A Safety Trial of Fedratinib in Subjects With DIPSS, Intermediate or High-Risk Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis and Previously Treated With Ruxolitinib With Concomitant Luspatercept for Subjects With Anemia

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT03755518	RECRUITING	NOVEMBER 28, 2018	AUGUST 23, 2021

STUDY DESCRIPTION

Brief Summary

This is Single-Arm, Open-Label Efficacy and Safety Trial of Fedratinib in 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) and Previously Treated with Ruxolitinib including a Sub-study with concomitant Luspatercept for subjects with anemia. The primary objective of the main study is to evaluate the percentage of subjects with at least a 35% reduction in spleen size and one of the secondary objectives is to evaluate the safety of fedratinib. The primary objective of the sub-study is to evaluate the safety and tolerability of Luspatercept when administered concomitantly with Fedratinib.

Condition or Disease: Myelofibrosis
Post-Polycythemia Vera
Primary Myelofibrosis

Intervention/treatment: Drug: FEDRATINIB
Drug: Luspatercept

Phase: Phase 3

DETAILED DESCRIPTION

This is Single-Arm, Open-Label Efficacy and Safety Trial of Fedratinib in 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) and Previously Treated with Ruxolitinib including a Sub-study with concomitant Luspatercept for subjects with anemia.
The spleen volume reduction at the end of Cycle 6 as the primary objective. The secondary objectives of the study are to further evaluate the safety and to assess and implement mitigation strategies for WE and for gastrointestinal (GI) adverse events.
The study will be at multiple centers to provide access to a broad population and have assurance the results are likely to have general applicability.
This is also conducted as an open-label study to collect efficacy and safety data with fedratinib use, no randomization or stratification will occur.
The primary objective of the sub-study is to evaluate the safety and tolerability of Luspatercept when administered concomitantly with Fedratinib for the treatment of anemia in subjects with MF who are red blood cell (RBC) transfusion dependent (Group A) or non-transfusion dependent (Group B).

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 110 participants

Intervention Model : Single Group Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase 3b, Multicenter, Single-Arm, Open-Label Efficacy and Safety Study of Fedratinib in 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) and Previously Treated With Ruxolitinib Including a Sub-study With Concomitant Luspatercept for Subjects With Anemia

Actual Study Start Date: March 2019

Estimated Primary Completion Date: November 2021

Estimated Study Completion Date: May 2022

ARMS AND INTERVENTIONS

Arm	Intervention/treatment

Experimental: Administration of Fedratinib 400mg/day Self-administered Investigational Product (IP) (400 mg/day) on an outpatient basis, once daily preferably with food during an evening meal at the same time each day in consecutive 4-week (28-day) cycles.	Drug: FEDRATINIB A potent and selective inhibitor of JAK2 kinase activity Drug: Luspatercept Luspatercept will be 1.33 mg/kg administered as a subcutaneous injection concomitantly with Fedratinib.
Experimental: Administration of Luspatercept 1.33 mg/kg Administered as a subcutaneous injection concomitantly with Fedratinib at 3-week (21 day) cycles	Drug: Luspatercept Luspatercept will be 1.33 mg/kg administered as a subcutaneous injection concomitantly with Fedratinib.

OUTCOME MEASURES

Primary Outcome Measures: 1. Main study - Proportion of subjects who have a ≥ 35% SVR at end of Cycle 6 [Time Frame: At the end of Cycle 6 (each cycle is 28 days)]
Spleen volume response rate (RR)
2. Sub study - Adverse Events (AEs) [Time Frame: From enrollment up until 42 days post last dose of luspatercept or 30 days post last dose of fedratinib]
To evaluate the safety and tolerability of luspatercept when administered concomitantly with fedratinib for the treatment of anemia in subjects with MPN-associated MF who are RBC transfusion dependent (Group A) or non-transfusion dependent (Group B).

