Novartis drug PKC412 (midostaurin) granted FDA Priority Review for newly-diagnosed FLT3-mutated AML and advanced systemic mastocytosis

- **Priority Review based on data from the largest clinical trials conducted to date in each indication**
- **Designation will shorten FDA expected review time to within six months**; EMA also accepted the PKC412 (midostaurin) file for review
- **The AML treatment strategy has remained unchanged for more than 25 years** and PKC412 (midostaurin) may represent first FLT3-mutated AML drug with a survival benefit

**Basel, November 14, 2016** – Novartis today announced that the US Food and Drug Administration (FDA) granted Priority Review to the PKC412 (midostaurin) new drug application (NDA) for the treatment of acute myeloid leukemia (AML) in newly-diagnosed adults with an FMS-like tyrosine kinase-3 (FLT3) mutation, as well as for the treatment of advanced systemic mastocytosis (SM). The prem market approval application (PMA) for the PKC412 (midostaurin) FLT3 companion diagnostic, developed in collaboration with Invivoscribe Technologies, Inc. (IVS)* has also been accepted for review by the FDA. Outside the US, the marketing authorization application for PKC412 (midostaurin) in these indications has already been accepted by the European Medicines Agency (EMA).

“FLT3-mutated AML and advanced SM are devastating and rare diseases, with significant unmet needs due to limited existing treatment options,” said Bruno Strigini, CEO, Novartis Oncology. “This regulatory designation signifies the importance of midostaurin as a potential therapy for these patients who haven’t had the benefit of targeted medicines.”

The NDA submission for PKC412 (midostaurin) includes data from the largest clinical trials conducted to date in each indication. In the Phase III RATIFY trial (CALGB 10603), which investigated PKC412 (midostaurin) plus standard chemotherapy versus placebo plus standard chemotherapy in adult patients less than 60 years of age with FLT3-mutated AML, those in the PKC412 (midostaurin) arm experienced a statistically significant improvement in overall survival (OS) with a 23% reduction in risk of death compared to the placebo arm (hazard ratio [HR] = 0.77, P = 0.0074). Based on these data, PKC412 (midostaurin) was also granted Breakthrough Therapy designation by the FDA earlier this year for newly-diagnosed FLT3-mutated AML.

In the RATIFY trial, no statistically significant differences were observed in the overall rate of grade 3 or higher hematologic and non-hematologic adverse events (AEs) in the PKC412 (midostaurin) treatment group versus the placebo group. The most frequent all grade AEs were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, petechiae (small red skin spots) and pyrexia. A total of 36 deaths occurring within 30 days of the last dose of study drug were reported, with no difference in treatment-related deaths observed between groups.
Data from the Phase II single-arm study (CPKC412D2201) evaluating the efficacy of PKC412 (midostaurin) in patients with advanced SM were also published in the New England Journal of Medicine in June 2016. The study showed that treatment with PKC412 (midostaurin) resulted in an overall response rate of 60% (defined as complete or partial resolution of organ damage) with a median duration of response of 24.1 months (95% CI, 10.8-not estimated [NE]) and a median OS of 28.7 months (95% CI, 18.1-NE)\(^2\). The most frequent AEs were low-grade nausea, vomiting and diarrhea. New or worsening grade 3 or 4 neutropenia, anemia and thrombocytopenia occurred mostly in patients with pre-existing cytopenias\(^3\).

A Priority Review designation is granted by the FDA to therapies that may provide significant improvements in the treatment, diagnosis or prevention of serious conditions\(^3\). According to the FDA, the goal is to take action on a Priority Review application within six months, compared to 10 months under the standard review process\(^3\). Novartis has been granted a growing number of Priority Review designations by the FDA, underscoring the company’s ongoing commitment to developing innovative therapies for rare diseases or underserved cancer patients.

Since PKC412 (midostaurin) remains investigational at this time, both within the US and globally, Novartis opened a Global Individual Patient Program (compassionate use program) and in the US, an Expanded Treatment Protocol, to enable access to eligible patients with newly-diagnosed AML and advanced SM. Physicians who wish to request PKC412 (midostaurin) for eligible patients should contact a Novartis medical representative in their respective countries. In the US, physicians can call 1-888-NOW-NOVA (1-888-669-6682) for more information.

**About AML and the FLT3 mutation**

AML is a rare and aggressive cancer of the blood and bone marrow\(^6\). It is the most common acute leukemia in adults\(^1\). Of the approximately 350,000 people with leukemias worldwide\(^6\), about 25% have AML\(^1\). AML has a low survival rate, with around 25% of patients surviving at 5 years\(^9\).

AML is associated with the accumulation of blood cells that are unable to mature properly, causing a buildup of immature “blast” cells that do not allow room for normal blood cell development\(^8\). Mutations in specific genes are found in many cases of AML, and molecular testing is recommended for newly-diagnosed patients to help determine prognosis and best possible treatment\(^8\).

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. The FLT3 gene mutation is one of the most common in AML, occurring in about one-third of patients, and commonly results in faster disease progression, a higher relapse rate and shorter survival\(^10\-12\).

**About the FLT3 companion diagnostic**

In order to help identify patients who may have a FLT3 mutation and potentially benefit from treatment with PKC412 (midostaurin), Novartis is collaborating with IVS for the development and FDA approval of the FLT3 companion diagnostic. The same test is being CE marked in Europe. Regulatory submissions for the companion diagnostic are being led by IVS.

**About advanced SM**

Systemic mastocytosis (SM) comprises a group of rare diseases, affecting between 1 in 20,000 to 40,000 people worldwide\(^13\). The disease is characterized by uncontrolled growth and accumulation of mast cells – or mediators of allergic responses – in one or more organs\(^14\). In advanced SM, mast cells accumulate in such high quantities that they begin to cause organ damage\(^15\). Patients also suffer from debilitating systemic symptoms such as pruritus (severe itching of the skin), among other symptoms, caused by mast cells releasing inflammatory mediators such as histamine into the blood\(^15\). Median OS is currently between 3.5 years to less than six months depending on subtype\(^14\).
The uncontrolled proliferation of mast cells is caused in many people by a KIT gene mutation – the most common mutation, encoding the D816V substitution, occurs in approximately 90% of patients\(^1\). The KIT gene mutation results in activation of the KIT enzyme, which triggers the abnormal proliferation and survival of mast cells\(^1\).

**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 and for patients with advanced SM. The safety and efficacy profile has not been fully established, and it is not approved for any indication in any market at this time. There is no guarantee that PKC412 (midostaurin) will become commercially available.

**Disclaimer**
The foregoing release contains forward-looking statements that can be identified by words such as “Priority Review,” “will,” “expected,” “may,” “potential,” “Breakthrough Therapy designation,” “goal,” “growing,” “commitment,” “investigational,” “potentially,” “currently,” “in development,” “at this time,” or similar terms, or by express or implied discussions regarding potential marketing approvals for PKC412, 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, 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 approximately 180 countries around the world. For more information, please visit [http://www.novartis.com](http://www.novartis.com).

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\* FLT3 detection is conducted by the Laboratory of Personalized Molecular Medicine pursuant to patents licensed by Invivoscribe technologies, Inc. from Takara Bio of Otsu, Japan.
References

1. 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.


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