Novartis combination Tafinlar® + Mekinist® receives positive CHMP opinion for adjuvant treatment of BRAF V600 mutation-positive melanoma

- Phase III trial showed a 53% reduction in risk of recurrence or death with the combination of a BRAF and MEK inhibitor as adjuvant therapy versus placebo

- Relapse-free survival benefit with Tafinlar + Mekinist combination was observed across all patient subgroups, including stage III A, B and C

- If approved, expected to be the first targeted combination therapy in the EU for adjuvant treatment of melanoma

Basel, July 27, 2018 – Novartis today announced the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion recommending approval of Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. The CHMP recommendation is based on findings from the COMBI-AD study, which was published in The New England Journal of Medicine (NEJM).

Patients who have been diagnosed with stage III melanoma are at a higher risk of recurrence after surgical resection. The COMBI-AD study found a statistically significant 53% reduction in the risk of recurrence or death in patients treated with the BRAF and MEK inhibitor combination therapy after surgical resection versus placebo.

With an estimated 6,000 stage III BRAF mutant melanoma skin cancers diagnosed across Europe each year, this potential approval may provide patients in the EU the opportunity for a targeted combination therapy that doubles relapsed-free survival versus a placebo.

"Melanoma is an aggressive, highly recurrent and often fatal disease. In advanced melanoma, we’ve demonstrated the ability to reduce the risk of death or recurrence by more than half," said Liz Barrett, CEO, Novartis Oncology. "Today’s CHMP opinion brings us another step closer to reimagining earlier stage therapy for patients throughout Europe and making strides to bring improved outcomes for people living with melanoma."

"These relapse-free survival results are unprecedented," said lead investigator Axel Hauschild, MD, PhD, Professor of Dermatology, University Hospital Schleswig-Holstein, in Kiel, Germany. "The overall survival improvements also demonstrated by Tafinlar in combination with Mekinist, among other key secondary endpoints, are encouraging in the treatment of stage III BRAF V600E/K mutation-positive melanoma. Adjuvant treatment options are critical for this patient community at risk for recurrence."
About COMBI-AD Study
The COMBI-AD study evaluated Tafinlar + Mekinist among patients with stage III, BRAF V600E/K-mutant melanoma without prior anticancer therapy, randomized within 12 weeks of complete surgical resection. Patients received the Tafinlar (150 mg BID) and Mekinist (2 mg QD) combination (n = 438) or matching placebos (n = 432). After a median follow-up of 2.8 years, the primary endpoint was met in that combination therapy significantly reduced the risk of disease recurrence or death by 53% vs. placebo (HR: 0.47 [95% CI: 0.39-0.58]; median not yet reached vs. 16.6 months, respectively; p<0.001). The relapse-free survival benefit among the combination arm was observed across all patient subgroups, including stage III A, B and C. The estimated one-year, two-year, and three-year RFS were consistently higher than placebo (one year: 88% vs. 56%; two year: 67% vs. 44%; three year: 58% vs. 39%). The combination treatment group also saw an improvement in a key secondary endpoint of OS (HR: 0.57 [95% CI: 0.42-0.79] p=0.0006, which did not cross the predefined interim analysis boundary of p=0.000019 to claim statistical significance). Other secondary endpoints where the combination demonstrated a clinically meaningful benefit include distant metastasis-free survival (DMFS) (HR: 0.51 [95% CI: 0.40-0.65]), and freedom from relapse (FFR) (HR: 0.47 [95% CI: 0.39-0.57])1.

Adverse events (AEs) were consistent with other Tafinlar + Mekinist studies, and no new safety signals were reported. Of patients treated with the combination, the most frequently reported AE's were pyrexia, fatigue, nausea, headache, chills, diarrhea, vomiting, arthralgia and rash.1

About Melanoma
There are nearly 200,000 new diagnoses of melanoma (stages 0-IV) worldwide each year, approximately half of which have BRAF mutations. Biomarker tests can determine whether a tumor has a BRAF mutation.2,4

Melanoma is staged by how far it has metastasized. In stage III melanoma, tumors have spread to the regional lymph nodes, presenting a higher risk of recurrence or metastases.4 Patients who receive surgical treatment for stage III melanoma may have a high risk of recurrence because melanoma cells can remain in the body after surgery; almost half (44%) of patients receiving placebo per the COMBI-AD study had a recurrence of disease within the first year.5 Adjuvant therapy is additional treatment given after surgical resection, and may be recommended for patients with high-risk melanoma to help reduce the risk of melanoma returning.6

About Tafinlar + Mekinist Combination
In the EU, Tafinlar in combination with Mekinist is approved for the treatment of patients with a BRAF V600 mutation in metastatic melanoma and advanced non-small cell lung cancer.

In the US, Tafinlar in combination with Mekinist is approved for the treatment of patients with a BRAF V600 E or K mutation, detected by an FDA-approved test, in unresectable or metastatic melanoma, adjuvant treatment of melanoma, non-small cell lung cancer (V600 E only) and anaplastic thyroid cancer.

Tafinlar and Mekinist are also indicated in more than 60 countries worldwide, including the US and EU, as single agents to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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

Tafinlar + Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat patients with a change (mutation) in the BRAF gene; therefore, doctors should test their patients before treatment, as patients without a BRAF mutation and with a RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

Doctors should also consider other treatment options for their patients if they had been previously treated with a BRAF inhibitor as single agent, as the limited data available have shown that the efficacy of Tafinlar + Mekinist is lower in these patients.