Secondary Outcome Measures: 1. Main study - Adverse Event(s) [Time Frame: Up to 12 months post last dose]
Number of participants with adverse event
2. Main study - Proportion of subjects who have ≥ 50% reduction in spleen size by palpation [Time Frame: At the end of Cycle 6 (each cycle is 28 days)]
Spleen response rate by palpation (RRP)
3. Main study - Symptom response rate (SRR) [Time Frame: At the end of Cycle 6 (each cycle is 28 days)]
Is defined as the proportion of subjects with ≥ 50% reduction from baseline to the end of Cycle 6 in total symptom score (TSS) measured by MFSAF version 4.0.
4. Main study - To evaluate durability of spleen volume response (DR) [Time Frame: From enrollment until treatment discontinuation (estimation of 12 months)]
Is defined as time from the first documented spleen response (ie, ≥ 35% reduction in spleen volume) to the first documented spleen volume reduction < 35%.
5. Main study - To evaluate the durability of spleen response by palpation (DRP) [Time Frame: From enrollment until treatment discontinuation (estimation of 12 months)]
Is defined as time from the first documented palpable spleen response, according to the IWG-MRT 2013 to the time of the first documented loss of response according to the IWG-MRT 2013.
6. Main study - Durability of symptoms response (DSR) [Time Frame: Up to 30 days post last dose]
Is defined as time from the first documented response in TSS (ie, reduction in TSS ≥ 50%) measured by MFSAF version 4.0 to the first documented TSS reduction < 50%.
7. Main study - Gastrointestinal Adverse Events [Time Frame: Up to 30 days post last dose]
Incidence of subjects with Grade 3 or higher Gastrointestinal events (nausea, diarrhea, or vomiting) according to CTCAE v5.0
8. Main study - Wernicke encephalopathy (WE) [Time Frame: Up to 30 days post last dose]
Occurrence of confirmed Wernicke encephalopathy events
9. Main study - Wernicke encephalopathy (WE) thiamine monitoring [Time Frame: Up to 30 days post last dose]
Monitoring and correction of thiamine levels as appropriate
10. Sub study - Anemia response related to modified Hematological Improvement - Erythroid Response (HI-E) [Time Frame: From SC1D1 through and including Sub-study Week 24 (Day 169) Also from SC1D1 through EOT]
it is defined as the proportion of subjects with hemoglobin increase by ≥ 1.5 g/dL OR reduction of units of RBC transfusion by an absolute number of at least 4 RBC transfusions over any consecutive 56-day (8 weeks) period compared with sub-study baseline.
11. Sub study - Anemia Response related to Reduction in Transfusion Burden [Time Frame: From SC1D1 through and including Sub-study Week 24 (Day 169) Also from SC1D1 through EOT]
it is defined as the proportion of RBC transfusion dependent subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units/12 weeks over any consecutive 12-week period compared with sub-study baseline.
12. Sub study - Anemia Response related to Mean Hemoglobin Increase [Time Frame: From SC1D1 through and including Sub-study Week 24 (Day 169) Also from SC1D1 through EOT]
it is defined as the proportion of subjects achieving a mean ≥ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion.
13. Sub study - Anemia response related to RBC-transfusion independence [Time Frame: From SC1D1 through and including Sub-study Week 24 (Day 169) Also from SC1D1 through EOT]
it is defined as the proportion of subjects who become RBC-transfusion free over any consecutive 84- day period. The response rate will be calculated using the number of responders divided by number of subjects in the sub-study Safety population.
14. Sub study - Duration of anemia response [Time Frame: Up to 12 months post last dose]
Maximum duration of anemia response in each of the endpoints and groups

