Jakavi® (ruxolitinib)
COMFORT-II Clinical Study Fact Sheet

Jakavi® (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases[1] and approved in more than 50 countries, including the European Union, Canada and some countries in Asia, Latin and South America for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic MF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF). The Canadian and European Union approvals of Jakavi were supported by two pivotal Phase III trials (COMFORT-I and COMFORT-II) comprising the largest clinical trial program in myelofibrosis to date[2,3].

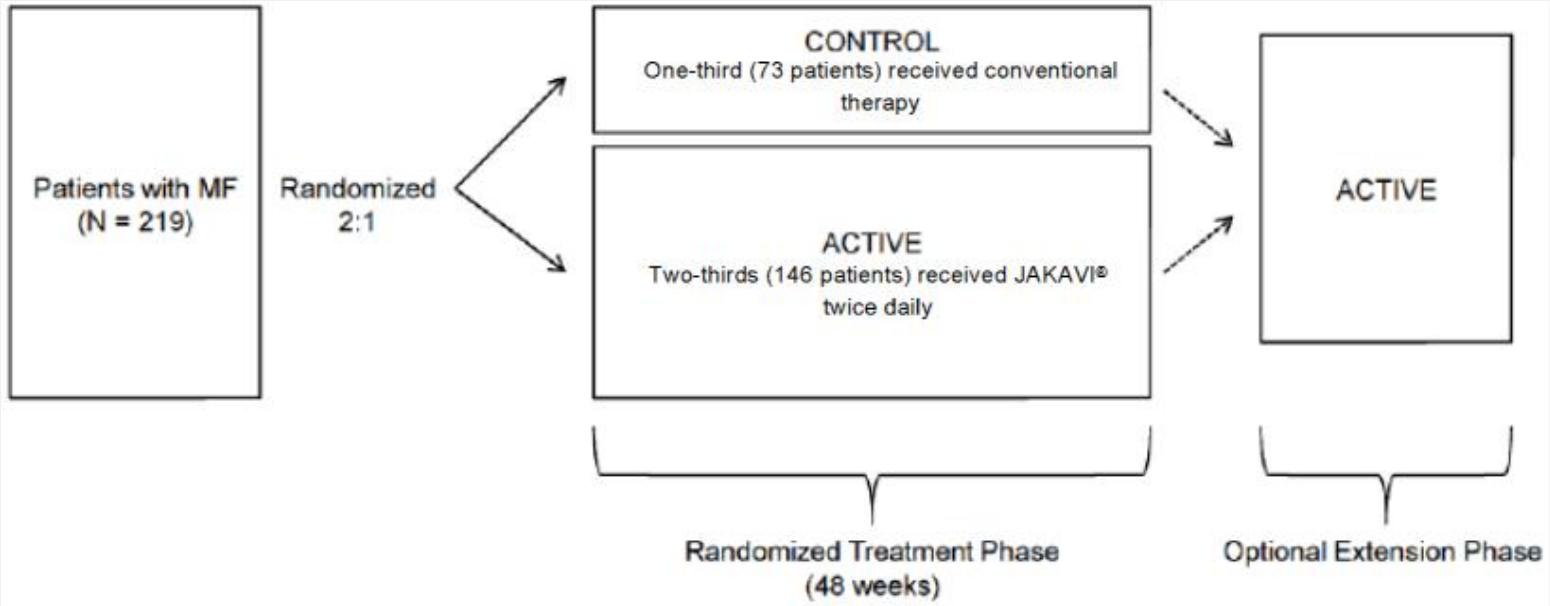
COMFORT-II (COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy) is a European study comparing the efficacy, safety and tolerability of Jakavi to conventional therapy at 48 weeks in patients with myelofibrosis, a life-threatening blood cancer arising in the bone marrow[4-6].

The COMFORT-II study evaluated Jakavi in patients with primary myelofibrosis, PPV-MF, or PET-MF who were either resistant or refractory to, intolerant of, or in the investigator's opinion not candidates for available therapy and for whom treatment of myelofibrosis was indicated[3]. A long-term follow-up update was designed to evaluate the long-term efficacy and safety of Jakavi therapy in patients with myelofibrosis at a two-year and three-year follow-up[6,7].

Primary Study Design (48 Weeks)

The randomized, open-label Phase III study included 219 patients with primary myelofibrosis, PPV-MF or PET-MF in 56 study locations in Europe. Two-thirds (146 patients) received Jakavi twice daily and one-third (73 patients) received conventional therapy, which was administered at doses and schedules determined by the investigator.

The trial consisted of a randomized treatment phase and an optional extension phase that consisted of a crossover control group[4]. Conventional therapy was selected by the investigator for each subject and could have included a combination of available agents to treat the disease and/or its symptoms. Further, therapy could have been changed at any time during the treatment phase. No experimental agents (e.g. those not approved for the treatment of any indication) could have been used[4].



