A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib vs. Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)

Published: 06-05-2014
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The primary objective of this study is:* The primary objective of this clinical trial will be to determine the efficacy of MMB compared with ruxolitinib as measured by splenic response rate at Week 24 (SRR24).The secondary objectives of this study...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Interventional

Summary

ID

NL-OMON44872

Source
ToetsingOnline

Brief title
GS-US-352-0101

Condition

- Bone disorders (excl congenital and fractures)

Synonym
Primary Myelofibrosis or Post-Polycythemia Vera Myelofibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: Double-Blind, Momelotinib, Myelofibrosis

Outcome measures

Primary outcome

For the primary efficacy analysis, non-inferiority of MMB will be evaluated by comparing the SRR24 in the MMB group to 60% of that in the ruxolitinib group at Week 24 with a 2-sided 0.05 level, using the Cochran-Mantel-Haenszel approach to adjust for the stratification factors. If non-inferiority is concluded, then superiority of MMB relative to ruxolitinib will also be evaluated.

Secondary outcome

Secondary endpoints will be response rate of total symptom score at Week 24, rate of RBC transfusion through Week 24, rate of RBC transfusion independence at Week 24, rate of RBC transfusion dependence at Week 24. The primary efficacy hypothesis relating to splenic response rate must be rejected at the 2-sided 0.05 significance level before the efficacy hypotheses for these secondary efficacy endpoints are tested. These 4 secondary endpoints will be tested sequentially

in the order listed, at the 2-sided 0.05 significance level.

If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints. For the first secondary endpoint, response rate in TSS at Week 24, non-inferiority of MMB will be evaluated by comparing the response rate in the MMB group to 67% of that in the ruxolitinib group with a 2-sided 0.05 level, using the CMH approach to adjust for the stratification factors. Superiority of MMB to ruxolitinib of the remaining 3 secondary endpoints will be evaluated subsequently.

Efficacy endpoints will be analyzed based on the ITT and PP analysis sets, with ITT analysis as primary. Categorical variables will be compared using Cochran-Mantel-Haenszel approach to adjust for the stratification factors. Continuous endpoints will be assessed using analysis of covariance (ANCOVA) with baseline values and stratification factors as covariates. Rate of event occurrences will be analyzed using negative binomial model. Time-to-event efficacy endpoints will be assessed using Kaplan-Meier methods and stratified log-rank tests. Overall survival (OS) will be assessed as a safety endpoint.

Based on the safety analysis set, information regarding IP administration, IP compliance, and safety variables will be described and summarized.

Using data from the PK and pharmacodynamic analysis sets, MMB plasma concentrations and pharmacodynamic markers will also be

described and summarized.

Study description

Background summary

See Page 17 of the protocol, section 1.1 Background

Study objective

The primary objective of this study is:
* The primary objective of this clinical trial will be to determine the efficacy of MMB compared with ruxolitinib as measured by splenic response rate at Week 24 (SRR24).

The secondary objectives of this study are:
* To determine the effect of MMB compared with ruxolitinib on the improvement of total symptom score (TSS) at Week 24
* To determine the effect of MMB compared with ruxolitinib on rate of RBC transfusions through Week 24.
* To determine the effect of MMB compared with ruxolitinib on RBC transfusion independence rate at Week 24.
* To determine the effect of MMB compared with ruxolitinib on transfusion dependence rate at Week 24.

Study design

This is a randomized, double-blind, active-controlled study. After the screening period, this study begins with a 24 week double-blind treatment phase. Subjects will be randomized on a 1:1 basis to receive MMB or ruxolitinib as described in protocol Section 5.1. Treatment assignment will be stratified by the following factors:
* Transfusion dependence (yes or no)
* Platelet count (< 100 x 109/L, * 100 x 109/L and * 200 x 109/L, or >200 x 109/L)

The investigational products (IPs) in this study will be MMB or its matching placebo (MMB IP) and ruxolitinib or its matching placebo (ruxolitinib IP). After completion of the double-blind treatment phase, subjects will be eligible to receive open-label MMB in the open-label phase.

Intervention

Patients will randomly be assigned to one of the following treatment arms;

* Group A: About 210 patients (50%) will receive momelotinib once daily together with ruxolitinib placebo twice daily for 24 weeks during the double blinded treatment phase with the option to receive momelotinib treatment for up to three and a half years in open-label afterwards.
* Group B: About 210 patients (50%) will receive ruxolitinib twice daily and momelotinib placebo once daily for 24 weeks during the double blinded treatment phase with the option to receive momelotinib treatment for up to three and a half years in open-label afterwards.

