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Novartis announces FDA and EMA filing acceptance of ofatumumab, a novel B-cell therapy for patients with relapsing forms of multiple sclerosis (RMS)

- *Filings are supported by Phase III ASCLEPIOS I and II studies, where ofatumumab showed highly significant and clinically meaningful reduction in the number of confirmed relapses, evaluated as annualized relapse rate (ARR)*[1]

- *Ofatumumab is a novel B-cell therapy that delivers sustained efficacy with a favorable safety profile*[1]

- *If approved, ofatumumab has the potential to become a first-choice treatment for a broad RMS population and the first B-cell therapy that can be self-administered at home using an autoinjector pen*

- *Regulatory approval for ofatumumab in the US is expected in June 2020 and in Europe by Q2 2021*

Basel, February 24, 2020 — Novartis today announced that both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have accepted the company's Supplemental Biologics License Application (sBLA) and Marketing Authorization Application (MAA), respectively, for ofatumumab (OMB157) for the treatment of relapsing forms of multiple sclerosis (RMS) in adults. Ofatumumab is a novel B-cell therapy that delivers sustained efficacy with a favorable safety profile[1]. If approved, ofatumumab has the potential to become a first-choice treatment for a broad RMS population and the first B-cell therapy that is easy to start and manage in a monthly subcutaneous injection that can be self-administered at home using an autoinjector pen.

The regulatory applications are based on positive data from the Phase III ASCLEPIOS I and II studies, which investigated the efficacy and safety of monthly subcutaneous ofatumumab 20mg versus once daily oral Aubagio®* (teriflunomide) 14mg in adults with RMS[2,3]. In both head-to-head studies, ofatumumab demonstrated superiority over Aubagio® in patients with RMS[1]. Both studies met the primary endpoints where ofatumumab showed a highly significant and clinically meaningful reduction in the number of confirmed relapses, evaluated as the annualized relapse rate (ARR)[1]. Key secondary endpoints of delaying time to confirmed disability progression† (CDP) were also met[1]. Data presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) showed that compared to Aubagio®, ofatumumab:

- Reduced the ARR by 50.5% (0.11 vs. 0.22) and 58.5% (0.10 vs. 0.25) ($p<0.001$ in both studies) in ASCLEPIOS I and II respectively[1]

- Showed highly significant suppression of both Gd+ T1 lesions and new or enlarging T2 lesions, demonstrating a profound abrogation of new inflammatory activity[1]
- Showed a relative risk reduction of 34.4% (p=0.002) in three-month CDP and 32.5% (p=0.012) in six-month CDP in pre-specified pooled analyses[1]

Overall ofatumumab, a potent, fully-human antibody targeting CD20 positive B-cells, delivered efficacy with a favorable safety profile[1]. The safety profile of ofatumumab as seen in the ASCLEPIOS studies is in line with the observations from Phase II results[1,4].

In addition, Novartis has completed the APLIOS study, an open-label Phase II study, to determine the bioequivalence of subcutaneous administration of ofatumumab via a pre-filled syringe – as used in ASCLEPIOS I and II – and an autoinjector pen in patients with RMS[5]. The positive results of the study will be presented at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum in Florida, US. These results show that ofatumumab offers a highly effective B-cell therapy that can be self-administered at home using a patient-friendly autoinjector pen.

“We are excited that ofatumumab has the potential to be a powerful first-choice treatment option for patients and physicians looking for an impactful intervention,” said Krishnan Ramanathan, Neuroscience Global Program Head at Novartis. “With ofatumumab, we underpin our relentless dedication to reimagine medicine for patients across the MS spectrum and will work closely with the regulatory authorities to ensure it is available for people living with MS as soon as possible.”

Regulatory approval for ofatumumab in the US is expected in June 2020 and in Europe by Q2 2021. Novartis is committed to bringing ofatumumab to patients worldwide and additional regulatory filings are currently underway.

About ofatumumab
Ofatumumab is a fully human anti-CD20 monoclonal antibody (mAb) self-administered by a once-monthly subcutaneous injection in development for RMS. Ofatumumab works by binding to the CD20 molecule on the B-cell surface, distinct from that of other anti-CD20 antibodies, and induces potent B-cell lysis and depletion[4]. The selective mechanism of action and subcutaneous administration of ofatumumab allows precise delivery to the lymph nodes, where B-cell depletion in MS is needed, while sparing those in the spleen that help maintain protective immunity[4,5]. Once-monthly dosing of ofatumumab also allows faster repletion of B-cells[4], and offers more flexibility as no first dose observations or laboratory monitoring is required. Novartis obtained rights for ofatumumab from Genmab in all indications, including MS, in December 2015.