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Study Design and Outcomes			
		Long-Term Updates	
	Primary Study (48 Week Analysis)[3]	Two-Year Follow-up Analysis[6]	Three-Year Follow-up Analysis[7]
Study Design	• The primary endpoint was the proportion of patients achieving ≥35% reduction in spleen volume from baseline to Week 48 as measured by MRI (or CT scan in applicable patients). • Secondary endpoints included: 1. Proportion of patients achieving a ≥35% reduction of spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable patients) 2. Duration of maintenance of a ≥35% reduction from baseline in spleen volume (measured baseline and every 12 weeks up to Week 72, after which this outcome was evaluated every 24 weeks) 3. Change in bone marrow histomorphology 4. Leukemia-free survival 5. Progression-free survival 6. Overall survival	• This update was designed to evaluate long-term efficacy and safety of Jakavi therapy in patients with myelofibrosis during a two-year follow-up period.	• This analysis evaluated efficacy and safety of Jakavi therapy in patients with myelofibrosis during a three-year follow-up period. • A total of 45.2% of patients remained on the Jakavi treatment arm after three years, while all patients randomized to conventional therapy discontinued treatment. Of patients on conventional therapy, 61.6% crossed over to the Jakavi treatment arm, with 48.9% of these patients ongoing in the extension phase of the study.
Study Outcomes	• Jakavi produced a spleen size reduction of 35% or greater (roughly equivalent to a reduction in spleen size by 50%) in 28% of patients compared to 0% of patients in the conventional therapy group at 48 weeks ($p<0.001$). • At week 24, 32% of patients treated with Jakavi demonstrated a 35% or greater spleen size reduction compared to 0% of patients treated with conventional therapy ($p<0.001$) for the key secondary endpoint. • No major changes in marrow histomorphologic features were observed in a pre-specified secondary analysis of data from patients receiving any therapy. • In the analyses of leukemia-free survival and overall survival, there were 10 events in total (all of which were deaths): 6 events (4%) with Jakavi, as compared with 4 events (5%) with conventional therapy. • Additionally, Jakavi was associated with improvements in myelofibrosis symptoms at each evaluation as compared to conventional therapy.	• Jakavi was associated with sustained reductions in splenomegaly (enlarged spleen). • Overall, 48.3% of patients treated with Jakavi achieved a ≥35% reduction in spleen size, with results sustained over two years. • In a rigorous intent-to-treat analysis, Jakavi-treated patients showed an overall survival advantage compared to patients receiving conventional therapy (HR=0.51; 95% CI, 0.26-0.99; p=0.041), which is any commercially available agent (monotherapy or in combination) or no therapy at all.	• Jakavi continued to improve overall survival and demonstrated sustained reduction in spleen size compared to conventional therapy. • Overall, 51.4% of patients treated with Jakavi achieved a ≥35% reduction from baseline in spleen volume. • Jakavi-treated patients showed a 52% overall survival advantage compared to patients receiving conventional therapy (HR=0.48; 95% CI, 0.28-0.85; p=0.009). • Additionally, at 144 weeks, the estimated probability of overall survival was significantly greater in the Jakavi arm than the conventional therapy arm (81% compared to 61%, respectively).

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About Jakavi®

Jakavi (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases[1] and was approved by the European Commission in August 2012 for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Jakavi is approved in more than 50 countries, including the European Union, Canada and some countries in Asia, Latin and South America. Additional worldwide regulatory filings are underway.

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the United States. Both the European Commission and the US Food and Drug Administration (FDA) granted ruxolitinib orphan drug status for myelofibrosis. Jakavi is marketed in the United States by Incyte Corporation under the name Jakafi® for the treatment of patients with intermediate or high-risk myelofibrosis.

Jakavi® Important Safety Information

The recommended starting dose for Jakavi is 15 mg twice daily for patients with a platelet count between 100,000 cubic millimeters (mm^3) and 200,000 mm^3, and 20 mg twice daily for patients with a platelet count of >200,000 mm^3. Doses may be titrated based on safety and efficacy. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and <100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and patients should be titrated cautiously[8].

Jakavi can cause serious side effects, including a decrease in blood cell count and infections. Complete blood count monitoring is recommended. Progressive multifocal leukencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML[8]. Dose reduction or interruption may be required in patients with severe hepatic or renal impairment or in patients developing hematologic adverse reactions such as thrombocytopenia, anemia and neutropenia. Dose reductions are also recommended when Jakavi is co-administered with strong CYP3A4 inhibitors or fluconazole. Use of Jakavi during pregnancy is not recommended and women should avoid becoming pregnant during Jakavi therapy. Women taking Jakavi should not breast feed.

The most common adverse drug reactions, occurring at any level of severity (incidence >10%) are urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, alanine aminotransaminase increased, asparte aminotransferase increased, bruising, bleeding and increased blood pressure. Other common adverse drug reactions (incidence 1 to 10%) are herpes zoster, weight gain, flatulence and tuberculosis (1%)[8].

Please see full Prescribing Information at www.jakavi.com.

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