

MEDIA RELEASE • MEDIA RELEASE • MEDIA RELEASE**Novartis receives positive CHMP opinion for Mayzent® (siponimod) for the treatment of adult patients with active secondary progressive multiple sclerosis (SPMS)**

- *If approved, Mayzent® (siponimod) will be the first and only oral treatment specifically indicated for patients with active secondary progressive multiple sclerosis (SPMS) in Europe¹*
- *CHMP opinion is based on the Phase III EXPAND trial, the largest randomized clinical study in a broad SPMS patient population (EDSS score 3.0 to 6.5 at baseline), showing Mayzent significantly reduced the risk of disease progression, including physical disability and cognitive decline²*
- *Up to 80% of patients with relapsing remitting multiple sclerosis (RRMS) will develop SPMS³; if approved, Mayzent would be a viable treatment option for those patients with active SPMS*

Basel, November 15, 2019 — Novartis today announced the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion for Mayzent® (siponimod) for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity (i.e. Gd-enhancing T1 lesions or active, new or enlarging, T2 lesions). While MS progression is different for each patient and influenced by multiple factors, including use of MS disease-modifying treatments, it is estimated that up to 80% of patients will eventually transition from RRMS to SPMS³. If approved, Mayzent is expected to be the first and only oral treatment specifically indicated for patients with active SPMS based on a randomized clinical trial of a broad SPMS patient population.

“Today’s CHMP opinion marks a milestone in supporting people in Europe who are living with active SPMS,” said Christoph Thalheim, Director External Affairs, European Multiple Sclerosis Platform. “This decision brings hope of a possible new and beneficial therapy.”

The positive CHMP opinion for Mayzent is based on groundbreaking data from the Phase III EXPAND study, a randomized, double-blind, placebo-controlled trial, comparing the efficacy and safety of Mayzent versus placebo in people with SPMS. EXPAND also investigated a subgroup of patients with active disease (n=779), defined as patients with relapses in the two years prior to the study and/or presence of Gd-enhancing T1 lesions at baseline. The baseline characteristics were similar except for signs of activity compared to the overall population. Results from EXPAND in the overall population showed that Mayzent significantly reduced the risk of three-month confirmed disability progression (CDP) (primary endpoint;

21% reduction versus placebo, $p=0.013$) and meaningfully delayed the risk of six-month CDP (26% versus placebo, $p=0.0058$)².

In the subgroup of Mayzent-treated patients with active disease, results showed:

- Time to onset of three-month and six-month CDP was significantly delayed by 31% compared to placebo and by 37% compared to placebo, respectively⁴.
- The annualized relapse rate (ARR – confirmed relapses) was reduced by 46% compared to placebo⁴.
- Significant favorable outcomes in other relevant measures of MS disease activity, including MRI disease activity and brain volume loss (brain shrinkage)⁴.

Additional analyses of the EXPAND study were presented this year at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), demonstrating that Mayzent:

- Can help patients keep their mobility for over four years longer on average⁵.
- Reduced grey matter volume loss at one and two years, a key driver of disability progression and cognitive decline in patients with SPMS^{6,7}.

“For people living with MS, it is extremely important to delay disability progression and preserve cognition, so that they can live independent lives for longer,” said John Tsai, Head Global Drug Development and Chief Medical Officer, Novartis. “Mayzent is a testament to the Novartis mission to reimagine medicine for an underserved population such as people living with active SPMS.”

In March 2019, Novartis received approval from the US Food and Drug Administration (FDA) for Mayzent for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome (CIS[†]), relapsing remitting disease, and active secondary progressive disease, in adults. In November 2019, Novartis received approval from the Australian Therapeutic Goods Administration (TGA) for Mayzent for adult patients with SPMS. Novartis is committed to bringing Mayzent to patients worldwide, and additional regulatory filings are currently underway in Switzerland, Japan, Canada and China.

About Mayzent[®] (siponimod)

Mayzent is a next generation, selective sphingosine 1-phosphate receptor modulator approved by the FDA for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome (CIS[†]), relapsing remitting disease, and active secondary progressive disease, in adults. Mayzent selectively binds to S1P1 and S1P5 receptors. In relation to the S1P1 receptor, it prevents the lymphocytes from egressing the lymph nodes and as a consequence, from entering the CNS of patients with MS². This leads to the anti-inflammatory effects of Mayzent⁸. Mayzent also enters the CNS^{9,10,11} and binds to the S1P5 sub-receptor on specific cells in the CNS, including astrocytes and oligodendrocytes and has shown pro-remyelinating and neuroprotective effects in preclinical models of MS^{12,13,14}.

About the EXPAND Study²

EXPAND is a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of Mayzent versus placebo in people with SPMS with varying levels of disability, EDSS scores of 3-0–6-5. It is the largest randomized, controlled study in SPMS to date, including 1,651 people with a diagnosis of SPMS from 31 countries. Mayzent demonstrated a safety profile that was overall consistent with the known effects of S1P receptor modulation. It reduced the risk of three-month CDP by a statistically significant 21% ($p=0.013$; primary endpoint). CDP was defined as a 1-point increase in EDSS, if the baseline score was 3-0 - 5-0, or a 0-5-point increase, if the baseline score was 5-5 - 6-5. No significant differences were found in the Timed 25-Foot Walk Test, however, T2 lesion volume was reduced by 79% as compared to placebo. Additional secondary endpoints included a relative reduction in the ARR by 55%, and compared to placebo, more patients were free from Gd-enhancing lesions (89% vs 67% for placebo) and from new or enlarging T2 lesions (57% vs 37% for placebo).

