A Study of Fedratinib in Japanese Subjects With DIPSS (Dynamic International Prognostic Scoring System)- Intermediate or High-risk Primary Myelofibrosis (PMF), Post-polycythemia Vera Myelofibrosis (Post-PV MF), or Post-essential Thrombocythemia Myelofibrosis (Post-ET MF)

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04446650	RECRUITING	JUNE 25, 2020	JULY 23, 2021

STUDY DESCRIPTION

Brief Summary

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements. This is a Phase 1/2 multicenter, single arm, open-label study in Japanese subjects with DIPSS intermediate or high-risk PMF, post-PV or post-ET MF. The study consists of 2 parts: Phase 1 part to determine safety and tolerability and a RP2D. The Phase 1 portion of the study will explore one or more drug doses for fedratinib (300 mg and 400 mg) using a mTPI-2 design. Following completion of dose escalation and determination of MTD and/or a RP2D, the study will progress into the Phase 2 part to further evaluate the efficacy and safety. The study will consist of 3 periods: a Screening Period, a Treatment Period including a 30-day follow-up after last dose visit and a survival follow-up period.

Condition or Disease: Primary Myelofibrosis

Intervention/treatment: Drug: Fedratinib

Phase: Phase 1/Phase 2

DETAILED DESCRIPTION

N/A

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 31 participants

Intervention Model : Single Group Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase 1/2, Multicenter, Single-arm, Open-label Study to Evaluate the Efficacy and Safety of Fedratinib in Japanese Subjects With DIPSS (Dynamic International Prognostic Scoring System)-Intermediate or High-risk Primary Myelofibrosis (PMF), Post-polycythemia Vera Myelofibrosis (Post-PV MF), or Post-essential Thrombocythemia Myelofibrosis (Post-ET MF)

Actual Study Start Date: October 2020

Estimated Primary Completion Date: November 2022

Estimated Study Completion Date: December 2024

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Fedratinib Administration The fedratinib dose is 300 or 400 mg/day PO (3 or 4 x 100 mg capsules) to be self-administered orally once daily continuously on an outpatient basis, preferably together with food during an evening meal, the same time each day.	Drug: Fedratinib Oral

OUTCOME MEASURES

Primary Outcome Measures:
1. Maximum Tolerated Dose (MTD) [Time Frame: Up to Cycle 1 (each cycle is 28 days)]
is the highest dose that causes DLTs in not more than 33% of the subjects treated with fedratinib in the first cycle with at least 3 evaluable subjects treated at this dose.
2. Recommended Phase 2 dose (RP2D) [Time Frame: Up to Cycle 1 (each cycle is 28 days)]
is a recommended Phase 2 dose that is determined as safe and tolerable by the Safety Review Committee based on the data from the first cycle with at least 3 evaluable subjects treated at each dose of the Phase 1 part.
3. Response Rate (RR) [Time Frame: Up to Cycle 6 (each cycle is 28 days)]
Proportion of subjects who have ≥ 35% SVR at end of Cycle 6 from baseline

Secondary Outcome Measures:
1. Adverse Events (AEs) [Time Frame: From ICF signature up until 30 days after last dose of IP]
An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE.
2. Pharmacokinetics - Cmax [Time Frame: Up to Cycle 1 (each cycle is 28 days)]
Peak (maximum) plasma concentration of the drug
3. Pharmacokinetics - AUC [Time Frame: Up to Cycle 1 (each cycle is 28 days)]
Area under the plasma concentration curve

4. Pharmacokinetics - Tmax [Time Frame: Up to Cycle 1 (each cycle is 28 days)]
Time to maximum plasma concentration
5. Symptom response rate (SRR) [Time Frame: Up to Cycle 6 (each cycle is 28 days)]
Proportion of subjects with ≥ 50% reduction in total symptom scores measured by MFSAF version 2.0 (Appendix C) at end of Cycle 6
6. Spleen volume response rate 25 (RR25) [Time Frame: Up to Cycle 6 (each cycle is 28 days)]
Proportion of subjects who have ≥ 25% reduction in spleen volume at the end of Cycle 6
7. Spleen Response Rate by Palpation (RRP) [Time Frame: Up to Cycle 6 (each cycle is 28 days)]
Proportion of subjects who have ≥ 50% reduction in spleen size by palpation at end of Cycle 6
8. Duration of spleen volume response (DR) [Time Frame: Up to 4 years]
Duration of ≥ 35% SVR by MRI/CT
9. Duration of spleen response by palpation (DRP) [Time Frame: Up to 4 years]
Time from the first documented palpable spleen response, according to the IWGMRT 2013 to the time of the first documented loss of response according to the IWG-MRT 2013.
10. Duration of symptoms response (DSR) [Time Frame: Up to 4 years]
Duration of ≥ 50% reduction in total symptom scores measured by MFSAF version 2.0
11. Spleen and Disease Progression Free Survival (SDPFS) [Time Frame: Up to 4 years]
Time from the start of fedratinib treatment to death due to any reason or disease progression (modified IWGMRT 2013 including ≥ 25% increase in spleen volume by MRI/CT)
12. Gastrointestinal adverse events [Time Frame: From ICF signature to the 30-day follow-up after last dose of IP]
Incidence of subjects with Grade 3 or higher Gastrointestinal events (nausea, diarrhea, or vomiting) according to CTCAE v5.0
13. Wernicke encephalopathy (WE) events [Time Frame: From ICF signature to the 30-day follow-up after last dose of IP]
Occurrence of confirmed Wernicke encephalopathy events
14. Overall Survival (OS) [Time Frame: Up to 4 years]
Time from the start of fedratinib treatment to death due to any reason

