Novartis drug PKC412 (midostaurin) receives Breakthrough Therapy designation from the FDA for newly-diagnosed FLT3-mutated acute myeloid leukemia (AML)

- PKC412 (midostaurin) significantly improved overall survival of adult patients eligible to receive standard induction and consolidation chemotherapy
- AML has the lowest survival rate of all adult leukemias and the treatment strategy with chemotherapy has remained unchanged for more than 25 years
- Currently there are no approved targeted AML treatments; global regulatory submissions for PKC412 (midostaurin) are on track to begin in H1 2016

Basel, February 19, 2016 – Novartis announced today that the United States Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to PKC412 (midostaurin). PKC412 (midostaurin) is an investigational treatment for adults with newly-diagnosed AML who are FLT3 mutation-positive, as detected by an FDA-approved test, and who are eligible to receive standard induction and consolidation chemotherapy.

The Breakthrough Therapy designation for PKC412 (midostaurin) is primarily based upon the positive results from the Phase III RATIFY (CALGB 10603) clinical trial. This study was conducted in partnership with the Alliance for Clinical Trials in Oncology and presented during a plenary session at the 57th American Society of Hematology (ASH) Annual Meeting.

Patients who received PKC412 (midostaurin) and standard induction and consolidation chemotherapy experienced a significant improvement in overall survival (OS) (hazard ratio = 0.77, \( P = 0.0074 \)) compared to those who received standard induction and consolidation chemotherapy alone. The median OS for patients in the PKC412 (midostaurin) treatment group was 74.7 months (95% confidence interval [CI]: 31.7, not attained), versus 25.6 months (95% CI: 18.6, 42.9) for patients in the placebo group. No statistically significant differences were observed in the overall rate of grade 3 or higher hematologic and non-hematologic adverse events in the PKC412 (midostaurin) treatment group versus the placebo group. A total of 37 deaths were reported, with no difference in treatment-related deaths observed between groups.

“For more than 25 years, medical developments have been limited for AML patients and the chemotherapy treatment strategy has essentially remained unchanged,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “We look forward to working closely with the FDA to bring PKC412 (midostaurin), the first potential AML targeted therapy, to patients as quickly as possible.”

According to the FDA, Breakthrough Therapy designation is intended to expedite the development and review of new medicines that treat serious or life-threatening conditions, if the therapy has demonstrated substantial improvement over an available therapy on at least one clinically significant endpoint. The designation includes all of the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program.
This designation adds to the growing number granted to Novartis by the FDA, illustrating the company's continued commitment to developing innovative therapies for diseases with a significant unmet medical need.

In the US, about 20,000 people were diagnosed with AML in 2015, the majority of whom were adults\(^6\). According to the latest research, approximately one-third of AML patients also harbor a FLT3 gene mutation\(^7\), which is associated with worse outcomes and shorter survival than in those without the mutation\(^8\). PKC412 (midostaurin) is the first drug targeting FLT3 to demonstrate an overall survival benefit in AML\(^4\).

Since PKC412 (midostaurin) is investigational at this time and is expected to be submitted for FDA approval, Novartis opened a Global Individual Patient Program (compassionate use program) and a US Expanded Treatment Protocol (ETP) to enable PKC412 (midostaurin) access. Patients 18 years of age and older with newly-diagnosed FLT3-mutated AML and able to receive standard induction and consolidation therapy will be considered.

In order to help identify patients who may have a FLT3 mutation and potentially benefit from treatment with PKC412 (midostaurin), Novartis is collaborating with Invivoscribe Technologies, Inc. who is leading regulatory submissions for a companion diagnostic.

**About acute myeloid leukemia (AML) and the FLT3 mutation**

AML is an aggressive cancer of the blood and bone marrow\(^9\). It prevents white blood cells from maturing, causing an accumulation of “blasts” which do not allow room for the normal blood cells\(^9\). AML is the most common acute leukemia in adults, but also has the lowest survival rate\(^1\). AML accounts for approximately 25% of all adult leukemias worldwide, with the highest incidence rates occurring in the United States, Europe and Australia\(^1\).

Mutations in specific genes are found in many cases of AML, and biomarker testing is considered standard of care for newly-diagnosed patients to help determine the best possible treatment option\(^7\). FMS-like tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase, a type of cell-surface receptor, which plays a role in the proliferation, or increase, in the number of certain blood cells\(^10\).

**About PKC412 (midostaurin)**

PKC412 (midostaurin) is an investigational, oral, multi-targeted kinase inhibitor in development for the treatment of patients with AML with a FLT3 mutation. The safety and efficacy profile has not been fully established. There is no guarantee that PKC412 (midostaurin) will become commercially available.

PKC412 (midostaurin) is also being investigated for the treatment of aggressive systemic mastocytosis/mast cell leukemia.

**Disclaimer**

The foregoing release contains forward-looking statements that can be identified by words such as "Breakthrough Therapy," "on track," "investigational," "look forward," "potential," "commitment," "expected," "will," "potentially," "being investigated," or similar terms, or by express or implied discussions regarding potential marketing approvals for PKC412 (midostaurin), or regarding potential future revenues from PKC412. 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 PKC412 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that PKC412 will be commercially successful in the future. In particular, management's expectations regarding PKC412 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 issues; unexpected manufacturing or quality 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 119,000 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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References
4. Stone RM, 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.

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

Fiona Phillips
Novartis Oncology
+1 862 778-7705 (direct)
+1 862 217-9396 (mobile)
fiona.phillips@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