Novartis presents data showing Jakavi® is superior to best available therapy in patients with less advanced polycythemia vera (PV)

- Three times as many patients with inadequately controlled PV without enlarged spleen had hematocrit control without phlebotomy on Jakavi® (ruxolitinib) vs BAT

- RESPONSE-2 complements data from pivotal RESPONSE study, showing that Jakavi is effective in certain PV patients with and without an enlarged spleen

- Myelofibrosis data suggest patients on Jakavi lived longer with 5-year survival showing a 31% reduced risk of death compared to those randomized to placebo

Basel, June 10, 2016 – Novartis today announced Phase III data from RESPONSE-2 showing that Jakavi® (ruxolitinib) helped patients with polycythemia vera (PV), who did not have an enlarged spleen and were resistant to or intolerant of hydroxyurea, achieve superior hematocrit control compared to best available therapy (BAT) at 28 weeks (62.2% vs 18.7%, respectively; p<0.0001). The findings were presented for the first time at the 21st Congress of the European Hematology Association (EHA) in Copenhagen, Denmark.

Polycythemia vera is a rare and incurable blood cancer associated with an overproduction of blood cells that can cause serious cardiovascular complications, such as blood clots, stroke and heart attack. As the disease progresses, the spleen can become enlarged as it works to clear a greater number of blood cells than normal. In this study, patients did not have an enlarged spleen as assessed by physical examination at baseline (spleen palpation) and a majority (approximately 70%) were previously treated with hydroxyurea only, therefore considered less advanced. The remaining patients were treated with multiple lines of therapy (approximately 30%).

“RESPONSE-2 is the first study of this scale to focus on patients with inadequately controlled polycythemia vera in a less advanced phase of the disease,” said lead study investigator, Francesco Passamonti, MD, the University of Insubria, Varese, Italy. “The study supports the use of Jakavi as a second-line treatment option to help this patient population gain better control of their disease.”

Patients with PV in the study were classified as inadequately controlled based on the modified European LeukemiaNet (ELN) criteria, which defines resistance to or intolerance of hydroxyurea as hematocrit levels greater than 45%, elevated white blood cell count and/or platelet count, and the presence of hydroxyurea-related non-hematologic toxicities.

“Given the limited research and treatment options for polycythemia vera, this trial was initiated to gain a better understanding of Jakavi in patients whose disease is not adequately controlled with hydroxyurea,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “The results demonstrate the potential benefit of Jakavi to help manage the disease in patients who have few other options.”
In addition to meeting its primary endpoint of proportion of patients achieving hematocrit control, the RESPONSE-2 study showed that nearly five times more patients with PV achieved complete hematologic remission with Jakavi compared to BAT at 28 weeks (23.0% vs 5.3%, respectively; p=0.0019). Patients taking Jakavi also experienced complete resolution of their symptoms related to PV compared to BAT (50.0% vs 7.7%, respectively). Overall, Jakavi was well tolerated. Findings from this study are consistent with data from the RESPONSE pivotal trial evaluating patients with inadequately controlled PV with an enlarged spleen1,2.

Additionally, Phase III data from the COMFORT-I study were also presented at EHA. These data suggest an overall survival advantage in patients with intermediate-2 or high-risk myelofibrosis (MF) randomized to Jakavi compared to patients randomized to placebo. The five-year survival showed a 31% reduced risk of death (HR=0.69; 95% CI: 0.50, 0.96; p=0.025) in the Jakavi arm despite more than 70% of patients randomized to the placebo arm crossing over to receive treatment with Jakavi (median time to crossover was 41.1 weeks). Patients treated with Jakavi maintained spleen response (≥35% reduction in size) for an average of three years. These findings further support the durable efficacy and long-term safety profile of Jakavi in MF3.

About the RESPONSE-2 Study
The Phase IIIb RESPONSE-2 (Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor Ruxolitinib Versus Best Available Care) study evaluated the efficacy and safety of Jakavi versus BAT. The trial randomized 149 patients with PV who were resistant to or intolerant of hydroxyurea, dependent on phlebotomy for hematocrit control and did not have an enlarged spleen. Patients were randomized 1:1, to receive either Jakavi (10 mg twice daily) or BAT, which was defined as investigator-selected monotherapy or observation only1.

The primary endpoint of the trial was the proportion of patients who achieved hematocrit control at week 28 (without phlebotomy from week 8 to 28 with no more than one phlebotomy eligibility between randomization and week 8). The key secondary endpoint was the proportion of patients who achieved complete hematologic remission (CHR) at week 28. CHR was defined as achieving hematocrit control without the use of phlebotomy, platelet count ≤400 x 10^9/L and white blood cell count ≤10 x 10^9/L, which are all important markers of disease control in PV1.

In the study, anemia occurred in 16.2% of patients in the Jakavi-treatment arm compared to 2.7% in the BAT arm. The most common non-hematologic adverse events (≥10% of patients) in either the Jakavi or BAT arm were headache (12.2% vs 10.7%, respectively), constipation (10.8% vs 5.3%, respectively), hypertension (10.8% vs 4.0%, respectively), pruritus (10.8% vs 20.0%, respectively), and weight increase (10.8% vs 1.3%, respectively), which were mainly Grade 1 or 2. Patients treated with Jakavi had fewer thromboembolic events compared to patients taking BAT (1 vs 3, respectively)1.