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ELIGIBILITY CRITERIA

Ages Eligible for Study: 20 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Subjects must satisfy the following criteria to be enrolled in the study:
1. Subject is ≥ 20 years of age at the time of signing the informed consent form (ICF)
2. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1 or 2
3. Subject has diagnosis of Primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-ET or post-Polycythemia vera (PV) Myelofibrosis (MF) according to the IWG-MRT 2007 criteria, confirmed by the most recent local pathology report
4. Subject has a Dynamic International Prognostic Scoring System (DIPSS) Risk score of Intermediate-1 with symptom(s), Intermediate-2 or High
5. Subject has a measurable splenomegaly during the screening period as demonstrated by spleen volume of ≥ 450 cm3 by magnetic resonance imaging (MRI) or computed tomography (CT) scan or by palpable spleen measuring ≥ 5 cm below the left costal margin.
6. Subject must meet at least one of the following criteria of (a or b).
Note: reason to discontinue ruxolitinib treatment (lack of efficacy and/or intolerability, etc) and physician decision as to the study participation as being appropriate should be recorded in the case report form:
1. Previously received ruxolitinib treatment for PMF or post-PV MF or post-ET MF for at least 14 days (exposure of < 14 days is allowed for subjects who discontinued ruxolitinib due to intolerability or allergy). 2. Never received ruxolitinib treatment and is expected to derive clinical benefit from this study participation based on the clinical judgement of the Investigator Only those subjects who previously received ruxolitinib treatment are eligible for the Phase 1 part of the study to avoid overestimating tolerability of fedratinib. 7. Subject must have treatment-related toxicities from prior therapy resolved to Grade 1 or pretreatment baseline before start of last therapy prior to starting the fedratinib treatment. 8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted. 9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements. 10. A female of childbearing potential (FCBP) must: 1. Have 2 negative pregnancy tests as verified by the Investigator during screening prior to starting fedratinib treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of fedratinib treatment. This applies even if the subject practices true abstinence* from heterosexual contact. 2. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use and be able to comply with highly effective contraception** without interruption, -14 days prior to starting investigational product, during the fedratinib treatment (including dose interruptions), and for 30 days after discontinuation of fedratinib treatment. 3. If breastfeeding, agree to stop breastfeeding prior to the participation in the study and not to resume breastfeeding for at least 30 days after treatment discontinuation of the fedratinib treatment. Note: A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy or amenorrhea due to other medical reasons does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). 11. A male subject must: Practice true abstinence (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 30 days following fedratinib discontinuation, or longer if required by local regulations, even if he has undergone a successful vasectomy. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception). Agreement to use highly effective methods of contraception that alone or in combination resulting in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly throughout the course of the study. Such methods include combined (estrogen and progestogen containing) hormonal contraception (oral), progestogen-only hormonal contraception associated with inhibition of ovulation (oral), placement of an intrauterine device, placement of an intrauterine hormone-releasing system, bilateral tubal occlusion, and vasectomized partner. Exclusion Criteria: The presence of any of the following will exclude a subject from enrollment: 1. Any of the following laboratory abnormalities: 1. Platelets < 50 x 109/L (without platelet transfusion) 2. Absolute neutrophil count (ANC) 100 x 109/L
4. Myeloblasts ≥ 5 % in peripheral blood
5. Estimated creatinine clearance 1.5 x upper limit of normal
7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN)
8. Total bilirubin > 1.5 x ULN, subject's total bilirubin between 1.5 - 3.0 x ULN are eligible if the direct bilirubin fraction is 10 mg/day prednisone or equivalent. Subjects who have had prior exposure to hydroxyurea (eg, Hydrea) in the past may be enrolled into the study as long as it has not been administered within 14 days prior to starting the fedratinib treatment.
10. Subject on treatment with myeloid growth factor (eg, granulocyte-colony stimulating factor [G-CSF]) within 14 days prior to starting the fedratinib treatment
11. Subject with previous exposure to JAK inhibitor(s) other than ruxolitinib treatment
12. Subject has received ruxolitinib within 14 days prior to starting the fedratinib treatment
13. Subject on treatment with aspirin with doses > 150 mg daily
14. Subject with major surgery within 28 days prior to starting the fedratinib treatment
15. Subject with diagnosis of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, non-alcoholic steatohepatitis)
16. Subject with prior malignancy other than the disease under study unless the subject has not required treatment for the malignancy for at least 3 years prior to the start of fedratinib treatment. However, subject with the following history/concurrent conditions provided successfully treated may enroll: non-invasive skin cancer, in situ cervical cancer, carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system), or is free of disease and on hormonal treatment only
17. Subject with uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4)
18. Seropositive for and with evidence of active viral infection with hepatitis B virus (HBV)
1. Subject who are hepatitis B surface antigen (HBsAg) negative but HB core anti-body (HBcAb) positive or HBsAb positive are eligible in case HBV viral deoxyribonucleoside (DNA) negative
2. Subject who had HBsAg positive but show non-detectable viral DNA for at least 6 months prior to starting the fedratinib treatment where appropriate anti-viral treatment should have been given/considered to prevent HBV reactivation based on the standard practice are eligible
3. Subject who are seropositive because of hepatitis B virus vaccine are eligible
19. Seropositive for and with active viral infection with hepatitis C virus (HCV)
• Subject who had hepatitis C but show no detectable HCV viral ribonucleotide (RNA) for at least 6 months prior to starting the fedratinib treatment are eligible.
20. Evidence of human immunodeficiency virus (HIV) infection.
21. Subject with serious active infection
• Additionally, subject with history of active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 4 weeks prior to screening, unless the subject has adequately recovered from coronavirus disease (COVID) symptoms and related complications as per investigator's discretion, and following a discussion with the Medical Monitor.
22. Subject with presence of any significant gastric or other disorder that would inhibit absorption of oral medication
23. Subject is unable to swallow capsule
24. Subject with any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
25. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if the subject were to participate in the study
26. Subject has any condition that confounds the ability to interpret data from the study
27. Subject with participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to starting the fedratinib treatment
28. Subject with a life expectancy of less than 6 months from the planned first dose of fedratinib.

