Novartis drug Jakavi® improved overall survival of patients with myelofibrosis in four separate analyses of long-term Phase III studies

- In two Phase III studies, Jakavi® reduced the risk of death and maintained spleen reductions at three years compared to conventional therapy and placebo
- Similar survival benefit seen in patients with and without high-risk mutations
- Separate analysis shows Jakavi may increase the probability of 10-year survival of myelofibrosis patients by more than 50% compared to conventional therapy
- Jakavi is the only JAK inhibitor approved in more than 50 countries for patients with myelofibrosis, a debilitating and life-threatening blood cancer

Basel, December 9, 2013 – Novartis today announced that patients with myelofibrosis initially randomized to treatment with Jakavi® (ruxolitinib) lived longer than those randomized to treatment with placebo or conventional therapy, as described in several analyses from the Phase III COMFORT-I and COMFORT-II studies. Results are being presented at the 55th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, LA.

Myelofibrosis is an uncommon blood cancer characterized by bone marrow scarring (fibrosis), enlarged spleen (splenomegaly), potential complications and symptoms including fatigue, fever, night sweats, itchy skin, bone pain, abdominal pain or discomfort and weight loss1,2. Historically, patients with myelofibrosis have had a poor prognosis and limited treatment options3.

“The COMFORT studies provide evidence that we’ve been able to extend the lives of patients with myelofibrosis with Jakavi, regardless of disease mutations and in comparison to conventional myelofibrosis therapies,” said Dr. Alessandro M. Vannucchi, Department of Hematology, University of Florence, Italy, and lead study author. “It’s promising to start seeing the long-term effects of this therapy, which has changed the treatment paradigm for most patients with this life-threatening disease.”

At the ASH Annual Meeting, study investigators presented the following analyses from the COMFORT clinical program demonstrating an overall survival benefit for patients with myelofibrosis treated with Jakavi:

- Impact of Prognostically Detrimental Mutations in COMFORT-II (abstract #107) Patients with certain disease mutations are considered to be at high molecular risk (HMR+) and tend to have shorter overall survival and greater risk of leukemia compared to those without these mutations, classified as low molecular risk (LMR). Investigators analyzed the impact of disease mutations on spleen size reduction, anemia development and overall survival in patients with myelofibrosis initially randomized to treatment with Jakavi in the COMFORT-II trial. Researchers found that Jakavi had a similar effect in patients with and without these mutations. The presence of mutations did not impact achievement of ≥35%
spleen volume reduction at 24 (34.8% vs 35.0% in HMR+ vs LMR respectively) and 48 weeks (26.1% vs 35.0% in HMR+ vs LMR respectively) in patients initially randomized to treatment with Jakavi. There was also a survival benefit in both groups in the Jakavi treatment arm (survival estimate of 0.79 vs 0.85 in HMR+ vs LMR respectively)\(^5\).

- Three-Year Update From COMFORT-I Study (abstract #396)
  In COMFORT-I, risk of death at three years was reduced by 31% in patients initially randomized to treatment with Jakavi compared to those randomized to the placebo group (HR=0.69; 95% CI: 0.46, 1.03; \(P = 0.067\)). The trial design allowed patients who were receiving placebo to cross over to be treated with Jakavi. At the time of analysis, placebo patients had received Jakavi therapy for a median of 104 weeks and the suggested risk of death for those patients had decreased to approach that for patients originally randomized to Jakavi. Consistent with observations at the two year follow-up, grade 3 or 4 anemia and thrombocytopenia typically only occurred early (≤6 months) in Jakavi treatment and decreased with long-term therapy\(^5\).

- A Pooled Overall Survival Analysis of the COMFORT Studies (abstract #2820)
  In the COMFORT-I and –II studies, risk of death at three years was reduced by 35% in patients initially randomized to treatment with Jakavi compared to patients randomized to the control group (HR = 0.65; 95% CI, 0.46-0.90; \(P = 0.01\)). Patients with high risk myelofibrosis who were initially randomized to treatment with Jakavi had an estimated survival similar to patients with intermediate-2-risk myelofibrosis in the control group. Additionally, among all patients in the study, bigger spleen size before treatment was associated with higher risk of death (HR = 1.09; 95% CI, 1.03-1.15; \(P = 0.003\))\(^6\).

- A Retrospective Comparison of the DIPSS and COMFORT-II Study (abstract #4066)
  An analysis of survival from diagnosis showed a better prognosis for patients initially randomized to treatment with Jakavi in the COMFORT-II study compared to patients from the multicenter Dynamic International Prognostic Scoring System (DIPSS) database. The probability of survival at 10 years from initial diagnosis was 28.6% in the COMFORT-II trial and 11.2% in the DIPSS (95% CI: 12.5-47.1 vs 4.8-20.6, HR = 0.51 95% CI: 0.30-0.88). This suggests that the risk of death is halved by introducing Jakavi in the treatment of patients with primary myelofibrosis\(^7\).

**COMFORT Studies Background**

The COMFORT (COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy) studies are randomized, Phase III studies comparing the safety and efficacy of Jakavi with conventional therapy (placebo or best available treatment (BAT)) in patients with intermediate-2– or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocytopenia myelofibrosis. COMFORT-I is a double-blind study whereas COMFORT-II is open label. Patients initially received Jakavi 15 or 20 mg bid based on their platelet counts at baseline (100-200 and > 200 x 109/L, respectively) and were individually titrated to maximize safety and efficacy. Patients were allowed to cross over from the control arms of each study upon protocol-defined progression events (primarily progressive splenomegaly, defined as a ≥ 25% increase in spleen volume from baseline or on-study nadir in COMFORT-I and –II, respectively). At the time of the analysis reported at ASH, all ongoing control patients had crossed over to Jakavi. Overall survival was a secondary endpoint in both studies\(^6\).

**About Myelofibrosis**

Myelofibrosis is a life-threatening blood cancer with a poor prognosis and limited treatment options\(^1,8\). Myelofibrosis develops when uncontrolled signaling in the JAK
pathway – which regulates blood cell production – causes the body to make blood cells that do not work properly, which scars the bone marrow and results in an enlarged spleen and other severe complications.\textsuperscript{1,2}

Studies show that patients with myelofibrosis have a decreased life expectancy, with a median overall survival of 5.7 years.\textsuperscript{9} Although allogeneic stem cell transplantation may cure myelofibrosis, the procedure is associated with significant morbidity and transplant-related mortality, and is available to less than 5% of patients who are young and fit enough to undergo the procedure.\textsuperscript{10}

**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 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.

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\textsuperscript{11}.

Jakavi is a registered trademark of Novartis AG in countries outside the United States. Jakafi is a registered trademark of Incyte Corporation.

**Jakavi® Important Safety Information**

Jakavi® can cause serious side effects, including a decrease in blood cell count and infections. Complete blood count monitoring is recommended. 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, 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\%). Progressive multifocal leukencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML.\textsuperscript{11}

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

**Disclaimer**
The foregoing release contains forward-looking statements that can be identified by terminology such as “may,” “are being,” “promising,” “suggests,” “underway,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Jakavi, or regarding potential future revenues from Jakavi. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Jakavi will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Jakavi will be commercially successful in the future. In particular, management’s expectations regarding Jakavi could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company’s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing issues, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventative vaccines and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2012, the Group achieved net sales of USD 56.7 billion, while R&D throughout the Group amounted to approximately USD 9.3 billion (USD 9.1 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 133,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit [http://www.novartis.com](http://www.novartis.com).

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