Novartis highlights long-term safety data of Revolade® in adults with chronic immune thrombocytopenia, a rare blood disorder

- **EXTEND study provides long-term safety data for Revolade that are consistent with the findings from the pivotal Phase III RAISE study**.\(^1,2\)

- Immune thrombocytopenia (ITP) is a rare and potentially serious blood disorder, characterized by bruising, bleeding and in some cases, serious hemorrhaging.\(^3\)

- **Novartis continues to build on its heritage in hematology to advance care for patients suffering from serious hematologic disorders such as ITP.**

**Basel, June 10, 2016** – Novartis today announced data from the largest study of its kind confirming the long-term safety profile of Revolade (eltrombopag) in adults with chronic immune (idiopathic) thrombocytopenia (ITP), with data for up to 6 years in some patients (median exposure was 2.4 years).\(^1,2\) Additional data from the study will also be presented that showed long-term oral administration of Revolade was effective in increasing and maintaining platelet counts in adult patients who had their spleens removed (splenectomized) as well as those who did not (non-splenectomized).\(^4\) The final results of the study and sub-analysis will be presented at the 21st Congress of the European Hematology Association (EHA) in Copenhagen, Denmark.

ITP is a rare and potentially serious blood disorder where the blood doesn’t clot as it should due to a low number of platelets. As a result, patients experience bruising, bleeding and, in some cases, serious hemorrhage that can be fatal. ITP may also affect a patient’s quality of life, as it is often associated with fatigue and depression as well as a fear of bleeding that may limit everyday activities.\(^3\)

“Patients living with chronic diseases will likely remain on therapy for many years, so data about the long-term use of treatments, particularly around safety, are critical,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “EXTEND is the largest study of its kind and reinforces Revolade as a trusted option that adults with chronic ITP can use for the long-term.”

The safety profile of Revolade seen in the EXTEND trial is consistent with that observed in the pivotal 24-week Phase III RAISE study.\(^1,2\) Long-term use of Revolade was not associated with a clinically relevant increase in bone marrow reticulin or collagen fibers.\(^5\) The most common adverse events were headache (28%), nasopharyngitis (25%), upper respiratory tract infection (23%), and fatigue (17%)\(^1,2\).

The efficacy results of EXTEND demonstrated that median platelet counts were elevated to \(\geq 50 \times 10^9/L\) within two weeks of Revolade treatment, with median platelet counts \(>50 \times 10^9/L\) maintained for more than four years. Post-baseline, overall bleeding rates declined and the majority of bleeding that occurred during more than six years of the study was Grade 1 according to the World Health Organization bleeding scale.\(^1,2\) In addition, 91.4% (276/302) of patients achieved platelet counts \(\geq 30 \times 10^9/L\) without rescue treatment, and 85.8% (259/302) achieved platelet counts \(\geq 50 \times 10^9/L\) without rescue treatment.\(^1,2\).
About the EXTEND Clinical Trial
EXTEND, an open-label extension study of four trials (including the pivotal trial) of Revolade, enrolled 302 adults with chronic ITP who had received prior therapy for their ITP, and is the largest study of its kind. The objectives were to assess the safety and efficacy of long-term treatment with Revolade, including the proportion of patients achieving stable platelet counts during treatment with Revolade; maximum duration of platelet count elevation ≥50×10⁹/L or ≥30×10⁹/L during treatment with Revolade, and the effect of Revolade on reducing and/or sparing concomitant ITP therapies, while maintaining a platelet count ≥50×10⁹/L[1,2].

Revolade was started at a dose of 50 mg/day and titrated to 25-75 mg/day or less often based on platelet counts. Maintenance dosing continued after minimization of concomitant ITP medication and optimization of Revolade dosing. The overall median duration of exposure was 2.4 years (range, 2 days to 8.8 years) and mean average daily dose was 50.2 (range, 1–75) mg/day[1,2]. One hundred thirty-five adult patients (45%) completed the study and 75 adult patients (25%) were treated for four or more years. Most patients were aged <65 years, female, and had platelet counts >15×10⁹/L at baseline. About one third were using concomitant medications at baseline, and 53% had received three or more prior ITP therapies[1,2].

Grade 3 and 4 adverse events (AEs) occurred in 26% and 6% of patients, respectively. Grade 3 cataract occurred in four (1%) patients and Grade 3 pain in extremity in six (2%) patients. Grade 3 AEs occurring in three (<1%) patients each included diarrhea, headache, migraine, dyspnea, platelet count decreased, and menorrhagia; those occurring in five (2%) patients each included pneumonia, fatigue, back pain, alanine aminotransferase increased, aspartate aminotransferase increased, anemia, and hypertension. Grade 4 anemia and thrombocytopenia occurred in three (<1%) and four (1%) patients, respectively. All other Grade 4 events occurred in one patient each[1,2].

Sub-analysis in patients with or without splenectomy
In addition, a planned sub-analysis compared the safety and efficacy of long-term Revolade treatment in patients with or without splenectomy in the EXTEND trial[4].

Of the 302 adult patients in the trial, 115 with splenectomy (38%) and 187 without splenectomy (62%) had similar characteristics at baseline, except that more splenectomized patients were receiving ITP medications (47% vs 25%) and had a history of clinically significant bleeding (23% vs 13%). More than half of the patients in both groups received Revolade for ≥24 months. After Revolade treatment, response rates (patients achieving platelets ≥50×10⁹/L without rescue therapy) were somewhat higher in the non-splenectomized patients. Overall, rates of some bleeding AEs were higher in splenectomized patients, but most occurred at comparable rates. Events occurring in ≥4% of patients in the splenectomized and non-splenectomized groups, respectively, included mouth hemorrhage (4% and 1%), epistaxis (14% and 6%), petechiae (8% and 2%), ecchymosis (2% and 4%), contusion (3% and 4%), and hematuria (2% and 4%). The proportion of patients in each splenectomy group who were able to discontinue or reduce concomitant medications from baseline were similar, with 13% in each group attempting to reduce/discontinue medication and 11–12% stopping at least one medication[4].

