Novartis drug Jakavi® improved overall survival of myelofibrosis patients and impacted an underlying mechanism of disease

- Jakavi® reduced risk of death by 52% and sustained reductions in spleen size in new three-year COMFORT-II study data
- Analysis from a separate trial suggested that long-term treatment with Jakavi may stabilize or improve bone marrow fibrosis, a key marker of worsening disease
- Jakavi continues to be well tolerated in myelofibrosis patients after three years of treatment

**Basel, June 16, 2013** – Novartis today announced results from a Phase III three-year follow-up study that showed Jakavi® (ruxolitinib) demonstrated improved overall survival and sustained reductions in spleen size compared to conventional therapy. In a separate long-term exploratory analysis, Jakavi slowed or stabilized the advancement of bone marrow fibrosis, one of the underlying disease mechanisms and consequences of myelofibrosis, an effect that has not been observed with conventional therapy in advanced myelofibrosis patients.

Findings are being presented at the 18th Congress of European Hematology Association (EHA) in Stockholm, Sweden.

In a three-year follow-up analysis of the COMFORT-II study, patients treated with Jakavi demonstrated an overall survival advantage compared to patients receiving conventional therapy. A 52% reduction in risk of death was observed in the Jakavi arm compared with conventional therapy (HR=0.48; 95% CI, 0.28-0.85; p=0.009)⁻¹, and the estimated probability of overall survival was significantly greater with Jakavi compared to conventional therapy (81% compared to 61%, respectively) at 144 weeks. Additionally, 51.4% of patients treated with Jakavi achieved a ≥35% reduction from baseline in spleen size. Patients continue to maintain their spleen response, with the median spleen reduction not yet reached in the study.

The results are consistent with previous COMFORT-II and COMFORT-I study analyses, which demonstrate that Jakavi provides significant clinical benefits over conventional therapy and placebo for patients suffering from myelofibrosis, a rare blood cancer.

“Jakavi is the first drug to demonstrate an improvement in overall survival in patients with advanced myelofibrosis,” said Dr. Alessandro M. Vannucchi, Department of Hematology, University of Florence, Italy and lead study author. “Moreover, we are encouraged by these latest study results, which reinforce that the rapid, positive effects of Jakavi in improving patients’ symptoms are sustained over the long-term.”

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 complications²,³. Jakavi directly targets the underlying mechanism of the disease.
and it significantly reduces spleen size and improves symptoms regardless of JAK mutational status, disease subtype or any prior treatment.\textsuperscript{4,5,6,7,8}

Data were also presented from an exploratory analysis of bone marrow morphology from a separate Phase I/II trial of Jakavi, compared with historical controls from patients treated with conventional therapy. After four years of Jakavi therapy, bone marrow fibrosis improved in 22% and stabilized in 56% of patients with myelofibrosis. A comparable effect was not seen with long-term conventional therapy.\textsuperscript{9}

“For the first time in advanced myelofibrosis, drug therapy showed evidence of bone marrow fibrosis stabilization or improvement, further supporting that Jakavi may modify the natural course of disease,” said Alessandro Riva, M.D., Global Head, Oncology Development and Medical Affairs, Novartis Oncology. “These data are of great interest because bone marrow transplantation, which carries a high risk of morbidity and mortality, is the only other option proven to impact bone marrow fibrosis in patients with advanced myelofibrosis.”

**COMFORT-II Three-Year Long-Term Study Background**

In the three-year analysis of COMFORT-II (COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy), a total of 45.2% of patients remained on the Jakavi treatment arm, while all patients randomized to conventional therapy discontinued treatment. For 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. The median duration of Jakavi exposure (randomized and extension phases) was 136 weeks and conventional therapy exposure (randomized treatment only) was 45 weeks. Overall survival was estimated using the Kaplan-Meier method.

All AEs were consistent with previous analyses of treatment with Jakavi. The most common hematologic AEs in either arm (Jakavi, conventional therapy) were anemia (50.0%; 16.4%) and thrombocytopenia (50.7%; 13.7%). The most common non-hematologic abnormalities for each arm (Jakavi, conventional therapy) include peripheral edema (swelling of extremities) (36.3%; 28.8%), diarrhea (32.2%; 17.8%) and asthenia (weakness) (24.0%; 12.3%)\textsuperscript{1}.

A total of 191 patients were exposed to Jakavi by the data cut-off date, 146 patients initially randomized to Jakavi treatment and 45 patients that eventually crossed over from the conventional therapy arm. Treatment discontinuations in the Jakavi arm were primarily due to adverse events (AEs) (16.4%) and disease progression (15.1%), while discontinuations in the conventional therapy arm were primarily due to consent withdrawal and other reasons (12.3% each). Only two patients discontinued due to anemia (1%) and seven patients due to thrombocytopenia (3.6%).

**Long-Term Bone Marrow Morphology Analysis Background**

The data from this separate exploratory analysis assessed the effect of long-term Jakavi treatment on bone marrow morphology in patients with myelofibrosis. An analysis of trephine biopsies were obtained from the cohort of myelofibrosis patients treated at MD Anderson Cancer Center who participated in Study 251, a Phase I/II trial of ruxolitinib\textsuperscript{9}.

Biopsies of myelofibrosis patients treated with Jakavi were obtained at baseline, 24 months (68 patients) and 48 months (18 patients). Samples were also collected from a multicenter observational database from three European Union countries (160 biopsies in a cohort of 139 patients) in patients treated with conventional therapy at 24 months (97 patients) and 48 months (63 patients)\textsuperscript{9}.

Bone marrow fibrosis grade (G) changes vs. baseline were categorized as improvement, stabilization, and worsening according to the World Health Organization (WHO) grading scale (0-3) and reviewers were blinded to patient characteristics and outcomes. Additional analyses were performed on biopsies from patients in the Jakavi-treated...
cohort: changes over time in the degree of collagen deposition, amount of osteosclerosis (abnormal bone density) and bone marrow cellularity. Bone marrow biopsies of Jakavi treated patients who were evaluated at baseline presented with 21% G1 fibrosis, 53% G2 fibrosis and 26% G3 fibrosis. Distribution of baseline WHO fibrosis grades between Jakavi- and conventionally-treated groups showed no noticeable difference (p=0.441 by Cochran Mantel-Haenszel test)

**About Myelofibrosis**
Myelofibrosis is a life-threatening blood cancer with a poor prognosis and limited treatment options. Studies show that patients with myelofibrosis have a decreased life expectancy, with a median overall survival of 5.7 years. 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.

**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 45 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 (mm³) and 200,000 mm³, and 20 mg twice daily for patients with a platelet count of >200,000 mm³. 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/mm³ and <100,000/mm³. The maximum recommended starting dose in these patients is 5 mg twice daily and patients should be titrated cautiously.

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, 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%). Progressive multifocal leukencephalopathy (PML)
has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML\textsuperscript{14}.

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

Disclaimer
The foregoing release contains forward-looking statements that can be identified by terminology such as “suggested,” “may,” “encouraged,” or similar expressions, or by express or implied discussions regarding potential future revenues from Jakavi. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Jakavi to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Jakavi will achieve any particular levels of revenue in the future. In particular, management’s expectations regarding Jakavi could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; government, industry and general public pricing pressures; unexpected manufacturing issues; competition in general; the company’s ability to obtain or maintain patent or other proprietary intellectual property protection; the impact that the foregoing factors could have on the values attributed to the Novartis Group’s assets and liabilities as recorded in the Group’s consolidated balance sheet, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. 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, preventive 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 129,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.novartis.com.

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