2. A confirmed diagnosis of ET
3. High-risk disease, defined as meeting at least one of the following criteria:
• Age > 60 years
• Platelet count > 1500 × 10^9/L (at any point during the patient*s disease)
• Previously documented thrombosis (including Transient Ischemic Attack [TIA]), erythromelalgia, or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered disease-related
• Previous hemorrhage related to ET
• Diabetes or hypertension requiring pharmacological therapy for > 6 months

4. Have at least 2 symptoms with an average score >= 3 over the 7-day period prior to Cycle 1 Day 1 or an average total score of >= 15 over the 7-day period prior to Cycle 1 Day 1 using the using the MPN-SAF
5. Platelets > 600 × 10^9/L
6. Resistant or intolerant to HU
7. ECOG performance status <= 2
8. Life expectancy of > 24 weeks
9. ANC >= 1 × 10^9/L in the absence of growth factors
10. Serum direct bilirubin < 2.0 × ULN
11. AST and ALT <= 2.5 × ULN
12. Calculated or measured CrCl >= 45 mL/min
13. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy
14. Male and female patients with reproductive potential must agree to use highly effective contraceptive methods
15. Patients must give written informed consent to participate in this study before the performance of any study-related procedure.

Exclusion criteria

Phase 2 (MF Expansion - Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Exclusion criteria

Patients who meet any of the following criteria will not be enrolled in the study:,
1. Patients in Cohorts 1B and 2B only: Patients who have had prior splenectomy
2. Patients in Cohorts 1B and 2B only: Patients who have had splenic irradiation within 3 months of starting study drug
3. Current known active or chronic infection with human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C.
4. Patients with active clinically significant infection will not be eligible for enrollment until
recovery for at least 2 weeks prior to the first dose of study drug.
5. Patients with anemia from iron deficiency, B12 and folate deficiencies, hemolytic anemia, or
infection
6. Serum ferritin level < lower limit of normal (LLN) as per institutional standards
7. Patient with a major bleeding event causing a decrease in hemoglobin of >= 2g/dL or leading to transfusion of >= 2 units of packed red cells in the last 6 months prior to enrollment.
8. Patients with Child-Pugh Class B or C
9. Impairment of GI function or GI disease that could significantly alter the absorption of CPI-0610 and/or ruxolitinib, including any unresolved nausea, vomiting, or diarrhea > CTCAE grade 1

10. Impaired cardiac function or clinically significant cardiac diseases, including any of the
following:
a. Acute myocardial infarction or unstable angina pectoris <= 6 months prior to starting study drug
b. QTcF > 500 msec on the screening ECG
c. Uncontrolled clinically significant cardiac arrhythmia
11. Ongoing uncontrolled hypertension despite maximal antihypertensive treatment
12. Any other concurrent severe and/or uncontrolled concomitant medical condition that in the opinion of the investigator could compromise participation in the study or analysis of study data.
13. Systemic anti-cancer treatment (other than ruxolitinib for the Combination Arm [Arm 2]; see inclusion criterion #2) other than hydroxyurea and anagrelide less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of CPI-0610.
14. Any investigational agent less than 2 weeks (or 5 halflives, whichever is longer) before the first dose of CPI-0610
15. Prior treatment with a BET inhibitor
16. Hematopoietic growth factor (granulocyte growth factor, erythropoiesis stimulating agent, thrombopoietin mimetic) or androgenic steroids less than 4 weeks before the first dose of study drug
17. Patients in the Combination Arm (Arm 2) who are receiving treatment with fluconazole.
18. Systemic corticosteroids at daily doses >= 10 mg of oral prednisone or equivalent within 2 weeks before the first dose of study drug.
19. Women who are lactating or pregnant females as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy, obtained within 72 hours prior to the first dose of CPI-0610.
20. Patients unwilling or unable to comply with this study protocol