About Chronic ITP
People who have ITP often have purple bruises or tiny red or purple dots on the skin. They also may have nosebleeds, bleeding from the gums during dental work, or other bleeding that is hard to stop. In most cases, an autoimmune response in which a person’s immune system attacks and destroys its own platelets is thought to cause ITP[3].
ITP is classified by duration into newly diagnosed, persistent (3-12 months’ duration) and chronic (>12 months’ duration). Chronic ITP is more likely to occur in adults, and women are affected two to three times more often than men\(^6,7,8\).

The goal of treatment in chronic ITP is to maintain a safe platelet count that reduces the risk of bleeding. Treatment is determined by the severity of the symptoms. In most cases, drugs that alter the immune system's attack on the platelets are prescribed to help manage bleeding and bruising in adults\(^6,8,9\).

**About Revolade® (eltrombopag)**

Revolade is approved in more than 100 countries for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an inadequate response or are intolerant to other treatments. Eltrombopag (marketed as Promacta\(^\circledast\) in the US) is approved in the EU and the US for patients one year and older with chronic ITP who have had an insufficient response to other treatments. Revolade is also approved in 45 countries for the treatment of patients with severe aplastic anemia (SAA) who are refractory to other treatments, and in more than 50 countries for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow them to initiate and maintain interferon-based therapy.

**Revolade Important Safety Information**

Revolade may cause serious side effects, such as liver problems, high platelet counts and a higher chance for blood clots, bleeding after stopping treatment, and bone marrow problems.

Revolade may damage the liver and cause serious, even life threatening, illness. Blood tests to check the liver are needed before taking Revolade and during treatment. When certain antiviral treatments are given together with Revolade for the treatment of thrombocytopenia due to hepatitis C virus (HCV) infections, some liver problems can get worse.

A doctor will order the blood tests and any other tests required. In some cases Revolade treatment may need to be stopped. Patients should tell a doctor right away if they have any of these signs and symptoms of liver problems: yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, unusual tiredness, right upper stomach area pain.

Patients have a higher chance of getting a blood clot if their platelet count is too high during treatment with Revolade, but blood clots can occur with normal or even low platelet counts. Patients who have cirrhosis of the liver are at risk of a blood clot in a blood vessel that feeds the liver. Patients may have severe complications from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. A doctor will check the patient’s blood platelet counts, and change the dose or stop Revolade if platelet counts get too high. Patients should tell their doctor right away if they have signs and symptoms of a blood clot in the leg, such as swelling or pain/tenderness of one leg.

When patients with chronic ITP stop taking Revolade, their blood platelet count will drop back down to what it was before they started taking Revolade. These effects are most likely to happen within 4 weeks after patients stop taking Revolade. The lower platelet counts may increase risk of bleeding. A doctor will check platelet counts for at least 4 weeks after patients stop taking Revolade. Patients should tell their doctor or pharmacist if they have any bruising or bleeding after they stop taking Revolade.

Patients being treated for the disease may have problems with their bone marrow. Medicines like Revolade could make this problem worse. Signs of bone marrow changes may show up as abnormal results in blood tests. A doctor may also carry out tests to directly check the bone marrow during treatment with Revolade.
The most common side effects of Revolade when used to treat adult patients with chronic ITP include headache, anemia, decreased appetite, insomnia, cough, nausea, diarrhea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral edema.

The most common side effects of Revolade when used to treat pediatric patients with chronic ITP include upper respiratory tract infection, nasopharyngitis, cough, diarrhea, pyrexia, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, increased AST and rhinorrhea.

The most common side effects of Revolade when used to treat patients with chronic HCV and antiviral agents include headache, anemia, decreased appetite, insomnia, cough, nausea, diarrhea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral edema.

The most common side effects of Revolade when used to treat patients with severe aplastic anemia (SAA) include headache, dizziness, insomnia, cough, dyspnea, oropharyngeal pain, rhinorrhea, nausea, diarrhea, abdominal pain, transaminases increased, ecchymosis, arthralgia, muscle spasms, pain in extremity, fatigue, febrile neutropenia, and pyrexia. Common side effects that may show up in blood tests include increase in some liver enzymes and laboratory tests that may show abnormal changes to the cells in the bone marrow.

Please see full EU Summary of Product Characteristics for Revolade (eltrombopag).

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “long-term,” “continues,” “may,” “will,” “can,” “goal,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Revolade (eltrombopag), or regarding potential future revenues from Revolade. 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 Revolade 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 Revolade will be commercially successful in the future. In particular, management’s expectations regarding Revolade 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.
References
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Novartis Media Relations
Central media line : +41 61 324 2200
Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Karen Hamel
Novartis Oncology Media Relations
+1 862 778 2836 (direct)
+1 862 210 5328 (mobile)
karen.hamel@novartis.com

e-mail: media.relations@novartis.com

Novartis Investor Relations
Central phone: +41 61 324 7944
Samir Shah +41 61 324 7944
Pierre-Michel Bringer +41 61 324 1065
Thomas Hungerbuehler +41 61 324 8425
Isabella Zinck +41 61 324 7188

North America:
Richard Pulik +1 212 830 2448
Sloan Pavsner +1 212 830 2417

e-mail: investor.relations@novartis.com

e-mail: investor.relations@novartis.com