Novartis reaches another regulatory milestone for CTL019 (tisagenlecleucel) with submission of its MAA* to EMA for children, young adults with r/r B-cell ALL and adult patients with r/r DLBCL

- Application follows sBLA submission to the FDA for r/r DLBCL which marked second US application for first-ever FDA approved CAR-T therapy
- Building on the US r/r B-cell ALL experience, Novartis is working closely with EMA and European treatment centers to make CTL019 available in this region
- Submission of MAA includes data from global, multi-center Phase II ELIANA and JULIET studies, including 6-month JULIET data to be presented at ASH 2017

Basel, November 6, 2017 – Novartis today announced that the company has submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for CTL019 (tisagenlecleucel) for two indications. The application is for the treatment of children and young adults with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) and for adult patients with r/r diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant (ASCT). CTL019 is a novel immunocellular therapy and a one-time treatment that uses a patient’s own T cells to fight cancer.

“Since the historic FDA approval of Kymriah, formerly CTL019, we have launched, manufactured and supplied this highly individualized immunocellular therapy in a commercial setting and the submission to the EMA is a major step toward our goal of delivering it to more critically ill cancer patients around the world,” said Vas Narasimhan, Global Head of Drug Development and Chief Medical Officer, Novartis. “We look forward to working with the EMA to make CTL019 available to the children and adults who may benefit from this novel therapy.”

There has been a dire need for innovative therapies to treat pediatric and young adult patients with r/r B-cell ALL and adult patients with r/r DLBCL, who have few options and historically poor outcomes. DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for 40% of all NHL cases globally¹. If left untreated, r/r DLBCL has a life expectancy of three to four months². In Europe, ALL accounts for approximately 80% of leukemia cases among children³. Less than 10% of patients with relapsed or refractory ALL survive five years⁴.

“When tisagenlecleucel became a reality for certain patients and their families in the US after approval by the FDA for patients with relapsed or refractory ALL this year, I believe it forever changed the face of cancer treatment,” said the study’s principal investigator Stephen J. Schuster, MD, the Robert and Margarita Louis-Dreyfus Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research in Penn’s Perelman School of Medicine and director of the Lymphoma Program at the Abramson Cancer Center. “The data show this is a groundbreaking immunocellular therapy that has the potential to alter outcomes in patients who have limited options. This submission brings us closer to realizing that potential for more patients with fatal blood cancers.”

*MAA: Marketing Authorization Application
CTL019 is an innovative immunocellular therapy that is a one-time treatment. CTL019 uses the 4-1BB costimulatory domain in its chimeric antigen receptor to enhance cellular expansion and persistence. In 2012, Novartis and the University of Pennsylvania (Penn) entered into a global collaboration to further research, develop and commercialize CAR-T cell therapies, including CTL019, for the investigational treatment of cancers.

“For patients in the EU living with these aggressive forms of blood cancer, we have very limited options to improve their chances of sustained remission after their disease has relapsed or become refractory to initial treatment,” said Professor Gilles Salles, MD, PhD, Head of Hematology Department, Hospices Civils de Lyon, Lyon, France. “The data for tisagenlecleucel has provided an optimistic look at the potential to achieve durable responses in two distinct and difficult-to-treat patient populations, helping to address a dire unmet need for patients.”

The MAA submission is based on the Novartis-sponsored global, multicenter, phase II ELIANA and JULIET trials, which were conducted in collaboration with Penn. ELIANA is the first pediatric global CAR-T cell therapy registration trial, examining patients in 25 centers in the US, Canada, Australia, Japan and the EU, including: Austria, Belgium, France, Germany, Italy Norway, and Spain.

JULIET is the first multi-center global registration study for CTL019 in adult patients with r/r DLBCL. JULIET is the largest study examining a CAR-T therapy exclusively in DLBCL, enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan and Europe, including: Austria, France, Germany, Italy, Norway and the Netherlands. Data from the six-month primary analysis of JULIET will be presented at the annual meeting of the American Society of Hematology (ASH) in December 2017.

Novartis plans additional regulatory submissions for CTL019 in pediatric and young adult patients with r/r B-cell ALL and adult patients with r/r DLBCL outside the US and EU in 2018.

About CAR-T
CAR-T is different from typical small molecule or biologic therapies because it is manufactured for each individual patient using their own cells. During the treatment process, T cells are drawn from a patient’s blood and reprogrammed in the laboratory to create T cells that are genetically coded to recognize and fight the patient’s cancer cells and other B cells expressing a particular antigen.

About CTL019 Manufacturing
CTL019 is manufactured for each individual patient using their own cells at the Novartis Morris Plains, New Jersey facility. Novartis has designed a reliable and integrated manufacturing and supply chain platform that allows for an individualized treatment approach on a global scale. This process includes cryopreservation of a patient’s harvested (or leukapheresed) cells, giving treating physicians and centers the flexibility to initiate therapy with CTL019 based on the individual patient’s condition. Building on the company’s experience, having manufactured CAR-T cells for over 250 patients from 11 countries across various indications in clinical trials, it has demonstrated a reproducible product. Novartis continues to advance its CAR-T manufacturing expertise and make investments to support the anticipated demand to meet the needs of patients.

