NEJM publishes full analysis of Rydapt® (midostaurin) Phase III RATIFY trial in newly diagnosed FLT3-mutated acute myeloid leukemia (AML)

- Significant overall survival benefit observed for FLT3+ AML patients consistent across FLT3 mutation subgroups, including ITD and TKD
- Detailed data show Rydapt plus standard chemotherapy improved event-free survival in FLT3-mutated AML versus chemotherapy alone
- First publication of RATIFY data following ASH 2015 presentation; result of over a decade’s collaboration with Alliance for Clinical Trials in Oncology/CALGB

Basel, June 23, 2017 – Novartis today announced that full results from the Rydapt® (midostaurin) Phase III RATIFY (CALGB 10603 [Alliance]) clinical trial were published in The New England Journal of Medicine (NEJM)1. Top-line data from this study were previously presented during the plenary session at the American Society of Hematology (ASH) Annual Meeting in 20152. New data include disease-free survival (DFS), further analysis of patients undergoing transplant and expanded safety information.

“The data from the CALGB 10603/RATIFY trial reinforce the efficacy and safety of Rydapt in patients with FLT3-mutated AML and set the stage for a shift in the way the medical community can approach this difficult-to-treat disease,” said Richard M. Stone, MD, Chief of Staff and Director of the Adult Leukemia Program at Dana-Farber Cancer Institute, and Alliance for Clinical Trials in Oncology study chair for the RATIFY trial. “This study has provided critical insights for the AML community and shows the potential of clinical research carried out by international investigators with support from both public and private sources.”

Study Results Published in NEJM
In RATIFY, patients aged 18-59 years treated with Rydapt in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy experienced significant improvement in overall survival (OS) with a 22% reduction in the risk of death compared with chemotherapy plus placebo. In patients in the Rydapt arm, OS was 74.7 months [95% CI, 31.5-not reached] vs. 25.6 months [95% CI, 18.6-42.9] in the placebo arm (one-sided stratified log-rank \( p=0.009 \), HR=0.78). At four years, OS was 51.4% in the Rydapt arm, compared with 44.3% in the placebo arm1.

The median event-free survival (EFS) was 8.2 months (95% CI, 5.4-10.7) in the Rydapt arm and 3.0 months (95% CI, 1.9-5.9) in the placebo arm (one-sided stratified log-rank \( p=0.002 \), HR=0.78). Median DFS was greater with the addition of Rydapt versus the placebo arm (26.7 months [95% CI, 19.4-not reached] vs. 15.5 months [95% CI, 11.3-23.5], respectively; \( p=0.01 \). The complete remission (CR) rate, defined as CR reported within 60 days of protocol therapy initiation, was 58% in the Rydapt arm and 53.5% in the placebo arm (\( p=0.15 \)). The benefit of Rydapt on OS and EFS was consistent across all FMS-like tyrosine kinase 3 (FLT3) mutation subgroups, including internal tandem duplication (ITD) and tyrosine kinase domain (TKD) FLT3 mutations1.
"The Rydapt RATIFY trial is a testament to Novartis’ dedication to exploring opportunities to create therapies for patients with difficult to treat diseases," said Vasant Narasimhan, Global Head of Drug Development and Chief Medical Officer, Novartis. "These results represent the culmination of years of work and dedication from investigators around the world who were driven to find a targeted treatment for these patients."

More patients in the Rydapt arm were able to undergo allogenic hematopoietic stem cell transplantation (HCT) during their first complete response versus placebo (28.1% vs. 22.7%, respectively; p=0.10). When censoring patients at the time of transplant (when protocol therapy was discontinued), OS was numerically better for those in the Rydapt arm versus placebo arm, with a 24.3% reduction in the risk of death at four years (63.7% vs. 55.7% respectively, p=0.08)³.

The most frequent Grade 3 to 5 non-hematologic adverse events (AEs) (incidence greater than or equal to 20%) in the Rydapt arm were febrile neutropenia and infection. In the placebo arm, the most common AEs were febrile neutropenia, infection and lymphopenia. There were few significant differences (greater than 5%) observed in the overall rate of Grade 3 to 5 AEs between the treatment arms - patients receiving Rydapt experienced higher rates of anemia and rash¹. Please see below for additional important US safety information³.

RATIFY, the largest clinical trial in FLT3-mutated AML to date, included 3,277 patients screened and 717 study participants from around the world. The full data from the randomized Phase III trial have now been published and include data outside the parameters of the US Prescribing Information and Swiss Product Information. Based on data from the RATIFY clinical trial, The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for AML now include use of midostaurin in FLT3-mutated AML⁴.

