Extended Access of Momelotinib for Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue neoplasms
Study type	Interventional

Summary

ID

NL-OMON52629

Source
ToetsingOnline

Brief title
SRA-MMB-4365

Condition

- Musculoskeletal and connective tissue neoplasms

Synonym
Primary Myelofibrosis or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Sierra Oncology, Inc.
Source(s) of monetary or material Support: Sierra Oncology;Inc.

Intervention

Keyword: Momelotinib, Myelofibrosis Post-polycythemia Vera, Post-essential Thrombocythemia Myelofibrosis, Primary Myelofibrosis

Outcome measures

Primary outcome

Safety: Safety will be evaluated by the incidence, severity, seriousness, and

causal relationship of AEs.

Efficacy: Survival will be evaluated overall and as leukemia-free (evidence of

leukemic transformation or death).

Pharmacokinetics: None

Secondary outcome

Not applicable

Study description

Background summary

Myeloproliferative neoplasm (MPN) is classified by the World Health Organization (WHO) into seven categories that include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, and MPN unclassifiable {Arber 2016}. Clonal hematopoiesis is a shared feature of the MPNs, with CML characterized by the presence of the Philadelphia chromosome, the product of a reciprocal translocation between the long arms of chromosomes 9 and 22. This translocation results in the formation of the BCR-ABL1 oncogene, the molecular pathogenetic event of CML {Quintas-Cardama 2009}. Subsequently, a single acquired point mutation in the Janus kinase (JAK) 2 gene at codon 617, resulting in the substitution of valine for phenylalanine (JAK2V617F), was identified in

patients with PV (~96%), ET (~50%), and myelofibrosis (~50%) {Baxter 2005, Hasselbalch 2012, James 2005, Kralovics 2005}. Positivity for the JAK2V617F mutation results in constitutive activation of the downstream Signal Transducer and Activator of Transcription (STAT), cytokine hypersensitivity, and formation of erythropoietin-independent erythroid colonies {Bogani 2013}.

Since the discovery of the JAK2V617F mutation in patients with MPN, additional mutations have been identified including signaling mutations that activate the thrombopoietin receptor (MPL). Somatic mutations of CALR, the gene encoding calreticulin, have also been identified in patients with wild type JAK2, as well as mutations in epigenetic regulators of DNA methylation and chromatin structure {Nangalia 2013}.

Myelofibrosis is associated with a characteristic marrow stroma pattern, leukoerythroblastosis, and elevated levels of inflammatory cytokines. Patients may experience anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocytosis, constitutional symptoms, and extramedullary hematopoiesis resulting in hepatosplenomegaly{Harrison 2012}. In a proportion of patients, myelofibrosis may transform into acute leukemia {Abdel-Wahab 2010}. Treatment for PMF, and the phenotypically similar post-PV/ET MF, are principally focused on symptom palliation, with allogeneic stem cell transplantation offering a potential cure for select patients {Patriarca 2008}.

Momelotinib (MMB) is a small molecule JAK1 and JAK2 inhibitor, with good selectivity over other JAK family kinases (JAK3, TYK2) and excellent selectivity over other tyrosine and serine/threonine kinases. MMB also potently inhibits bone morphogenic protein activin A receptor, type 1 (ACRV1) * mediated hepcidin expression that stimulates erythropoiesis {Asshoff 2017}.

Study objective

The primary objective of this study is to provide extended access to momelotinib (MMB) and assess long-term safety in 4 cohorts of subjects who are currently receiving treatment with MMB and have not experienced progression of disease:

* Cohort 1: Study GS-US-352-0101, subjects with primary myelofibrosis (PMF) or post-polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF)
* Cohort 2: Study GS-US-352-1214, subjects with PMF or post-PV/ET MF
* Cohort 3: Study GS-US-352-1154, subjects with PMF or post-PV/ET MF
* Cohort 4: Study SRA-MMB-301, subjects with PMF or post-PV/ET MF

The secondary objective is to assess overall survival (OS) and leukemia-free survival (LFS) in all subjects

Study design

This is an open-label, extended-access, long-term safety and survival study for subjects with PMF, post-PV MF, or post-ET MF whose disease has not progressed and who have tolerated MMB treatment while enrolled in a previous MMB clinical trial. Subjects in all cohorts continuing MMB treatment will discontinue MMB tablets from the previous study and initiate MMB tablets in this study at the same dose they were receiving in the previous study.

After the last dose of study drug, follow-up for assessment for survival and leukemic transformation will be every 12 weeks for all subjects up to approximately 7 years after the first dose in a prior study or until the study ends, unless the subject dies, withdraws consent, or is lost to follow-up.

Additional subjects who discontinued treatment in study SRA-MMB-301 may enroll for survival follow-up only.