Phase 2 (MF Expansion - JAKi Naive Arm 3) Exclusion criteria

Patients who meet any of the following criteria will not be enrolled in the study:
1. Prior treatment with a BET inhibitor
2. Patients who have had a prior splenectomy
3. Patients who have had splenic irradiation within 3 months of starting study drug
4. Current known active or chronic infection with HIV, Hepatitis B or Hepatitis C. Screening of patients with serologic testing for these viruses is not required.
5. Patients with active clinically significant infection will not be eligible for enrollment until
recovery for at least 2 weeks prior to the first dose of study drug.
6. Patients with anemia from iron deficiency, B12 and folate deficiencies, hemolytic anemia or infection
7. Serum ferritin level < LLN as per institutional standards

8. Patient with a major bleeding event causing a decrease in Hgb of >= 2g/dL or leading to transfusion of >= 2 units of packed red cells in the last 6 months prior to enrollment.
9. Patients with Child-Pugh Class B or C
10. Impairment of GI function or GI disease that could significantly alter the absorption of CPI0610 and/or ruxolitinib, including any unresolved nausea, vomiting, or diarrhea > CTCAE grade 1
11. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or patients with hypersensitivity to any ingredient in the formulation of ruxolitinib
12. Patients who have or have had PML
13. Impaired cardiac function or clinically significant cardiac diseases, including any of the
following:
a. Acute myocardial infarction or unstable angina pectoris <= 6 months prior to starting study drug
b. QTcF > 500 msec on the screening ECG
c. Uncontrolled clinically significant cardiac arrhythmia
14. Ongoing uncontrolled hypertension despite maximal antihypertensive treatment
15. Any other concurrent severe and/or uncontrolled concomitant medical condition that in the opinion of the investigator could compromise participation in the study or analysis of study data.
16. Systemic anti-cancer treatment other than hydroxyurea and anagrelide less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of CPI-0610.
17. Any investigational agent less than 2 weeks (or 5 halflives, whichever is longer) before the first dose of CPI-0610
18. Hematopoietic growth factor or androgenic steroids less than 4 weeks before the first dose of study drug
19. Patients receiving treatment with fluconazole, or who have received a strong CYP3A4 inhibitor or inducer within 2 weeks prior to the first dose of study drug.
20. Systemic corticosteroids at daily doses >= 10 mg of oral prednisone or equivalent within 2 weeks before the first dose of study drug.
21. Women who are lactating or pregnant females as documented by a serum β-hCG pregnancy test consistent with pregnancy, obtained within 72 hours prior to the first dose of CPI-0610.
22. Patients unwilling or unable to comply with this study protocol

Phase 2 Arm 4 (ET Expansion) Exclusion Criteria

Patients who meet any of the following criteria will not be enrolled in the study:
1. Prior treatment with a BET inhibitor
2. Current known active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
3. Patients with active clinically significant infection will not be eligible

for enrollment until recovery for at least 2 weeks prior to the first dose of study drug.
4. Patients with liver cirrhosis Child-Pugh Class B or C
5. Impairment of GI function or GI disease that could significantly alter the absorption of CPI-0610, including any unresolved nausea, vomiting, or diarrhea > CTCAE Grade 1.
6. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
• Acute myocardial infarction or unstable angina pectoris <= 6 months prior to starting study drug
• QTcF > 500 msec on the screening ECG
• Uncontrolled clinically significant cardiac arrhythmia
7. Ongoing uncontrolled hypertension despite maximal antihypertensive treatment
8. Any other concurrent severe and/or uncontrolled concomitant medical condition that in the opinion of the investigator could compromise participation in the study or analysis of study data.
9. Systemic treatment for ET other than HU and ANA less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of CPI-0610.
10. Any investigational agent less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of CPI-0610.
11. Hematopoietic growth factor or androgenic steroids less than 4 weeks before the first dose of study drug.
12. Systemic corticosteroids at daily doses >= 10 mg of oral prednisone or equivalent within 4 weeks before the first dose of study drug.
13. Have a history of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	24-06-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pelabresib
Generic name:	CPI-0610 monohydrate

Ethics review

Approved WMO Date:	06-11-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-04-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	24-06-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-07-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-05-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-01-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-04-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-04-2021

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-08-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-01-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	30-12-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-03-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-04-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-11-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-12-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000579-34-NL
ClinicalTrials.gov	NCT02158858
CCMO	NL67485.068.18