CONTACTS AND LOCATIONS

Contacts

Contact: Recruiting sites have contact information. Please contact the sites directly. If there is no contact information, please email: Clinical.Trials@bms.com
Contact: First line of the email MUST contain NCT # and Site #.

Locations

Japan	Aomori Prefectural Central Hospital	Aomori
Japan	Juntendo University Hospital	Bunkyo-ku
Japan	Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital	Bunkyo-ku
Japan	University of Yamanashi Hospital	Chuo
Japan	Kyushu University Hospital	Fukuoka
Japan	Tokai University Hospital	Isehara City, Kanagawa
Japan	Kameda General Hospital	Kamogawa
Japan	Gunma University Hospital	Maebashi
Japan	University of Miyazaki Hospital	Miyazaki
Japan	Japanese Red Cross Nagasaki Genbaku Hospital	Nagasaki-shi
Japan	Kindai University Hospital	Osaka-Sayama
Japan	Osaka City University Hospital	Osaka
Japan	Sapporo Hokuyu Hospital	Sapporo
Japan	NTT Medical Center Tokyo	Shinagawa-ku, Tokyo
Japan	Tokyo Women's Medical University Hospital	Shinjuku City
Japan	Tokyo Medical University Hospital	Shinjyuku-ku

Sponsors and Collaborators

Celgene

Investigator

Study Director :	Kiyoshi Okazuka, MD	Bristol-Myers Squibb K.K.

MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT04446650
Other Study ID Numbers :	FEDR-MF-003, U1111-1252-2577
First Posted :	June 25, 2020
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Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Yes
Plan Description:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Supporting Materials:	Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), Clinical Study Report (CSR), Analytic Code
Time Frame:	See Plan Description
Access Criteria:	See Plan Description
URL:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No
Keywords provided by Celgene:	*Japanese* *Myelofibrosis Fedratinib*

Additional relevant MeSH terms :	*Thrombocythemia, Essential* *Thrombocytosis* *Polycythemia*	*Primary Myelofibrosis* *Polycythemia Vera*