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MEDIA & INVESTOR RELEASE

Novartis Adakveo® receives positive CHMP opinion for the prevention of recurrent vaso-occlusive crises in patients with sickle cell disease

- *If approved, Adakveo would be the first targeted sickle cell disease therapy available for use in Europe*
- *CHMP opinion supported by data showing Adakveo significantly reduced the rate of vaso-occlusive crises, with patients on Adakveo spending fewer days in hospital*
- *Vaso-occlusive crises are sudden, unpredictable, and associated with an increased risk of organ damage and mortality*[1]

Basel, July 24, 2020 — Novartis announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending conditional marketing authorization of Adakveo® (crizanlizumab) for the prevention of recurrent vaso-occlusive crises (VOCs), or pain crises, in patients with sickle cell disease aged 16 years and older. Adakveo can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

“Sickle cell disease is a lifelong and devastating condition that affects patients, families and communities,” said Professor Jo Howard, Professor in Haemoglobinopathies, Guy's and St Thomas' NHS Foundation Trust in London. “Today’s positive opinion by CHMP means that we are one step closer to potentially having an important new medicine to treat thousands of vulnerable patients.”

If approved by the European Commission, Adakveo will be the first targeted medicine available in Europe for the prevention of VOCs in patients with sickle cell disease. Adakveo binds to P-selectin – a cell adhesion protein that plays a central role in the multicellular interactions that can lead to vaso-occlusion.[2,3] Though considered a rare condition, tens of thousands of people in Europe have sickle cell disease.[4,5]

“The positive CHMP opinion for Adakveo underscores the potential of this new medicine to prevent recurrent sickle cell pain crises, which can affect all aspects of patients’ lives,” said Susanne Schaffert, PhD, President, Novartis Oncology. “Novartis is dedicated to innovation where there is significant unmet need, and we are grateful for the support we have received from the community of sickle cell patients, advocates and medical experts in Europe and around the world who continue to help us reimagine medicine for this devastating disease.”

The CHMP opinion was based on results of the 52-week, randomized, placebo-controlled SUSTAIN trial, which showed that Adakveo significantly lowered the median annual rate of

VOCs to 1.63 vs 2.98 compared to placebo (*P*=.010), equivalent to a 45% reduction. Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use.[6]

Additional results from the SUSTAIN study include:

- A decrease in the median annual rate of days hospitalized to 4 vs 6.87 days when compared with placebo (a 42% reduction)
- Median time to first VOC, 4.1 months for Adakveo vs 1.4 months for placebo

The European Commission reviews the CHMP recommendation and usually delivers its final decision in approximately two months. In addition, the Committee for Orphan Medicinal Products is currently reviewing the maintenance of the orphan designation of Adakveo. Adakveo is currently approved in the United States and seven other countries for reducing the frequency of vaso-occlusive crises in patients with sickle cell disease aged 16 years and older.

About Sickle Cell Disease

Sickle cell disease is one of the most common genetic blood disorders in the world.[7] It is a chronic, lifelong, debilitating disease that can range in clinical severity.[1] It affects the shape of the red blood cells and can make blood cells stickier than usual.[8] When blood cells stick to one another they can form clusters in the bloodstream.[9,10] These clusters can block and reduce the flow of blood and oxygen and can cause damage to the blood vessels and organs.[1,11] When blood cell clusters get big enough, they can block and slow blood flow that can lead to unpredictable painful crises, also referred to as vaso-occlusive crises.[1] Sickle cell pain crises disrupt patients' lives physically, socially, and emotionally – and can worsen into acute and long-term complications.[12]

People living with sickle cell disease inherited two sickle cell genes from their parents.[8] Those who have the sickle cell trait inherited one sickle cell gene and one normal gene.[8] The sickle cell trait can be asymptomatic, but individuals with the disease can pass the trait on to their children.[9] If both parents have the trait, individuals have a 25% chance of having sickle cell disease, a 50% chance of having sickle cell trait and a 25% chance of having two normal genes or of having neither sickle cell trait or sickle cell disease.[13] A simple blood test can identify whether a person is a carrier of the sickle cell trait.[13]