About the COMFORT-I Study
The Phase III COMFORT-I (CONTROLed MYELOFIBROSIS Study with QRAl JAK Inhibitor Therapy) study included 309 patients with primary MF, post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF) in 89 study locations in Canada, Australia and the United States. Half of the patients (155) received Jakavi (starting dose 15 or 20 mg twice daily) and half (154) received placebo. Patients receiving placebo could crossover to the Jakavi arm after the primary analysis or at any time if they had pre-specified worsening of their enlarged spleen. A final analysis of the study at five years was performed to evaluate the safety and efficacy of Jakavi in patients with MF3.

Notable adverse events (AE) at the five-year analysis included herpes zoster (10.3% and 13.5% in Jakavi patients and patients who crossed over from placebo, respectively),...
basal cell carcinoma (7.7% and 9.0%, respectively) and acute myeloid leukemia (5 patients in each arm)².

**About Polycythemia Vera**

Polycythemia vera affects up to three per 100,000 people globally each year⁷. The disease is driven by the dysregulation of the JAK-STAT pathway⁸. It is typically characterized by elevated hematocrit, the volume percentage of red blood cells in whole blood, which can lead to a thickening of the blood and an increased risk of blood clots, as well as an elevated white blood cell and platelet count⁹. This can cause serious cardiovascular complications, such as stroke and heart attack, resulting in increased morbidity and mortality⁹. PV can also persist for many years and in some cases evolve to myelofibrosis (post-PV MF) or acute myeloid leukemia (AML)¹⁰.

A common PV treatment includes phlebotomy, a procedure to remove blood from the body to reduce the concentration of red blood cells, which is used to help maintain a hematocrit level below 45%⁴,⁹. However, for a subset of patients, phlebotomy may be unsuitable as a permanent treatment option due to its inability to control symptoms or effectively manage the overproduction of red blood cells, therefore cytoreductive agents, such as hydroxyurea, may be added⁶. For patients requiring phlebotomy in combination with hydroxyurea, hematocrit may fluctuate and remain at unsafe levels for significant periods of time¹¹. Unfortunately, approximately 25% of patients with PV become resistant to or intolerant of hydroxyurea treatment according to ELN criteria, resulting in inadequate disease control and an increased risk of progression¹².

**About Myelofibrosis**

Myelofibrosis is a rare and life-threatening blood cancer that affects approximately one in every 100,000 people and has similar survival rates as other malignancies, such as breast cancer and colon cancer⁷,¹³,¹⁴,¹⁵,¹⁶,¹⁶. In patients with MF, their bone marrow can no longer produce enough normal blood cells, causing the spleen to enlarge¹³. As a result, patients may suffer from debilitating symptoms and have a poor quality of life¹⁷. Approximately 90% of patients with MF have mutations that directly or indirectly activate the JAK/STAT signaling pathway, which may explain the development of the disease¹⁸.

Although allogeneic stem cell transplantation may cure MF, 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 procedure¹⁹.

**About Jakavi**

Jakavi (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases. Jakavi is approved by the European Commission for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea and 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 MF or post-essential thrombocythemia MF. Jakavi is approved in more than 95 countries for patients with MF, including countries in the European Union, Canada, Japan and countries in Asia, Latin and South America, and in 60 countries for patients with PV, including countries in the European Union, Japan and Canada. The exact indication for Jakavi varies by country. Additional worldwide regulatory filings are underway in MF and PV.

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the United States. Jakavi is marketed in the United States by Incyte Corporation as Jakafi® for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea and for the treatment of patients with intermediate or high-risk MF.
The recommended starting dose of Jakavi in PV is 10 mg given orally twice daily. The recommended starting dose of Jakavi in MF is 15 mg given orally 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 MF and PV 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 is a registered trademark of Novartis AG in countries outside the United States. Jakafi is a registered trademark of Incyte Corporation. The safety and efficacy profile of Jakavi has not yet been established outside the approved indications.

**Jakavi Important Safety Information for Treatment of Myelofibrosis (MF) and Polycythemia Vera (PV)**

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 any hepatic impairment or severe 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.

Progressive multifocal leukoencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. Hepatitis B viral load (HBV-DNA titer) increases have been reported in patients with chronic HBV infections. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Non-melanoma skin cancer (NMSC) has been reported in Jakavi treated patients. Periodic skin examination is recommended. Very common adverse reactions in MF (>10%) include urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, alanine aminotransferase increased, aspartate aminotransferase increased, bruising and weight gain. Common adverse reactions in MF (1 to 10%) include herpes zoster and flatulence. Uncommon adverse reactions in MF include tuberculosis. Very common adverse reactions in PV (>10%) include anemia, thrombocytopenia, hypercholesterolemia, hypertriglyceridemia, dizziness, alanine aminotransferase increased and aspartate aminotransferase increased. Common adverse reactions in PV (1 to 10%) include urinary tract infections, herpes zoster, weight gain, constipation and hypertension.

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 words such as "suggests," "supports," "potential," "support," "may," "underway," "yet," 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 safety, quality or 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 and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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