Study burden and risks

For a detailed overview, see Main ICF Netherlands - Section 5: 'What risks or discomforts can be expected?'

POSSIBLE MOMELOTINIB SIDE EFFECTS
In a randomized study of people with myelofibrosis taking momelotinib up to 6 months, the most common adverse (bad or harmful) events in at least 5 out of 100 people were:

* Some patients have reported a feeling of light-headedness and flushing (reddening of the face), low blood pressure, nausea and headache when they take the very first dose of momelotinib (7%). This effect typically lasts for between 30 minutes to 3 hours in most patients and often resolves by the second day of treatment.
* Infections (36%)
o Low levels of white blood cells can increase the risk of infections, such as pneumonia, upper respiratory tract infections, urinary tract infections, infectious colitis (inflammation in your intestine that leads to diarrhea), and localized infections. Tell your study doctor if you develop symptoms such as chills, nausea, vomiting, aches, weakness, or fever. If you develop a fever when your white blood count is low you may need to be hospitalized to receive treatment.
* Kidney problems (i.e. elevation of uric acid [27%] and creatinine [13%]). Elevated kidney tests can indicate kidney damage.
* Liver problems (i.e., elevation of liver enzymes [22 to 25%]). Elevated liver tests can indicate liver damage. Your laboratory values will be monitored closely.
* Low levels of certain blood cells, such as:
o Platelets (cells that help your blood to clot) leading to an increased risk of bleeding or bruising. (19%)
o Red blood cells (cells that carry oxygen to all parts of the body) leading to fatigue, shortness of breath, lightheadedness, an increase in your heart rate and palpitations. You may also experience headaches and chest pain. (14%)
o Transfusions may be required to counteract the effects of a low platelet count or low red blood cell counts.

* Diarrhea (18%), nausea (16%), constipation (10%), abdominal pain (10%), and vomiting (9%).
* Headache (17%)
* Lightheadedness (16%)
* Fatigue (tired feeling) (15%)
* Sensory Neuropathy in the feet and hands (a condition affecting the nerves supplying the arms and legs). You may experience numbness and tingling in these areas (10%)
* Low blood pressure (9%)
* Bruising (8%)
* Shortness of breath (8%)
* Cough (8%)
* Arm or leg pain (7%) and joint pain (6%)
* Fever (7%)
* Flushing (6%)
* Weakness (6%)

Other uncommon, but potentially serious or life-threatening events seen in patients taking momelotinib:
* High blood pressure (4%)
* Heart failure (i.e., the pumping chambers of the heart can*t pump blood efficiently throughout your body) (<1%).
* Jaundice (yellowing of the skin and eyes) or if you contract viral hepatitis infection. In patients who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as momelotinib. This could lead to liver failure or even death. You will be tested for viral hepatitis infection before you are allowed to participate in this study (<1%)
* Adrenal insufficiency. Inability of the adrenal glands (glands located on top of the kidneys) to produce a normal quantity of hormones (<1%).
* Pleural effusion (build-up of fluid between the layers of tissue that line the lungs and chest cavity) (<1%).
* Awkward, uncoordinated walking, double vision, and/or confusion (<1%)

Other Possible Momelotinib Side Effects
In studies with animals given momelotinib for 9 months with about twice the amount of momelotinib in the blood compared to the amount in the human studies, cataracts were observed. Cataracts were not observed at lower doses. In human studies, increased rates of cataracts have not been observed; however, you should tell your Study Doctor if you notice any changes in your vision.

Possibility of interaction with other medications
Momelotinib may affect your body*s reaction to other medicines. In particular, momelotinib may block the ability of a protein called BCRP to transport other medicines into and out of cells.

Other drugs may affect your body*s reaction to momelotinib. In particular,

medicines that are called CYP3A inducers could lead to lower blood levels of momelotinib, and this can decrease the potential benefit to you.

Your study doctor will inform you of any medications that you should not be taking while you are participating in this study.