About ASCLEPIOS I and II studies
The ASCLEPIOS I and II studies are twin, identical design, flexible duration (up to 30 months), double-blind, randomized, multi-center Phase III studies evaluating the safety and efficacy of ofatumumab 20mg monthly subcutaneous injections versus Aubagio® 14mg oral tablets taken once daily in adults with RMS[2,3]. The ASCLEPIOS I and II studies enrolled 1,882 patients with MS, between the ages of 18 and 55 years, with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5[2,3]. The studies were conducted in over 350 sites in 37 countries. Ofatumumab demonstrated a reduction in ARR by 50.5% (0.11 vs. 0.22) and 58.5% (0.10 vs. 0.25) compared to Aubagio® ($p<0.001$ in both studies) in ASCLEPIOS I and II respectively. It showed highly significant suppression of both Gd+ T1 lesions and new or enlarging T2 lesions, demonstrating a profound suppression of new inflammatory activity. Ofatumumab also showed a relative risk reduction of 34.4% (p=0.002) in three-month CDP and 32.5% (p=0.012) in six-month CDP compared to Aubagio® in pre-specified pooled analyses. Overall ofatumumab, a potent, fully-human antibody targeting CD20 positive B-cells, delivered efficacy with a favorable safety profile. The safety profile of ofatumumab as seen in the ASCLEPIOS studies is in line with the observations from Phase II results[1,4]. Additional

secondary endpoints included confirmed disability improvement at six months, serum levels of neurofilament light chain (NfL), and rate of brain volume loss[2,3].

About APLIOS study[5]
The APLIOS study is a 12-week, open-label, Phase II bioequivalence study to determine the bioequivalence of subcutaneous administration of ofatumumab via a pre-filled syringe – as used in ASCLEPIOS I and II – and an autoinjector pen in patients with RMS and to evaluate the onset of B-cell depletion with ofatumumab subcutaneous monthly injections. Patients were randomized according to injection device and site including the abdomen and the thigh. B-cell depletion was measured nine times over 12 weeks. The positive results of the study will be presented at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum in Florida, US.

About Multiple Sclerosis
MS disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss[6]. MS, which affects approximately 2.3 million people worldwide[7], is often characterized into three forms: primary progressive MS (PPMS)[8], relapsing-remitting MS (RRMS), and secondary progressive multiple sclerosis (SPMS), which follows from an initial RRMS course and is characterized by physical and cognitive changes over time, in presence or absence of relapses, leading to a progressive accumulation of neurological disability[9]. Approximately 85% of patients initially present with relapsing forms of MS[7].

About Novartis in MS
In addition to ofatumumab, the Novartis MS portfolio also includes Gilenya® (fingolimod, an S1P modulator), which is indicated in the EU for the treatment of adult patients and children and adolescents 10 years of age and older with RRMS. In the US, Gilenya is approved for the treatment of adults and pediatric patients aged 10 years and older with RMS, to include CIS‡, relapsing remitting disease and active secondary progressive disease.

Mayzent is a sphingosine 1-phosphate receptor modulator that selectively binds to S1P1 and S1P5 receptors. In the US, Mayzent is approved for the treatment of relapsing forms of MS, to include CIS‡, relapsing remitting disease and active secondary progressive disease. In the EU, Mayzent is indicated for the treatment of adult patients with SPMS with active disease evidenced by relapsing or imaging features of inflammatory activity. In November 2019, Novartis received approval from the Australian Therapeutic Goods Administration (TGA) for Mayzent for adult patients with SPMS.

Extavia® (interferon beta-1b for subcutaneous injection) is approved in the US for RMS, to include CIS‡, relapsing remitting disease and active secondary progressive disease. In Europe, Extavia is approved to treat people with RRMS, SPMS with active disease and people who have had a single clinical event suggestive of MS.

In the US, the Sandoz Division of Novartis markets Glatopa® (glatiramer acetate injection) 20mg/mL and 40mg/mL, generic versions of Teva's glatiramer acetate.

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,” “may,” “could,” “would,” “expect,” “anticipate,” “seek,” “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, 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. 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, 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 and economic conditions; 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 more than 750 million people globally and we are finding innovative ways to expand access to our latest treatments. About 109,000 people of more than 145 nationalities work at Novartis around the world. Find out more at www.novartis.com

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*Aubagio® is a registered trade mark of Genzyme, a Sanofi company.
†CDP synonymously used for confirmed disability worsening (CDW).
‡Clinically isolated syndrome (CIS) is defined as a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the central nervous system[10].

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