Novartis continues to innovate in CML with long-term treatment-free remission results following Tasigna® use and promising combination data with investigational compound asciminib (ABL001)

- Results from two Phase II trials, ENESTfreedom and ENESTop, support and extend previous findings of long-term durability of molecular response after stopping Tasigna, reducing time on drug for many CML patients1,2

- New Phase I data for asciminib in combination with imatinib, nilotinib or dasatinib in heavily pre-treated Ph+ CML-CP patients demonstrate potential molecular response and a well-tolerated safety profile3,4

Basel, June 14, 2019 – Long-term follow-up data from the ongoing, pivotal open-label ENESTfreedom and ENESTop trials showed sustained treatment-free remission (TFR) after stopping frontline and second-line Tasigna (nilotinib) therapy in eligible adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase (CP). Separate data demonstrate promising results for asciminib (ABL001), an investigational allosteric BCR-ABL inhibitor, in combination with three different tyrosine kinase inhibitors (TKIs) in heavily pre-treated Ph+ CML-CP patients. The results will be presented at the 24th Congress of the European Hematology Association (EHA) in Amsterdam1-4.

"We are pleased to report many of our Tasigna clinical-trial patients continue to maintain treatment-free remission for nearly four years with a low adverse event burden," said John Tsai, MD, Head of Global Drug Development and Chief Medical Officer, Novartis. "Long-term trials like ENESTfreedom and ENESTop, as well as promising Phase I data from asciminib, are helping us to reimagine medicine and the way CML is treated."

Results from the ENESTfreedom study showed that about 44% of patients remained in TFR (84/190) for 192 weeks after stopping frontline Tasigna treatment. The treatment-free survival rate at 192 weeks was nearly 49%. About 99% (90/91) and 92% (84/91) of patients who resumed nilotinib due to loss of major molecular response (MMR) during the TFR phase regained MMR and molecular response4,5, respectively. Among 91 patients who resumed nilotinib, the most common adverse events (AEs) were nasopharyngitis (18.7%) as well as pruritus, fatigue and increased lipase (14.3% each). The majority of AEs were grade 1/21.

Consistent results were observed in the ENESTop trial: About 46% of patients remained in TFR (58/126) for 192 weeks after stopping second-line Tasigna treatment. The treatment-free survival rate at 192 weeks was over 50%. Among 59 patients who resumed nilotinib, the most common adverse events (AEs) were hypertension (20.3%) and arthralgia (13.6%). The majority of AEs were grade 1/22.

Novartis will also present data from a Phase I trial of asciminib in combination with ATP-competitive TKI in heavily-pretreated patients with Ph+ CML-CP. Importantly, each
combination was evaluated in a dose finding study assessing different asciminib dose levels, so results are not comparable across the three treatment arms. The preliminary results showed:

Among patients who at baseline did not achieve BCR-ABL1 International Scale [IS] <1%, by 48 weeks\textsuperscript{3,4}:
- 60% (9/15) achieved molecular response <1% in the asciminib-plus-imatinib arm, and
- 43% (6/14) and 56% (5/9) patients achieved molecular response <1% in the asciminib-plus-nilotinib and asciminib-plus-dasatinib arms, respectively.

In evaluable patients without MMR at baseline, by 48 weeks\textsuperscript{3,4}:
- 42% (8/19) achieved MMR with asciminib plus imatinib with median treatment exposure of 54.6 weeks, and
- 31% (4/13) patients with asciminib plus nilotinib and 36% (5/14) patients with asciminib plus dasatinib, respectively, achieved MMR.

No patients with MMR at baseline lost MMR due to either of the three combination therapies. All combinations showed tolerable safety profile in heavily pretreated CML patients\textsuperscript{3,4}:
- Among patients who received asciminib plus imatinib, the most common any-grade AEs were nausea (32%), increased lipase (20%), as well as abdominal pain, peripheral edema and vomiting (16% each).
- Among patients who received asciminib plus nilotinib, most common any-grade AEs were myalgia (35%), increased lipase (29%), and increased amylase, fatigue and pruritus (24% each).
- Among patients who received asciminib plus dasatinib, most common any-grade AEs were increased lipase (35%) and diarrhea, headache and nausea (18% each).

“While the introduction of TKIs has changed the CML treatment paradigm, there remains a subset of patients who are intolerant or resistant to TKI therapy,” said Jorge Cortes, MD, Deputy Chair and Professor of Medicine in the Department of Leukemia at MD Anderson Cancer Center, Houston Texas. “These initial results from combination therapy with currently available TKIs and a BCR-ABL1 inhibitor like asciminib are encouraging – and give us the potential to increase molecular response and prevent development of mutations.”

