Jakavi® (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases and was 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 (MF) (also known as chronic idiopathic MF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocytemia 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 MF to date.

COMFORT-I (COnrolled MyoelFibrosis Study with ORal JAK Inhibitor Therapy) compared the efficacy, safety and tolerability of Jakavi to placebo at 24 weeks in patients with MF, a life-threatening blood cancer arising in the bone marrow. Building on results from previously established data, a long-term follow-up update was conducted to evaluate efficacy and safety of Jakavi therapy at 102 weeks and three-year follow-up. The COMFORT-I study was performed under a Special Protocol Assessment (SPA) agreement with the US Food and Drug Administration (FDA) and was sponsored by Incyte Corporation.

**Primary Study Design (24 Weeks)**
The randomized, double-blind Phase III study included 309 patients with primary MF, PPV-MF or PET-MF in 89 study locations in the United States, Canada and Australia. Half of the patients (155) received Jakavi twice daily (starting dose 15 or 20 mg twice-daily) and half (154) received placebo. The study consisted of a randomized treatment phase and includes an optional extension phase, during which patients on placebo could begin receiving Jakavi open label.
### Study Design and Outcomes

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Primary Study (24-Week Analysis)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Long-Term Update (102 Week Analysis)&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Long-Term Update (3-Year Analysis)&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **Study Design** | • The primary endpoint was the proportion of patients achieving a reduction in spleen volume of 35% or more from baseline at week 24 as measured by MRI (or CT scan in applicable patients).  
  • Secondary endpoints included:  
    1. Durability of spleen volume response  
    2. Changes in myelofibrosis-related symptoms (assessed by Total Symptom Score (TSS)* using the modified Myelofibrosis Symptom Assessment Form v2.0 diary)  
    3. Overall survival  
  *TSS = Collected scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the ribs on left and early satiety. | • The long-term update was designed to evaluate efficacy and safety of Jakavi therapy in patients randomized to Jakavi at a median follow-up of 102 weeks.  
  o Quality of life was evaluated beyond week 24 using the EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire-Core 30 (QLQ-C30).  
  o Overall survival was assessed according to original randomized treatment. | • The additional long-term update was designed to evaluate efficacy and safety of Jakavi therapy in patients randomized to Jakavi at a median follow-up of 149 weeks.  
  o Reduction in spleen volume and symptoms continued to be assessed at week 24, and quality of life continued to be evaluated beyond week 24.  
  • Overall survival was assessed according to original randomized treatment and statistical modeling of survival was conducted using a generalized Gamma distribution to better understand the effect of crossover on the placebo arm. |
About Jakavi

Jakavi® (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases 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 available in 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 is a registered trademark of Novartis AG in countries outside the United States. Jakafi is a registered trademark of Incyte Corporation.

### Study Outcomes

- **41.9% of Jakavi-treated patients achieved at least a 35% reduction in spleen volume at 24 weeks from baseline compared to 0.7% of patients in the placebo group, thus improving quality of life and potentially impacting overall survival.**

- **In this long-term update, Jakavi treatment resulted in sustained reductions in spleen volume and improvements in quality of life compared to placebo:**
  - Among patients with a ≥35% reduction in spleen volume, response was maintained With a median duration of 108 weeks
  - Patients showed sustained improvements in Global Health Status/Quality of Life and the 5 functional domains of EORTC QLQ-C30

- Consistent with data presented at the European Hematology Association (EHA) meeting in 2012, the update demonstrated a continued overall survival benefit in favor of Jakavi:
  - 83% of patients survived at the 102 week follow-up period, compared to 73% of patients on placebo (HR=0.58; 95% CI, 0.36-0.95; p=0.028)

- **In this long-term update, Jakavi treatment resulted in sustained reductions in spleen volume and durable improvements in quality of life compared to placebo:**
  - Of the patients treated with Jakavi, 59% experienced at least a 35% reduction in spleen size at any time during the study
  - Patients who continued on therapy experienced durable improvements in the Global Health Status/Quality of Life and the functional domains of EORTC QLQ-C30

- **After a median follow-up of 149 weeks, the hazard ratio for overall survival favored patients originally randomized to placebo, the majority of whom crossed over to ruxolitinib; the hazard of death for patients originally randomized to placebo decreased as patients crossed over to ruxolitinib**
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.

Jakavi® can cause serious side effects, including a decrease in blood cell count and infections. Complete blood count monitoring is recommended. Progressive multifocal leukoencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. 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 aminotransferase increased, aspartate 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%).

Please see full Prescribing Information available at [www.jakavi.com](http://www.jakavi.com).

**References**