About AML
AML, a rare and aggressive cancer of the blood and bone marrow, is the most common acute leukemia in adults. It accounts for approximately 25% of all adult leukemias worldwide, with the highest incidence rates occurring in the US, Europe and Australia⁵. It also has the lowest survival rate of all adult leukemias⁶.

AML prevents white blood cells from maturing, causing an accumulation of “blasts,” which do not allow room for the normal blood cells⁶. Mutations in specific genes are found in many cases of AML⁷, and genetic testing for mutations in newly diagnosed AML patients can help to determine prognosis and potential treatment strategies⁸.

Approximately one-third of AML patients will have a FLT3 gene mutation⁷. FLT3 is a type of cell-surface receptor which plays a role in increasing the number of certain blood cells⁹. The FLT3 gene mutation can result in faster disease progression, higher relapse rates and lower rates of survival than other forms of AML⁷,⁹,¹⁰.

About Rydapt® (midostaurin)
Rydapt® (midostaurin) is an oral, multi-targeted inhibitor of multiple kinases, including FLT3 and KIT, which help regulate many essential cell processes, interrupting cancer cells’ ability to grow and multiply⁹.

In the US, Rydapt is Food and Drug Administration (FDA)-approved for the treatment of adults with newly diagnosed AML who are FLT3 mutation-positive (FLT3+) as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation⁷. Rydapt is not indicated in the US as a single-agent induction therapy for the treatment of patients with AML. For a description of the experience with single-agent treatment beyond induction and consolidation, healthcare professionals in the US should refer to the Clinical Studies section of the US Prescribing Information (14.1)⁶.
The full US Prescribing Information for Rydapt can be found at:

Rydapt is also approved in Switzerland for use in combination with standard induction and consolidation chemotherapy, followed by maintenance monotherapy for treatment of newly diagnosed adult AML patients who have an FLT3 mutation. Novartis has submitted a regulatory application for Rydapt to the European Medicines Agency (EMA) and this application is currently under review.

Indications vary by country and not all indications are available in every country. The safety and efficacy profile of Rydapt has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that Rydapt will become commercially available for additional indications anywhere else in the world.

**Rydapt Important Safety Information**

Patients who are allergic to midostaurin or any of the ingredients in Rydapt should not take Rydapt. If a patient taking Rydapt develops signs of an allergic reaction, they should seek medical help immediately. Signs of an allergic reaction include trouble breathing, flushing, chest pain, throat tightness, and swelling of lips, mouth or throat.

Rydapt should be not be used during pregnancy since Rydapt may harm an unborn baby. Pregnancy testing should be conducted for women who might become pregnant. Effective birth control should be used during treatment and for at least four months after stopping Rydapt. If a patient becomes pregnant or thinks she may be, the patient should tell their doctor right away. Women should not breastfeed during treatment with Rydapt and for at least four months after the final dose. Men taking Rydapt who have female partners that are able to become pregnant should use effective birth control during his treatment with Rydapt and for at least four months after the last Rydapt dose. Rydapt may cause fertility problems in women and men, which may affect their ability to have children.

Rydapt may cause lung problems that may lead to death. Patients on Rydapt who develop a new or worsening cough, shortness of breath, or chest discomfort should get medical help right away. These may be signs of serious lung problems.

Common sides effects reported during Rydapt treatment for AML included low level of white blood cells with fever (febrile neutropenia); nausea; redness, pain or ulcers inside the mouth (mucositis); vomiting; headache; bruising; muscle or bone pain; nose bleeds; device-related infection; high blood sugar levels (hyperglycemia) and upper respiratory infections.

If side effects including nausea, vomiting, and diarrhea occur, get worse or do not go away during treatment with Rydapt, patients should contact their doctor. Depending on the side effect and/or severity of the side effect that occur, their doctor may decrease their dose, temporarily stop, or completely stop treatment with Rydapt.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Rydapt may affect how these medicines work or these other medicines may affect how Rydapt works.

**Disclaimer**

The foregoing release contains forward-looking statements that can be identified by words such as "set the stage," "can," "potential," "dedication," "under review," "yet," "will," or similar terms, or by express or implied discussions regarding potential additional marketing approvals for Rydapt, potential new indications or labeling for Rydapt, or regarding potential future revenues from Rydapt. 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 Rydapt will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that Rydapt will be submitted or approved for sale in any additional markets, or at any particular time. Nor can there be any guarantee that Rydapt will be commercially successful in the future. In particular, management’s expectations regarding Rydapt 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; 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 and reimbursement pressures; 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, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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References
2. Stone RM, Mandrekar SJ, Sanford BL, et al. The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P- Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance]). Presented at the 57th Annual Meeting of the American Society of Hematology. Abstract 6.

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