Sickle cell disease impacts many different populations around the world, but disproportionately affects people from sub-Saharan Africa.[7] It also is common among people with ancestry from South America, Central America, and India, as well as several Mediterranean countries, such as Italy and Turkey, and other populations.[7]

About Adakveo

Adakveo® (crizanlizumab) – previously known as SEG101 – is indicated for the prevention of recurrent VOCs in sickle cell patients aged 16 years and older. It can be given as an add-on therapy to HU/HC or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. It is the first and only targeted biologic that works by binding to P-selectin, a cell adhesion protein that plays a central role in the multicellular interactions that can lead to vaso-occlusion in sickle cell disease.

By binding to P-selectin on the surface of the activated endothelium and platelets, Adakveo blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes.

About SUSTAIN

SUSTAIN is a randomized, multicenter, placebo-controlled, double-blind study. A total of 198 sickle cell disease patients aged 16 to 63 years (inclusive; mean age 30.1±10.3 years), with any sickle cell disease genotype (including HbSS [71.2%], HbSC [16.2%], HbSbeta^0-thalassaemia [6.1%], HbSbeta+-thalassaemia [5.1%], and others [1.5%]) and a history of between 2 and 10 VOCs in the previous 12 months (62.6% and 37.4% of the

patients had 2-4 or 5-10 VOCs, respectively), were randomized 1:1:1 to Adakveo 5 mg/kg, Adakveo 2.5 mg/kg or placebo. The majority of patients were Black or African American (91.9%). Patients received Adakveo with (62.1%) or without (37.9%) HU/HC. Randomization was stratified by patients already receiving HU/HC (Y/N) and by number of VOCs in the previous 12 months (2 to 4, 5 to 10). Patients were allowed to take medicinal products to relieve pain (i.e. paracetamol, NSAIDs and opioids) and to receive occasional transfusions on an “as needed” basis. Patients participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) were excluded from the study.

Treatment with Adakveo 5 mg/kg resulted in a 45.3% lower median annual rate of VOCs compared to placebo (Hodges-Lehmann, median absolute difference of -1.01 compared with placebo, 95% CI [-2.00, 0.00]), which was statistically significant (p=0.010). The median annual rates of uncomplicated VOCs (any VOCs as defined above, excluding acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism) and days hospitalized were 62.9% and 41.8% lower in the Adakveo 5 mg/kg than in the placebo group, respectively. The VOCs occurring during the study were assessed by an independent review committee.

Important Safety Information
Adakveo may cause serious side effects, including infusion-related reactions. Infusion-related reactions may happen within 24 hours of receiving an infusion of Adakveo. Patients should tell their doctor or nurse immediately if they experience any of the following, which may be signs and symptoms of an infusion-related reaction, such as fever, chills or shivering, nausea, vomiting, tiredness, dizziness, sweating, hives, itching, or shortness of breath or wheezing. In the event of a severe reaction, crizanlizumab should be discontinued and appropriate therapy should be instituted.

The most common side effects (incidence > 10%) were arthralgia, nausea, back pain, pyrexia, and abdominal pain. Other side effects which may affect up to 1 in every 10 people are diarrhea, itching (including vulvovaginal itching), vomiting, muscle pain (myalgia), pain in the muscles or bones of the chest (musculoskeletal chest pain), sore throat (oropharyngeal pain), and redness or swelling and pain at the site of the infusion.

Adakveo may interfere with a laboratory test used to measure the number of platelets in the blood. Patients should tell their doctor or nurse that they are on treatment with Adakveo. It is recommended to run the tests as soon as possible (within 4 hours of blood collection) or use tubes containing citrate.

It is preferable to avoid the use of Adakveo during pregnancy and in woman of childbearing potential not using contraception.

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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, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity 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 nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 110,000 people of more than 145 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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