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Main Study Inclusion Criteria
1. Subject is at least 18 years of age at the time of signing the informed consent form (ICF)
2. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Score (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-PV myelofibrosis according to the IWG-MRT 2007 criteria, confirmed by the most recent local pathology report
4. Subject has a DIPSS Risk score of Intermediate or High
5. Subject has a measurable splenomegaly during the screening period as demonstrated by spleen volume of ≥ 450 cm3 by MRI or CT-scan assessment or by palpable spleen measuring ≥ 5 cm below the left costal margin.
6. Subject has been previously exposed to ruxolitinib, while diagnosed with MF (PMF, post-ET MF or post-PV MF), and must meet at least one of the following criteria (a or b)
1. Treatment with ruxolitinib for ≥ 3 months
2. Treatment with ruxolitinib for ≥ 28 days complicated by any of the following:
- Development of a red blood cell transfusion requirement (at least 2 units/month for 2 months) or
- Grade ≥ 3 AEs of thrombocytopenia, anemia, hematoma, and/or hemorrhage while on treatment with ruxolitinib
7. Subject must have treatment-related toxicities from prior therapy resolved to Grade 1 or pretreatment baseline before start of last therapy prior to 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. Participants must agree to use effective contraception
Sub-Study Inclusion Criteria
1. Subject must understand and voluntarily sign an optional sub-study ICF prior to any sub study-related assessments/procedures being conducted
2. Subject must have been taking fedratinib for at least 32 weeks (~ 8 cycles)
3. Subject must be on a stable dose of fedratinib for at least 16 weeks (~ 4 cycles) [no dose level changes] in the time immediately up to the projected date of enrollment (SC1D1)
4. Subject has anemia defined as either:
1. Group A - Transfusion dependent (TD) anemia
- RBC-transfusion frequency: 4 to 12 RBC units/84 days immediately up to the SC1D1 date (Sub-study Cycle 1 Day 1), with no interval of > 6 weeks (42 days) without an RBC transfusion.
- Subjects must have a Hgb value of < 11.5 g/dL on SC1D1 prior to luspatercept administration. 2. Group B - Non-transfusion dependent (NTD) anemia - RBC-transfusion frequency: < 4 RBC units/84 days immediately up to the SC1D1 date. OR - At least 3 Hgb levels of ≤ 9.5 g/dL recorded on ≥ 3 different days, including the day of dosing, in the 84-day period immediately up to Sub-study C1D1 date. There must be ≥ 14 days in between each Hgb measurement. No subjects with an interval ≥ 42 days between hemoglobin measurements will be enrolled. Baseline is defined as the 84-day rolling period (3 cycles at 28 days each) prior to Sub-study Cycle 1 Day 1. Any transfusions given either at a Hgb ≤ 7 or for a Hgb ≤ 9.5 g/dL with symptoms will be counted towards baseline transfusion needs. Transfusions given only for bleeding or infections will not be counted towards eligibility baseline transfusion requirements. 5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2. Exclusion Criteria: Main Study Exclusion Criteria 1. Any of the following laboratory abnormalities: 1. Platelets < 50,000/µL 2. Absolute neutrophil count (ANC) 100 x 10^9/L
4. Myeloblasts > 5 % in peripheral blood
5. Estimated glomerular filtration rate 1.5 x ULN (upper limit of normal)
7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x 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 the start of fedratinib treatment
10. Subject has received ruxolitinib within 14 days prior to the start of fedratinib
11. Subject on treatment with myeloid growth factor (eg, granulocyte-colony stimulating factor [G-CSF]) within 14 days prior to the start of fedratinib treatment
12. Subject with previous exposure to Janus kinase (JAK) inhibitor(s) for more than 1 cycle other than ruxolitinib treatment
13. Subject on treatment with aspirin with doses > 150 mg daily
14. Subject with major surgery within 28 days before starting 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 enrollment. 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. Subject with known human immunodeficiency virus (HIV), known active infectious Hepatitis B (HepB), and/or known active infectious Hepatitis C (HepC)
19. Subject with serious active infection
20. Subject with presence of any significant gastric or other disorder that would inhibit absorption of oral medication
21. Subject is unable to swallow capsule
22. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
23. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
24. Subject has any condition that confounds the ability to interpret data from the study
25. Subject with participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to start of fedratinib treatment
26. Subject with life expectancy of less than 6 months.
Sub- Study Exclusion Criteria
1. Subject with anemia from causes other than MPN-associated MF or JAK2 inhibitor therapy (eg, iron deficiency, vitamin B12 and/or folate deficiencies, autoimmune or hemolytic anemia, infection, or any type of known clinically significant bleeding or sequestration).
2. Subject with any of the following laboratory abnormalities at SC1D1:
1. Neutrophils 100 x 10^9/L
3. Platelets 1000 x 10^9/L
4. Peripheral blood myeloblasts > 5%.
5. Estimated glomerular filtration rate 3.0 x upper limit of normal (ULN)
7. Direct bilirubin ≥ 2 x ULN (higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis))
3. Subject with diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg before SC1D1 despite appropriate treatment.
4. 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 enrollment. However, subject with the following history/concurrent conditions is allowed:
1. Basal or squamous cell carcinoma of the skin
2. Carcinoma in situ of the cervix
3. Carcinoma in situ of the breast
4. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
5. Subject with stroke, deep venous thrombosis, pulmonary or arterial embolism within 6 months immediately up to SC1D1.
6. Subject with major surgery within 2 months up to the enrollment date. Subject must have completely recovered from any previous surgery immediately up to the enrollment date.
7. Subject with inadequately controlled heart disease and/or have a known left ventricular ejection fraction < 35%. 8. Subject with uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment). 9. Subject with prior therapy of luspatercept or sotatercept. 10. Subject with history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational products (see luspatercept IB). 11. Subject with a major bleeding event (defined as symptomatic bleeding in a critical area or organ and/or bleeding causing a decrease in Hgb of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed red cells) in the last 6 months prior to enrollment. 12. Subject use of erythropoietin-stimulating agents (ESA) ≤ 56 days prior to SC1D1.

