Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
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MEDIA & INVESTOR RELEASE

Novartis announces NEJM publication of Phase III ASCLEPIOS trials demonstrating superior efficacy of ofatumumab in patients with relapsing multiple sclerosis

- *Ofatumumab is a targeted B-cell therapy that delivers superior efficacy with a similar safety profile when compared with teriflunomide, a commonly prescribed oral treatment for multiple sclerosis*[1]

- *ASCLEPIOS I and II demonstrated significant reductions in risk of relapses, confirmed disability worsening and profound reduction of active or new brain lesions*[1]

- *The US Food and Drug Administration and European Medicines Agency are currently reviewing ofatumumab for the treatment of relapsing forms of multiple sclerosis (RMS) in adults*

- *If approved, ofatumumab will be the first B-cell therapy that can be self-administered at home and has the potential to become a first-choice treatment for use in RMS patients*

Basel, August 5, 2020 — Novartis today announced that *The New England Journal of Medicine* (NEJM) published the positive results from the ASCLEPIOS I and II studies evaluating the safety and efficacy of ofatumumab (OMB157) 20 mg monthly subcutaneous injections versus teriflunomide 14 mg oral tablets taken once daily in adults with relapsing forms of multiple sclerosis (RMS). Both studies met the primary endpoints where ofatumumab showed a significant reduction in the number of confirmed relapses, evaluated as the annualized relapse rate (ARR)[1].

“ASCLEPIOS I and II demonstrate the efficacy and safety of ofatumumab and its potential to become a first-choice treatment option that offers RMS patients the flexibility as they continue to live their lives,” said Krishnan Ramanathan, Neuroscience Global Program Head at Novartis. “Ofatumumab is a testament to our commitment to advance science and investigate potential treatments that reimagine care and address significant unmet needs at all parts of the RMS journey.”

Results from the ASCLEPIOS I and II studies showed that compared with teriflunomide, ofatumumab:

- Significantly reduced the ARR by 51% (0.11 vs 0.22) and 58% (0.10 vs 0.25) in ASCLEPIOS I and II, respectively (P<.001 in both studies) (primary endpoints)[1]

- Showed a relative risk reduction of 34% (*P*=.002) in 3-month confirmed disability worsening (CDW) and 32% (*P*=.01) in 6-month CDW in a pre-specified meta-analysis, as defined in ASCLEPIOS (disability-related secondary endpoints)[1]
- Showed significant reduction of both gadolinium enhancing (Gd+) T1 lesions with a 97% and 94% relative reduction in ASCLEPIOS I and II, respectively, (both *P*<.001), and an 82% and 85% relative reduction in new or enlarging T2 lesions in ASCLEPIOS I and II, respectively (both *P*<.001) (MRI-related secondary endpoints)[1]
- Showed superiority in reducing neuroaxonal damage in both studies, as measured by neurofilament light chain (NfL) serum concentrations (biomarker secondary endpoint)[1]; axonal loss, which begins at disease onset, is a detrimental consequence of central nervous system (CNS) inflammation and is a major determinant of irreversible neurological disability in MS patients[2]
- Demonstrated a favorable trend in rate of 6-month confirmed disability improvement (CDI) events but did not reach significance (disability-related secondary endpoint)[1]
- Showed the annual rate of brain volume loss was not significantly different (MRI-related secondary endpoint)[1]
- Demonstrated an overall safety profile similar to teriflunomide, the frequency of serious infections and neoplasms was similar across both treatment groups. Injection-related reactions, nasopharyngitis, headache, injection-site reactions, upper respiratory tract infection and urinary tract infection were the most commonly observed adverse events across both treatment groups, occurring in ≥10% of patients[1,3]

“The ASCLEPIOS studies found that ofatumumab produced a significant reduction in new inflammation, as well as fewer clinical relapses and progression events,” said Professor Stephen L. Hauser, Director of the UCSF Weill Institute for Neurosciences and co-chair of the steering committee for the ASCLEPIOS I and II studies. “A separate post hoc analysis demonstrated that nearly 9 out of 10 patients experienced no evidence of disease activity in the second year of treatment[4]. Ofatumumab represents a potential new option for RMS patients with greater efficacy compared to teriflunomide, a comparable safety profile, and the convenience of once monthly self-administration without the need for infusions."

These data were published in the August 6, 2020 issue of *The New England Journal of Medicine*.

In February, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) accepted the company’s Supplemental Biologics License Application (sBLA) and Marketing Authorization Application (MAA), respectively, for ofatumumab for the treatment of relapsing forms of multiple sclerosis in adults. If approved, ofatumumab will be the first B-cell therapy that can be self-administered at home and has the potential to become a first-choice treatment for use in RMS patients.