Intervention

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

Study burden and risks

MOMELOTINIB (MMB) COMMON ADVERSE EVENTS
Momelotinib is an experimental drug that is being studied in people with myelofibrosis.
There are risks involved with taking MMB.
The information below is based on the reported side effects of momelotinib which occurred in at least 5 out of 100 people during the first 24 weeks of three randomized clinical trials involving approximately 450 people with myelofibrosis.

Side effects and frequency in 448 patients:
* Infections (all types; including COVID-19) (40%)
* Diarrhea (23%)
* Low platelet count in the blood (21%)
* Nausea (17%)
* Low red blood cells (14%)
* Headache (13%)
* Dizziness (13%)
* Fatigue (tiredness) (12%)
* Abdominal pain (11%)
* Weakness (11%)
* Constipation (10%)
* Cough (10%)
* Nerve damage (numbness, tingling, pain, weakness) (9%)
* Fever (9%)
* Shortness of breath (9%)

* Itchy skin (9%)
* Vomiting (8%)
* Joint pain (8%)
* Weight loss (7%)
* Swelling in arm or leg (7%)
* Prickling or burning sensation (7%)
* Low white blood cell count (6%)
* Low blood pressure (6%)
* Bruising (6%)
* Decreased appetite (6%)
* Elevation of blood uric acid (6%)
* Elevation of blood creatinine (6%)
* Pain in hands or feet (5%)
* Nosebleed (5%)
* High blood pressure (5%)
* Some subjects have reported a feeling of dizziness or light-headedness, flushing (reddening of the face), low blood pressure, nausea, or headache when they take the very first dose of momelotinib (6.5% of subjects experienced this adverse event in one randomized trial). This can occur up to 3 hours after the first dose of study medication, and in most subjects resolves by the second day.
* Momelotinib may increase the likelihood of contracting COVID-19. Two of the patients who got COVID-19 and died were in this extended access study and six who died were in a different momelotinib trial that is ongoing. These subjects contracted COVID-19 before COVID-19 vaccines were available. It is important that patients follow their doctor*s advice on COVID-19 vaccination and treatment.

If patients experience any of the following conditions (which occurred in previous momelotinib study subjects at the frequency indicated below) they should contact their study doctor immediately.
* High blood pressure (9%)
* Heart failure (i.e., the pumping chambers of the heart can not pump blood efficiently throughout the body (<2%). Symptoms patients might feel if this were to happen include: shortness of breath, swelling in their legs, feeling tired or weak, feeling that their heart is beating fast, wheezing, and/or coughing which could include white or pink blood-tinged phlegm.
* Jaundice (yellowing of the skin and eyes) or if patient contracts 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 the immune system, such as momelotinib. This could lead to liver failure or even death.
* Pleural effusion (build-up of fluid between the layers of tissue that line the lungs and chest cavity) (<1%). Symptoms patients might feel if this were to happen include: chest pain, dry cough, fever, difficulty breathing when lying down, shortness of breath, and/or difficulty taking deep breaths.
* Awkward, uncoordinated walking, double vision, and/or confusion.

Possibility of interaction with other medications:
Momelotinib may affect patient's body*s reaction to other medicines. In particular, momelotinib may block the ability of a protein called BCRP (Breast Cancer Resistance Protein) to transport some other medicines into and out of cells.

Other drugs may affect the body of the patient'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 the patient.

The patient's study doctor will inform him/her of any medications that he/she should not be taking while they are taking the study drug.

UNKNOWN/UNEXPECTED RISKS AND DISCOMFORTS
There are adverse events that are not known or happen rarely when subjects take this study drug. The patients will be told of any new information that might cause them to change their mind about continuing to take part in this study.

As with any new drug, extra care has to be taken to monitor the side effects that are not always obvious. If patient's feel any side effects or unusual symptoms, they should notify their study doctor as soon as possible at the phone number listed in the ICF.

PREGNANCY AND BREAST-FEEDING
Female participants:

Because the effects of the momelotinib on an unborn baby or a nursing infant are not known, any female who is pregnant or breast feeding an infant will not be enrolled in this study for treatment with momelotinib. Information from animal studies suggests that momelotinib taken at doses resulting in similar or higher exposures than the doses in this study may cause fetal death or reduced body weight, or possible death to the baby through exposure to momelotinib through breast milk. The female patient should not nurse a baby while taking study treatment and for 30 days after the last dose of study drug because of the risk that the baby might be exposed to momelotinib that comes out of her body into the breast milk.

If a female patient becomes pregnant or suspects that she has become pregnant while she is taking the study drug or within 30 days after the last dose of study drug, she must stop taking the study drug and notify her study doctor immediately. She will be discontinued from the study. The study doctor will request to track her pregnancy and will report the pregnancy to the study sponsor.