Commitment to CML
Our ongoing research in Ph+ CML has helped transform the disease from a fatal leukemia to a chronic condition in most patients. Novartis maintains an unwavering commitment to scientific innovation and access to care for patients worldwide. As an organization committed to patients, Novartis continues to reimagine CML care by pursuing ambitious goals with courage, passion and commitment for the global CML community.

About Tasigna
Tasigna (nilotinib) is approved in more than 130 countries for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in chronic phase and with chronic and accelerated phase Ph+ CML resistant or intolerant to at least one prior therapy, including Glivec\textsuperscript{©} (imatinib). Tasigna is also approved for the treatment of pediatric patients with newly diagnosed Ph+ CML in the chronic phase and with resistance or intolerance to prior TKI therapy.

About asciminib
Asciminib (ABL001) is an investigational allosteric BCR-ABL inhibitor with a mechanism of action distinct from currently available TKI treatments for patients with CML. There is a broad clinical development program underway for asciminib both as a potential monotherapy such as the Phase III ASCEmBL third-line CML study and in combination with other therapies, such as the Phase II ASC4MORE study investigating asciminib plus imatinib for patients with CML-CP without deep molecular response. It is currently being studied in patients with and without
genetic mutations that make them resistant to many targeted CML therapies. If proven safe and effective, asciminib has the potential to be a meaningful therapy, increasing the treatment options in CML and addressing the treatment needs of patients.

**IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules**

Use with caution in patients with uncontrolled or significant cardiac disease and in patients who have or may develop prolongation of QTc. Low levels of potassium or magnesium must be corrected prior to Tasigna administration. Monitor closely for an effect on the QTc interval. Baseline ECG is recommended prior to initiating therapy and as clinically indicated. Cases of sudden death have been reported in clinical studies in patients with significant risk factors. Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Avoid food 2 hours before and 1 hour after taking dose.

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving TKI treatment.

Use with caution in patients with liver impairment, with a history of pancreatitis and with total gastrectomy. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not use Tasigna. Tasigna may cause fetal harm in pregnant women. If pregnancy is planned during the treatment-free remission phase, the patient must be informed of a potential need to re-initiate treatment with Tasigna during pregnancy. Women should not breastfeed while taking Tasigna and for 2 weeks after the last dose.

Cases of cardiovascular events included ischemic heart disease-related events, peripheral arterial occlusive disease, and ischemic cerebrovascular events have been reported. Serious cases of hemorrhage from various sites including gastrointestinal were reported in patients receiving Tasigna. Grade 3 or 4 fluid retention including pleural effusion, pericardial effusion, ascites and pulmonary edema have been reported. Cases of tumor lysis syndrome have been reported in Tasigna-treated patients who were resistant or intolerant to prior CML therapy.

In pediatric patients the long-term effects of prolonged treatment with Tasigna is unknown.

Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5 (BCR-ABL/ABL <=0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation. Loss of major molecular response (MMR=BCR-ABL/ABL <=0.1% IS) or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4=BCR-ABL/ABL <=0.01% IS) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. It is crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission. For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Musculoskeletal pain, myalgia, pain in extremity, arthralgia, bone pain and spinal pain may occur upon discontinuing treatment with Tasigna within the framework of attempting treatment-free remission.

The most frequent Grade 3 or 4 adverse events are hematological (neutropenia, thrombocytopenia, anemia) which are generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. Chemistry panels, including electrolytes, lipid profile, liver enzymes, and glucose should be checked prior to therapy and periodically. Tasigna can cause increases in serum lipase. The most frequent non-hematologic adverse
events were rash, pruritus, nausea, fatigue, headache, alopecia, myalgia, constipation and diarrhea.

Please see full Prescribing Information at http://www.tasigna.com/.

Disclaimer
This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations 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 the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, 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 is reimagining medicine to improve and extend people’s lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world’s top companies investing in research and development. Novartis products reach more than 750 million people globally and we are finding innovative ways to expand access to our latest treatments. About 105 000 people of more than 140 nationalities work at Novartis around the world. Find out more at www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References
2. François-Xavier Mahon, et al. ENESTop 192-wk results: durability and impact on quality of life of treatment-free remission (tfr) following second-line (2) nilotinib (nil) in patients (pts) with chronic myeloid leukemia (cml).


###

-----

Novartis Global External Communications
E-mail: media.relations@novartis.com

Antonio Ligi  
Novartis Global External Communications  
+41 61 324 1374 (direct)  
+41 79 723 3681 (mobile)  
antonio.ligi@novartis.com

Michael Billings  
Novartis Hematology Communications  
+1 662 778 8656 (direct)  
+1 201 400 1854 (mobile)  
michael.billings@novartis.com

Eric Althoff  
Novartis US External Communications  
+ 1 646 438 4335  
eric.althoff@novartis.com

-----

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central  
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  
Cory Twining  +1 212 830 2417