An Open-Label Phase 2 Study of Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone Following Ruxolitinib in Subjects With Myelofibrosis

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Primary objectiveTo evaluate preliminary efficacy of itacitinib (INCB039110) on spleen volume reduction (SVR) from baseline at Week 24 in the 2 following cohorts of MF subjects:- Cohort A: in combination in subjects with ruxolitinib low dose (less...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Interventional

Summary

ID

NL-OMON48854

Source
ToetsingOnline

Brief title
INCB_39110-209

Condition

- Anaemias nonhaemolytic and marrow depression

Synonym
excessive scar tissue in the bone marrow, Myelofibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Corporation
Source(s) of monetary or material Support: Incyte Corporation

Intervention

Keyword: Itacitinib (INCB039110), Myelofibrosis, Ruxolitinib (Jakavi)

Outcome measures

Primary outcome

Change and percentage change in SVR as measured by magnetic resonance imaging [MRI] (computed tomography [CT] scan in subjects who are not candidates for MRI or when MRI is not readily available) at Week 24 when compared with baseline.

Secondary outcome

- Safety and tolerability through assessment of frequency, severity, and duration of adverse events (AEs); changes in clinical safety assessments; and changes in clinical laboratory parameters.
- Change and percentage in SVR from baseline through Week 12 as measured by MRI (or CT scan in applicable subjects).
- Change and percentage change on spleen length reduction from baseline through Week 12 and Week 24 as measured by palpation.
- Change and percentage change in Total Symptom Score (TSS) from baseline through Week 12 and Week 24 as measured by the Myelofibrosis Symptom Assessment Form version 2.0 (MFSAF v2.0) symptom diary and by the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF).
- Patient Global Impression of Change score at each visit where the variable is measured.

- Number of subjects with responses according to the 2013 IWG-MRT consensus

criteria for treatment response.

- Calculation of the PK parameters such as AUC, CL/F, Cmax, and tmax along with

summarization of the observed concentration data by timepoint will be performed

for both ruxolitinib and itacitinib.

Study description

Background summary

Despite statistically significant improvements in the signs and symptoms of MF and overall survival rates compared to placebo or best available therapy in the registration studies, there are patients for whom ruxolitinib monotherapy does not provide an adequate and / or sustained response.

Itacitinib is being studied as a treatment for patients with MF. It may have less potency than other drugs to cause side effects such as anemia and low platelets, and in previous clinical studies it has been shown to reduce the size of the spleen and control the symptoms of MF. This makes tacitinib a potential second-line therapy option

Study objective

Primary objective
To evaluate preliminary efficacy of itacitinib (INCB039110) on spleen volume reduction (SVR) from baseline at Week 24 in the 2 following cohorts of MF subjects:
- Cohort A: in combination in subjects with ruxolitinib low dose (less than 20mg daily).
- Cohort B: as monotherapy in subjects who progressed (per revised European LeukemiaNet [ELN] 2013 response criteria for MF) after initial reduction in spleen on ruxolitinib or discontinued for hematologic toxicities.

Secondary objective
- To evaluate preliminary safety and tolerability of itacitinib alone.
- To evaluate preliminary safety and tolerability of itacitinib in combination with ruxolitinib.
- To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib on SVR from baseline at Week 12.
- To evaluate preliminary efficacy of itacitinib alone or in combination with

ruxolitinib on spleen length reduction from baseline at Week 12 and Week 24.
- To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib with respect to MF symptoms at Week 12 and Week 24.
- To evaluate preliminary efficacy of itacitinib using International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria.
- To assess the pharmacokinetics (PK) of itacitinib and ruxolitinib.

Study design

This is an open-label Phase 2 study with 2 cohorts:
- Cohort A: MF subjects who are tolerating a ruxolitinib dose of less than 20 mg daily will receive a combination of the JAK1 inhibitor itacitinib at the dose of 200 mg once daily (QD) and the JAK1/2 inhibitor ruxolitinib.
- Cohort B: MF subjects who progressed after initial reduction in spleen with ruxolitinib treatment or discontinued for hematologic toxicities will receive treatment with JAK1 inhibitor itacitinib alone at the dose of 600 mg QD.

Subjects will continue study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment are met. Subjects who are receiving benefit will continue receiving study treatment until withdrawal criteria are met.

All subjects will be followed for safety (eg, reporting of AEs and serious AEs) 30 to 35 days after last dose of study treatment.

Intervention

A total of 42 patients worldwide (10 patients in the Netherlands) are treated in cohort A or B.

Itacitinib is formulated as 100 mg sustained-release tablet. Itacitinib will be administered orally QD in the morning on an outpatient basis as follows:
- Cohort A only: 200 mg QD, without regard to food, for the combination treatment with ruxolitinib.
- Cohort B only: 600 mg QD, without regard to food, for the monotherapy treatment.

Reference Therapy, Dosage, and Mode of Administration:
- Cohort A only: Ruxolitinib will be administered orally, twice daily (BID), approximately 12 hours apart using the stable dose of less than 20 mg daily established before entering the study.
- Cohort B only: Not applicable.

Study burden and risks

Subjects will have a regularly scheduled study visit at screening, baseline,

Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 and every 12 weeks thereafter if continuing on treatment, where assessments, including urine samples (for pregnancy test, if applicable), blood samples and spleen measurements, will be obtained. All laboratory parameters (serology, lipid profile, urinalysis, blood chemistry, hematology, and coagulation) will be assessed using local laboratories. Blood pharmacodynamic and PK samples will be collected and analyzed by the sponsor or sponsor's designee.
Additional laboratory assessments may be performed at investigator's discretion, including following changes in dose, or if laboratory parameters are at Grade 3 or Grade 4 levels based on the CTCAE v4.03.