POSSIBLE RUXOLITINIB SIDE EFFECTS
The medical problems listed below have been observed in people with myelofibrosis who have taken ruxolitinib. These are not all of the possible medical problems seen with ruxolitinib. You will be given a Patient Information leaflet.
* Low levels of certain blood cells, such as:
o red blood cells (cells that carry oxygen to all parts of the body) leading to fatigue, shortness of breath, lightheadedness, an increase in your heart rate and palpitations. You may also experience headaches and chest pain. (82,4%)
o white blood cells (cells that protect you against infection) leading to an increased risk of infection. If you should develop a fever when your white blood count is low, you may need to be hospitalized to receive treatment. (16,6%)
o platelets (cells that help your blood to clot) leading to an increased risk of bleeding or bruising. (69,8%)
o Transfusions may be required to counteract the effects of a low platelet count or low red blood cell count.
* Bruising and/or bleeding (32,6%)
* High blood pressure (31,5%)
* Abnormal liver function test results (27,2%)
* High cholesterol (16,9%)
* Dizziness (15,3%)
* Headache (14,0%)
* Constipation (8,2%)
* Weight gain (7,1%)
* Shingles (Herpes Zoster 6,4*)
* Flatulence (5,2%)
* Infections. You may be at risk for developing a serious infection while taking ruxolitinib. Urinary tract infections, tuberculosis, and higher hepatitis B viral loads have been reported in patients who are receiving ruxolitinib
* A rare disease that causes progressive damage of the brain and skin cancer (non-melanoma) have also been reported in patients who are receiving ruxolitinib
* Tell your study doctor if you develop symptoms such as; chills, nausea, vomiting, aches, numbness, tingling, weakness, paralysis, fever, painful skin rash, unusual pale skin, blisters, difficulty walking, confusion, decline in mental function, or problems with vision.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age * 18 years old
2. Palpable splenomegaly at least 5 cm below left costal margin
3. Confirmed diagnosis of PMF or post-PV/ET MF in accordance with the World Health Organization (WHO) or International
Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria (Appendix 3)
4. Requires myelofibrosis therapy, in the opinion of the investigator
5. High risk OR intermediate-2 risk as defined by the International Prognostic Scoring System (IPSS) for Primary Myelofibrosis (Appendix 6); OR intermediate-1 risk as defined by IPSS and associated with symptomatic splenomegaly, hepatomegaly, anemia (Hgb < 10.0 g/dL), and/or unresponsive to available therapy
6. Acceptable laboratory assessments obtained within 14 days prior to the first dose of IP: Absolute neutrophil count (ANC) > 0.75 x 109/L in the absence of growth factor in the prior 7

days, Platelet count > 50 x 109/L (> 100 x 109/L if AST/SGOT or ALT/SGPT > 2 x ULN) in the absence of platelet transfusion(s) or thrombopoietin mimetics in the prior 7 days, > Peripheral blood blast count < 10%, AST/SGOT and ALT/SGPT * 3 x ULN (* 5 x ULN if liver is involved by extramedullary hematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days), Calculated creatinine clearance of * 45 mL/min, Direct bilirubin * 2.0 x ULN
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
8. Life expectancy of > 24 weeks
9. Negative serum pregnancy test for female subjects (unless surgically sterile or greater than 2 years post-menopausal)
10. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5
11. Females who are nursing must agree to discontinue nursing before the first dose of IP
12. Able to understand and willing to sign the informed consent form

Exclusion criteria

1. Prior splenectomy
2. Splenic irradiation within 3 months prior to the first dose of IP
3. Eligible for allogeneic bone marrow or stem cell transplantation
4. Uncontrolled intercurrent illness including, but not limited to: active uncontrolled infection (subjects receiving outpatient antibacterial treatments and/or antiviral treatments for infection that is under control or as infection prophylaxis may be included in the study); active or chronic bleeding within 4 weeks prior to the first dose of IP; symptomatic congestive heart failure; unstable angina pectoris; uncontrolled cardiac arrhythmia; or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician
5. QTc interval > 450 msec, unless attributed to bundle branch block
6. History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for * 1 year prior to randomization, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for * 5 years
7. Criterion Removed
8. Known positive status for human immunodeficiency virus (HIV)
9. Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier
10. Prior use of a JAK1 or JAK2 inhibitor

11. Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers or dual inhibitors of CYP3A4 and CYP2C9 within 1 week prior to the first dose of IP
12. Use of chemotherapy, immunomodulating therapy, biologic therapy, radiation therapy, or investigational therapy within 4 weeks of the first dose of IP
13. Changes to dose of iron chelator therapy within 14 days of the first dose of IP
14. Unresolved non-hematologic toxicities from prior therapies that are > CTCAE Grade 1
15. Presence of peripheral neuropathy * CTCAE Grade 2
16. Unwilling or unable to undergo a MRI or CT Scan per requirements in Section 6.2.9.2
17. Known hypersensitivity to the IPs, the metabolites, or formulation excipients

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-05-2015
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	06-05-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-10-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-03-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	10-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	30-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2013-002707-33-NL
ClinicalTrials.gov	NCT01969838
CCMO	NL46619.091.14