Regulatory approval for ofatumumab in the US is expected in September 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 (OMB157) is a fully human anti-CD20 monoclonal antibody (mAb) in development for RMS that is self-administered by a once-monthly injection, delivered subcutaneously[1,3]. As shown in preclinical studies, ofatumumab is thought to work by binding to a distinct epitope on the CD20 molecule inducing potent B-cell lysis and depletion[5]. 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, and preclinical studies have shown that it may preserve the B-cells in the spleen[6]. Once-monthly dosing of ofatumumab also allows faster repletion of B-cells and offers flexibility[7]. Ofatumumab was originally developed by Genmab and licensed to GlaxoSmithKline. Novartis obtained rights for ofatumumab from GlaxoSmithKline in all indications, including RMS, in December 2015[8].

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 20 mg monthly subcutaneous injections versus teriflunomide 14 mg oral tablets taken once daily in adults with RMS. The ASCLEPIOS I and II studies enrolled 1882 patients with MS, between the ages of 18 and 55 years, with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5[1]. The studies were conducted in over 350 sites in 37 countries[9]. Ofatumumab demonstrated a significant reduction in ARR by 51% (0.11 vs 0.22) and 58% (0.10 vs 0.25) compared with teriflunomide (*P*<.001 in both studies) in ASCLEPIOS I and II, respectively (primary endpoint). Ofatumumab also showed a relative risk reduction of 34% (*P*=.002) in 3-month CDW and 32% (*P*=.01) in 6-month CDW compared with teriflunomide in a pre-specified meta-analysis, as defined in ASCLEPIOS[1].

Ofatumumab showed significant reduction of both Gd+ T1 lesions and new or enlarging T2 lesions. It significantly reduced the mean number of both Gd+ T1 lesions (97% and 94% relative reduction in ASCLEPIOS I and II, respectively, both *P*<.001) and new or enlarging T2 lesions (82% and 85% relative reduction in ASCLEPIOS I and II, respectively, both *P*<.001) vs teriflunomide[1]. Ofatumumab demonstrated that it lowered NfL levels in serum at the first assessment at Month 3 compared with teriflunomide. There was no difference in slope of brain volume change from baseline between treatments. In a measure of 6-month CDI events, a favorable trend for ofatumumab was seen but this did not reach significance vs teriflunomide[1].

Ofatumumab had a similar safety profile to teriflunomide, with the frequency of serious infections and neoplasms also being similar across both treatment groups[1]. Injection-related reactions, nasopharyngitis, headache, injection-site reactions, upper respiratory tract infection and urinary tract infection were the most commonly observed adverse events across both treatment groups, occurring in ≥10% of patients[1].

Overall, ofatumumab, a fully-human antibody targeting CD20 positive B-cells, delivered superior efficacy and demonstrated a safety profile with infection rates similar to teriflunomide[1].

About Multiple Sclerosis
Multiple sclerosis (MS) is a chronic inflammatory disease of the CNS characterized by myelin destruction and axonal damage of the brain, optic nerves and spinal cord[10]. MS, which affects approximately 2.3 million people worldwide[11], can be characterized into four main types of MS: clinically isolated syndrome (CIS), relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS)[12]. The various forms of MS can be distinguished based on whether a patient experiences relapses (clearly defined acute inflammatory attacks of worsening neurological function), and/or whether they experience progression of neurologic damage and disability from the onset of the disease[10].

Novartis in Neuroscience
Novartis has a strong ongoing commitment to neuroscience and to bringing innovative treatments to patients suffering from neurological conditions where there is a high unmet need. We are committed to supporting patients and physicians in multiple disease areas, including MS, migraine, Alzheimer's disease, Parkinson's disease, epilepsy and attention deficit hyperactivity disorder, and have a promising pipeline in MS, Alzheimer's disease, spinal muscular atrophy and specialty neurology.

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, 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.

Dr. Hauser's statements reflect his professional opinion and not necessarily the views of The Regents of the University of California. Nothing in his statements shall be construed to imply any support or endorsement of Novartis, or any of its products, by The Regents of the University of California.

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 109,000 people of more than 140 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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# # #

Novartis Media Relations
E-mail: media.relations@novartis.com

Antonio Ligi
Novartis External Communications
+41 79 723 3681 (mobile)
antonio.ligi@novartis.com

Michael Amos
Novartis Global Pharma Communications
+41 61 324 2705 (direct)
+41 79 123 7806 (mobile)
michael.amos@novartis.com

Eric Althoff
Novartis US External Communications
+1 862 778 3243
+1 646 438 4335
eric.althoff@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 778 5052
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		