In addition, it is important to prevent pregnancy during the study. For this study, a woman is considered to be of childbearing potential unless she meets

certain criteria that will be reviewed by the study doctor. If the patient is a sexually active female of childbearing potential, it is required that she uses highly effective contraceptive measures from the screening visit, while she is taking the study drug, and for at least 30 days after the last dose of study drug.

Highly effective contraceptive measures in this study are:
Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject*s preferred and usual lifestyle; OR
* intrauterine devices (IUD) with a failure rate of < 1% per year
* tubal sterilization
* intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
* vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after the procedure
* one barrier method [diaphragm with spermicide or cervical cap with spermicide or male condom (with or without spermicide)] combined with one hormonal method [oral contraceptive pill (estrogen and progesterone or progesterone only) or transdermal contraceptive patch or injectable progesterone or implants of levonorgestrel or contraceptive vaginal ring]
* Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

Other not yet identified adverse events could occur to the female patient, her embryo or fetus should she become pregnant during the time she participates in the study or after she has completed the study.

Information from animal studies suggests that MMB at doses that result in blood levels approximately 40 fold higher than the recommended human dose causes decreased female fertility.

Male participants:

Male participants should share this information with the their partner if it is appropriate.

The effects of momelotinib are not known on the developing fetus (unborn baby) in humans. It is very important that the patient does not cause others to become pregnant and avoid sperm donation while he is taking the study drug and for at least 90 days after the last dose of study drug. Not having sex is the only certain way to prevent pregnancy.

If a male patient chooses to have sex with a female partner of childbearing potential, he must use condoms during treatment and until 90 days following discontinuation of the study drug. Additional contraception recommendations

should also be considered if the female partner is not pregnant. Male participants should speak with their study doctor to determine the best method of birth control for them and their female partner during this study.

If a male patient causes his female sex partner to become pregnant while he is taking the study drug or within 90 days after his last dose of study drug, the study drug may harm an unborn baby. If a male patient has a female partner who becomes pregnant or suspects that she has become pregnant while he is in the study or within 90 days after his last dose of study drug, the male patient will be required to notify his study doctor immediately. As the risk to his partner and unborn baby is not known, it is recommended for his female partner to receive appropriate prenatal care. Upon agreement, the female partner will be asked to sign a consent form to allow disclosure of medical information related to pregnancy. The male patient's study doctor may need to disclose to the female partner details of this study and him taking part in it. The study sponsor and the study doctor will not be responsible for the costs related to the pregnancy, delivery, or care of the child.

Information from animal studies also suggests that momelotinib at doses that result in blood levels approximately 50 fold higher than the recommended human dose causes reduced male fertility, sperm counts, and sperm movement.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?
There is no guarantee that the patient will receive personal benefit from taking part in this study. The study drugs are not expected to cure the patient's Myelofibrosis. However, clinical research study such as this is a way for doctors to provide extended access of MMB for patient who have not experienced recurrence of disease while receiving treatment with MMB.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligibility Criteria for Subjects Continuing MMB Treatment:
1) Currently enrolled in Studies GS-US-352-0101, GS-US-352-1214, GS-US-352-1154, or SRA-MMB-301
2) Did not discontinue treatment with MMB for any reason while enrolled in Studies GS-US-352-0101, GS-US-352-1214, GS-US-352-1154, or SRA-MMB-301
3) Negative serum or urine pregnancy test is required for female subjects of childbearing potential as described in Appendix 3
4) 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 3
5) Any Grade 3 or 4 (Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) non-hematologic toxicity in the prior study that the investigator considers related to previous MMB use must have resolved, reverted to Grade 1, or reverted to baseline within the 30 days from the last MMB administration to Day 1 of this study
6) Any adverse event (AE) requiring MMB interruption during the prior study must have resolved, reverted to Grade 1, or reverted to baseline within the 30 days from last MMB administration to Day 1 of this study
7) Ability and agreement to attend protocol-specified visits at the study site
8) Able to comprehend and willing to sign the informed consent form

Eligibility Criteria for Subjects Enrolling for Survival Follow-Up Only:
1) Participating in survival follow-up after discontinuation of treatment in study SRA-MMB-301

Exclusion criteria

1) Known hypersensitivity to MMB, its metabolites, or formulation excipients
2) Incomplete recovery from major surgery prior to Day 1 of this study
3) Pregnant or lactating females
4) Presence of * Grade 3 (CTCAE Version 4.03) peripheral neuropathy
5) Known positive status for human immunodeficiency virus (HIV)
6) Known chronic active or acute viral hepatitis A, B, or C infection

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-05-2019
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Momelotinib
Generic name:	Momelotinib

Ethics review

Approved WMO

Date:	26-07-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-01-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-06-2019
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:	03-03-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-04-2020

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2022
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:	18-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-11-2022
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	EUCTR2017-004350-42-NL
ClinicalTrials.gov	NCT03441113
CCMO	NL64867.068.18