Every visit takes 1-8 hours. This depends on the examinations that are scheduled.

Subjects will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline, at Week 12 and Week 24, and every 12 weeks thereafter. Computed tomography scan will be substituted for subjects who are not candidates for MRI or when MRI is not readily available. A bone marrow test will take place during screening, week 24 and then every 12 weeks if they continue with the treatment (the bone marrow at screening may be fulfilled with a recent biopsy (if available)).

Patient Global Impression of Change questionnaire will be completed at each study visit from Week 4. Determination of spleen length below the left costal margin will be measured by palpation at each study visit using a flexible ruler. They will also have 2 ECG (screening and end of treatment)

Subjects will complete an electronic symptom diary (MFSAF v2.0) daily from baseline through the Week 24 visit (total of 25 weeks) and they will also complete the MPN-SAF at baseline; at Weeks 12 and 24; and every 12 weeks thereafter.

Please refer to the IB and patient information regarding side effects that are expected and for other risks and discomforts.

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

Cohort A only
• Receiving ruxolitinib dose of less than 20 mg daily with no dose increase or no dose modification in the last 8 weeks before screening visit.
Cohort B only
• Must have had initial reduction in spleen on ruxolitinib treatment (response is defined by any spleen length or volume reduction, by palpation or MRI/CT assessment, from baseline while on previous ruxolitinib treatment per IWG-MRT ELN 2013 guidelines):
- Followed by documented evidence of progression in spleen length or volume OR
- Discontinued ruxolitinib for hematologic toxicities, after the initial reduction in spleen length or volume.
All subjects
• Men and women, aged 18 years or older.
• Confirmed diagnosis of PMF, PPV-MF, or PET-MF according to revised WHO 2016 criteria.
• Must have palpable spleen of >= 5 cm below the left subcostal margin on physical examination at the screening visit. (If spleen is not palpable due to body habitus, spleen enlargement must be documented by other means [eg, ultrasound or MRI] and study sponsor medical monitor be contacted for acceptance).
• ECOG performance status of 0, 1, or 2.
• Screening bone marrow biopsy specimen available or willingness to undergo a

bone marrow biopsy at screening/baseline; willingness to undergo bone marrow biopsy at Week 24.
• Life expectancy of at least 24 weeks.
• Willingness to avoid pregnancy or fathering children based on the following criteria:
- Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR >= 12 months of amenorrhea and at least 50 years of age).
- Woman of childbearing potential who has a negative serum pregnancy test at screening and negative urinary test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
- Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

Exclusion criteria

All subjects
• Lack of recovery from all toxicities from previous therapy (except ruxolitinib) to Grade 1 or better.
• Previous treatment with itacitinib or JAK1 inhibitors (JAK1/JAK2 inhibitor ruxolitinib is permitted).
• Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
• Unwillingness to be transfused with blood components.
• Recent history of inadequate bone marrow reserve as demonstrated by the following:
- Platelet count < 50 × 109/L in the 4 weeks before screening or platelet transfusion within 8 weeks before screening.
- Absolute neutrophil count levels < 0.5 × 109/L in the 4 weeks before screening.
- Peripheral blood blast count of > 10% at the screening or baseline hematology assessments.
• Inadequate liver function at screening and baseline visits as demonstrated by the following:
- Direct bilirubin >= 2.0 × the upper limit of laboratory normal (ULN). (NOTE: direct bilirubin may be assumed to be within limits if total bilirubin is <= 2.0 × ULN).
- Alanine aminotransferase or aspartate aminotransferase > 2.5 × ULN.
• Inadequate renal function at screening and baseline visits as demonstrated by creatinine clearance < 40 mL/min measured or calculated by Cockroft-Gault

equation, or glomerular filtration rate < 40 mL/min/1.73 m2 as calculated using the Modification of Diet in Renal Disease formula.
• Active bacterial, fungal, parasitic, or viral infection that requires therapy. Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
• Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of reactivation: HBV DNA and HCV RNA must be undetectable. Subjects cannot be positive for hepatitis B surface antigen or anti-hepatitis B core antibodies. Subjects who have positive anti-HBs as the only evidence of prior exposure may participate in the study provided that there is both 1) no known history of HBV infection and 2) verified receipt of hepatitis B vaccine.
• Known human immunodeficiency virus infection.
• Clinically significant or uncontrolled cardiac disease, including unstable angina; acute myocardial infarction within 6 months of Day 1 of study drug administration; New York Heart Association Class III or IV congestive heart failure; and arrhythmia requiring therapy unless approved by medical monitor/sponsor.
• Active invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin, completely resected intraepithelial carcinoma of the cervix, and completely resected papillary thyroid and follicular thyroid cancers. Subjects with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
• Splenic irradiation within 6 months before receiving the first dose of itacitinib.
• Use of any prohibited concomitant medications.
• Active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
• Use of any potent/strong cytochrome P450 3A4 inhibitors within 14 days or 5 half-lives (whichever is longer) before the first dose of itacitinib or anticipated during the study.
• Use of concomitant treatment of fluconazole at a dose > 200 mg (for ruxolitinib subjects treated in Cohort A only).
• Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
• Currently breastfeeding or pregnant.
• Inability to comprehend or unwilling to sign the informed consent form.
• Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

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):	03-06-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Itacitinib

Ethics review

Approved WMO

Date:	28-06-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	13-12-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	19-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-04-2019
Application type:	Amendment
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:	15-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-02-2020
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	EUCTR2017-005109-11-NL
ClinicalTrials.gov	NCT03144687
CCMO	NL65688.068.18