CONTACTS AND LOCATIONS

Contacts

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Locations

United States, Colorado	University of Colorado Cancer Center	Aurora
United States, Florida	Baptist Health - Miami Cardiac & Vascular Institute	Miami
United States, Georgia	Augusta University - Georgia Cancer Center	Augusta
United States, Illinois	Rush University Medical Center - University Cardiovascular Surgeons	Chicago
United States, Illinois	The University of Chicago Medical Center - Duchossois Center for Advanced Medicine	Chicago
United States, Illinois	Advocate Medical Group	Park Ridge
United States, Kansas	University of Kansas Medical Center	Kansas City
United States, Maryland	St. Agnes - Medical Center	Baltimore
United States, Maryland	Center for Cancer and Blood Disorders, P.C.	Bethesda
United States, Maryland	Maryland Oncology Hematology PA	Columbia
United States, Michigan	University of Michigan Comprehensive Cancer Center	Ann Arbor
United States, Missouri	Washington Univ School of Medicine	Saint Louis
United States, New Jersey	Newark Beth Israel Medical Center	Newark
United States, New York	Brookdale University Hospital and Medical Center	Brooklyn
United States, New York	Icahn School of Medicine at Mount Sinai	New York
United States, New York	Columbia University Medical Center	New York
United States, New York	SUNY Upstate Medical University	Syracuse
United States, North Carolina	North Carolina Women's Hospital	Chapel Hill
United States, North Carolina	Duke University Medical Center	Durham
United States, Ohio	UC Health Barrett Cancer Center	Cincinnati
United States, Pennsylvania	Western Pennsylvania Cancer Institute	Pittsburgh
United States, South Dakota	Avera Cancer Institute	Sioux Falls
United States, Texas	UT Southwestern Medical Center Simmons Comprehensive Cancer Center	Dallas
United States, Texas	Texas Oncology- Fort Worth Cancer Center	Fort Worth
United States, Texas	The University of Texas MD Anderson Cancer Center	Houston
United States, Texas	UT Health - San Antonio	San Antonio
United States, Washington	Fred Hutchinson Cancer Research Center	Seattle
United States, Wisconsin	University of Wisconsin Medical School	Madison
Canada, British Columbia	Providence Hematology	Vancouver
Canada, Ontario	London Health Sciences Centre	London
Canada, Ontario	Ottawa Hospital	Ottawa
Canada, Ontario	Princess Margaret Hospital University Health Network	Toronto
Canada, Quebec	Hopital Maisonneuve-Rosemont	Montreal
Canada, Quebec	Jewish General Hospital	Montreal
Canada, Quebec	CIUSSS de l'Estrie - CHUS	Sherbrooke

Sponsors and Collaborators

Celgene

Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation

Investigator

Study Director :	Shelo Rose, MD	Celgene

MORE INFORMATION

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