Novartis has also successfully established the CTL019 manufacturing process at the Fraunhofer-Institut für Zelltherapie and Immunologie (Fraunhofer-Institut für Zelltherapie und Immunologie) facility in Leipzig, Germany, which currently supports the manufacturing of CTL019 for global clinical trials.
Novartis Leadership in Immuno-Oncology
Novartis is at the forefront of investigational immunocellular therapy as the first pharmaceutical company to initiate global CAR-T trials, and has significantly invested in CAR-T research and worked with pioneers in the field. Kymriah™, the first approved CAR-T cell therapy, is the cornerstone of this strategy. Active research programs are underway targeting other hematologic malignancies and solid tumors, and include efforts focused on next generation CAR-Ts that involve simplified manufacturing schemes and gene edited cells.

Kymriah™ (tisagenlecleucel) US Important Safety information (for pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia)
The full prescribing information, including Boxed WARNING, for Kymriah can be found at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf

Kymriah may cause side effects that are severe or life-threatening, such as Cytokine Release Syndrome (CRS) or Neurological Toxicities. Patients with CRS may experience symptoms including high fever, difficulty breathing, chills/shaking chills, severe nausea, vomiting and diarrhea, severe muscle or joint pain, very low blood pressure, or dizziness/lightheadedness. Patients may be admitted to the hospital for CRS and treated with other medications.

Patients with neurological toxicities may experience symptoms such as altered or decreased consciousness, headaches, delirium, confusion, agitation, anxiety, seizures, difficulty speaking and understanding, or loss of balance. Patients should be advised to call their health care provider or get emergency help right away if they experience any of these signs and symptoms of CRS or neurological toxicities.

Because of the risk of CRS and neurological toxicities, Kymriah is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) in the US called Kymriah REMS.

Serious allergic reactions, including anaphylaxis, may occur after Kymriah infusion. Kymriah can increase the risk of life-threatening infections that may lead to death. Patients should be advised to tell their health care provider right away if they develop fever, chills, or any signs or symptoms of an infection.

Patients may experience prolonged low blood cell counts (cytopenia), where one or more types of blood cells (red blood cells, white blood cells, or platelets) are decreased. The patient’s health care provider will do blood tests to check all of their blood cell counts after treatment with Kymriah. Patients should be advised to tell their health care provider right away if they get a fever, are feeling tired, or have bruising or bleeding.

Patients may experience hypogammaglobulinemia, a condition in which the level of immunoglobulins (antibodies) in the blood is low and the risk of infection is increased. It is expected that patients may develop hypogammaglobulinemia with Kymriah, and may need to receive immunoglobulin replacement for an indefinite amount of time following treatment with Kymriah. Patients should tell their health care provider about their treatment with Kymriah before receiving a live virus vaccine.

After treatment with Kymriah, patients will be monitored life-long by their health care provider, as they may develop secondary cancers or recurrence of their leukemia.

Patients should not drive, operate heavy machinery, or do other dangerous activities for 8 weeks after receiving Kymriah because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, weakness, dizziness, and seizures.

Some of the most common side effects of Kymriah are difficulty breathing, fever (100.4°F/38°C or higher), chills/shaking chills, confusion, severe nausea, vomiting and diarrhea, severe muscle or joint pain, very low blood pressure, and
dizziness/lightheadedness. However, these are not all of the possible side effects of Kymriah. Patients should talk to their health care provider for medical advice about side effects.

Prior to a female patient starting treatment with Kymriah, their health care provider may do a pregnancy test. There is no information available for Kymriah use in pregnant or breast-feeding women. Therefore, Kymriah is not recommended for women who are pregnant or breast feeding. If either sex partner has received Kymriah, patients should talk to their health care provider about birth control and pregnancy.

Patients should tell their health care provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

After receiving Kymriah, patients should be advised that some commercial HIV tests may cause a false positive test result. Patients should also be advised not to donate blood, organs, or tissues and cells for transplantation after receiving Kymriah.

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 “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, regarding our ability to implement, scale and sustain commercial manufacturing for the investigational or approved products described in this press release, regarding our ability to build and sustain a network of treatment centers to offer the investigational or approved products described in this press release, or regarding potential future revenues from such 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 the investigational or approved products described in this press release 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 Novartis will successfully implement, scale and sustain commercial manufacturing for the investigational or approved products described in this press release, or successfully build and sustain a network of treatment centers to offer the investigational or approved products described in this press release. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, our ability to successfully implement, scale and sustain commercial manufacturing and build and sustain a network of treatment centers; 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; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; 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 121,000 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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