When Tafinlar is used in combination with Mekinist, or when Tafinlar is administered as monotherapy, it can cause new cancers (both skin cancer and non-skin cancer). Patients should be advised to contact their doctor immediately for any new lesions, changes to existing lesions on their skin, or signs and symptoms of other malignancies.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause severe bleeding, and in some cases can lead to death. Patients should be advised to call their healthcare provider and get medical help right away if they have headaches, dizziness, or feel weak, cough up blood or blood clots, vomit blood or their vomit looks like "coffee grounds," have red or black stools that look like tar, or any unusual signs of bleeding.

Tafinlar in combination with Mekinist, or either drug alone, can cause severe eye problems that can lead to blindness. Patients should be advised to call their healthcare provider right away if they get these symptoms of eye problems: blurred vision, loss of vision, or other vision changes, seeing color dots, halo (seeing blurred outline around objects), eye pain, swelling, or redness.

Tafinlar in combination with Mekinist, or Tafinlar alone, can cause fever which may be serious. When taking Tafinlar in combination with Mekinist, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Patients should be advised to call their healthcare provider right away if they get a fever above 38.5°C (101.3°F) while taking Tafinlar.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause abnormal kidney function or inflammation of the kidney. Abnormal kidney function may happen more often for patients with fever or too much fluid loss. Patients should be advised to call their healthcare provider right away if they have any of the following signs and symptoms of a heart problem: feeling like their heart is pounding or racing, shortness of breath, swelling of their ankles and feet, or feeling lightheaded.

Tafinlar in combination with Mekinist, or Tafinlar alone, can cause abnormal liver function. A patient may feel tired, lose appetite, yellow skin, dark urine colour, or discomfort in abdomen. The liver function abnormality needs to be assessed by laboratory test of the blood. Patients should consult their healthcare provider if they have such experience. Administration of
Tafinlar or Mekinist should be done with caution in patients with moderate to severe hepatic impairment.

Elevations in blood pressure have been reported in association with Mekinist in combination with Tafinlar, or with Mekinist alone, in patients with or without pre-existing hypertension. Patients should be advised to monitor blood pressure during treatment with Mekinist and control potential hypertension by standard therapy, as appropriate.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause inflammation of the lung tissue. Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Rash is a common side effect of Tafinlar in combination with Mekinist, or with Mekinist alone. Tafinlar in combination with Mekinist, or Mekinist alone, can also cause other skin reactions which can be severe, and may need to be treated in a hospital. Patients should be advised to call their healthcare provider if they get any of the following symptoms: skin rash that bothers them or does not go away, acne, redness, swelling, peeling, or tenderness of hands or feet, skin redness.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause muscle breakdown, a condition called Rhabdomyolysis. Patients experiencing muscle pain, tenderness, weakness or a swelling of their muscles should contact their healthcare provider immediately.

Tafinlar in combination with Mekinist, or Tafinlar alone, can uncommonly cause an inflammation of the pancreas (pancreatitis). Patients should be promptly investigated if they experience unexplained abdominal pain and closely monitored if they re-start Tafinlar after a prior episode of pancreatitis.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause blood clots in the arms or legs, which can travel to the lungs and can lead to death. Patients should be advised to get medical help right away if they have the following symptoms: chest pain, sudden shortness of breath or trouble breathing, pain in their legs with or without swelling, swelling in their arms or legs, or a cool or pale arm or leg.

Mekinist in combination with Tafinlar, or Mekinist alone, may increase the risk of developing holes in the stomach or intestine (gastrointestinal perforation). Treatment with Mekinist alone or in combination with Tafinlar should be used with caution in patients with risk factors for gastrointestinal perforation, including concomitant use of medications with a recognized risk of gastrointestinal perforation.

Tafinlar and Mekinist both can cause harm to an unborn baby when taken by a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

The most common side effects of Tafinlar + Mekinist combination include fever, nausea, diarrhea, fatigue, chills, headache, vomiting, joint pain, high blood pressure, rash and cough. The incidence and severity of fever is increased when Mekinist is used in combination with Tafinlar.

Patients should tell their doctor of any side effect that bothers them or does not go away. These are not all of the possible side effects of Tafinlar + Mekinist combination. For more information, patients should ask their doctor or pharmacist.

Patients should take Tafinlar + Mekinist combination exactly as their health care provider tells them. Patients should not change their dose or stop taking Tafinlar + Mekinist combination unless their health care provider advises them to. Mekinist should be taken only once daily.
(either in the morning or evening, at the same time as Tafinlar). The first and second doses of Tafinlar should be taken approximately 12 hours apart. Patients should take Tafinlar + Mekinist at least 1 hour before or 2 hours after a meal. Do not take a missed dose of Tafinlar within 6 hours of the next dose of Tafinlar. Do not open, crush, or break Tafinlar capsules. Do not take a missed dose of Mekinist within 12 hours of the next dose of Mekinist.

Please see full Prescribing Information for Tafinlar and Mekinist.

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 “positive CHMP opinion,” “expected,” “recommending,” “recommendation,” “potential,” “may,” “reimagining,” “encouraging,” “will,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Tafinlar and Mekinist, or regarding potential future revenues from Tafinlar and Mekinist and such other 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 Tafinlar and Mekinist will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that Tafinlar and Mekinist will be commercially successful in the future. In particular, our expectations regarding Tafinlar and Mekinist 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, payer and general public pricing and reimbursement pressures; 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.

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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 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 125,000 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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