About Multiple Sclerosis

MS disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss¹⁵. MS, which affects approximately 2.3 million people worldwide³, is often characterized into three forms: primary progressive MS (PPMS)¹⁶, relapsing-remitting MS (RRMS), and 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 disability¹⁷. Approximately 85% of patients initially present with relapsing forms of MS³. There remains a high unmet need for safe and effective treatments to help delay disability progression in SPMS with active disease (with relapses and/or evidence of new MRI activity)¹⁷.

About Novartis in MS

The Novartis multiple sclerosis portfolio includes Gilenya® (fingolimod, an S1P modulator), which is indicated in the European Union for the treatment of adult patients and children and adolescents 10 years of age and older with RMS. In the United States, 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.

In March 2019, the FDA approved Mayzent for the treatment of relapsing forms of MS, to include CIS†, relapsing remitting disease and active secondary progressive disease. The approval is based on the Phase III EXPAND trial, the largest controlled clinical study of a broad SPMS patient population, showing Mayzent significantly reduced the risk of disease progression, including impact on physical disability and cognitive decline². In November 2019, Novartis received approval from the Australian TGA for Mayzent for adult patients with SPMS. Novartis is committed to bringing Mayzent to patients worldwide, and additional regulatory filings are currently underway with other health authorities outside the US.

Ofatumumab (OMB157), a fully human anti-CD20 monoclonal antibody (mAb) that targets B-cells, is in development for treating RMS. Positive Phase III data presented in September 2019 show ofatumumab met primary endpoints to reduce the ARR in patients with RMS¹⁸. Novartis plans to initiate submissions to health authorities by the end of 2019. If approved, ofatumumab will potentially become a treatment for a broad RMS population and the first subcutaneous B-cell therapy that can be self-administered at home.

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,” “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, 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 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 108,000 people of more than 140 nationalities work at Novartis around the world. Find out more at www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at <http://twitter.com/novartisnews>
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

*As measured by prolonged time to wheelchair dependence for patients with SPMS by an average of 4.3 years versus placebo.

†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 system¹⁹.

References

1. National MS Society Brochure. Disease Modifying Therapies for MS. <http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-The-MS-Disease-Modifying-Medications.pdf>. Accessed March 2019.
2. Kappos L, Cree B, Fox R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet*. Published online March 22, 2018. [http://dx.doi.org/10.1016/S0140-6736\(18\)30475-6](http://dx.doi.org/10.1016/S0140-6736(18)30475-6).
3. Multiple Sclerosis International Federation. Atlas of MS 2013. <http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf>. Accessed March 2019.
4. Gold R, Kappos L, Bar-Or A, et al. Efficacy of Siponimod in Secondary Progressive Multiple Sclerosis Patients With Active Disease: The EXPAND Study Subgroup Analysis. P750. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, September 2019.
5. Vermersch P, Gold R, Kappos L, et al. Siponimod Delays the Time to Wheelchair in Patients with SPMS: Results from the EXPAND study. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 2019.
6. Arnold D, Giovannoni G, Cree B, et al. Relationship Between Grey Matter Atrophy, Disability and Cognition in Patients with Secondary Progressive Multiple Sclerosis: Analysis from the EXPAND Study. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 2019.
7. Arnold D, Fox R, Bar-Or A, et al. Effect of Siponimod on Cortical Grey Matter and Thalamic Volume in Patients with Secondary Progressive Multiple Sclerosis - Results of the EXPAND Study. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 2019.
8. Gergely P, Nuesslein-Hildesheim B, Guerini D, et al (2012) The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Brit J Pharm*; 167:1035-47.

9. Tavares A, Barret O, Alagille D, et al. Brain distribution of MS565, an imaging analogue of siponimod (BAF312), in non-human primates. *Eur J Neurol.* 2014;21(Suppl 1):504-PP2067.
10. Briard E, Rudolph B, Desrayuad S, et al. MS565: A SPECT tracer of evaluating the brain penetration of BAF312 (sipinomod). *Chem Med Chem.* 2015; 10(6):1008-18.
11. Bigaud M, Perdoux J, Ramseier P et al. Pharmacokinetic/Pharmacodynamic Characterization of Siponimod (BAF312) in Blood versus Brain in Experimental Autoimmune Encephalomyelitis Mice. *Neurology.* 2019;P2.2-066.
12. Mannioui A, Vauzanges Q, Fini JB, et al. The *Xenopus* tadpole: An in vivo model to screen drugs favoring remyelination. *Mult Scler.* 2018;24(11):1421-32.
13. Martin E, Urban B, Beerli C, et al. Siponimod (BAF312) is a potent promyelinating agent: preclinical mechanistic observation. P1376. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, September 2019.
14. Dietrich M, Hecker C, Ramseier P, et al. Neuroprotective potential for siponimod (BAF312) revealed by visual system readouts in a model of experimental autoimmune encephalomyelitis-optic neuritis (EAEON). P844. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, September 2019.
15. PubMed Health. Multiple Sclerosis (MS). <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001747/>. Accessed March 2019.
16. MS Society. Types of MS. <https://www.mssociety.org.uk/what-is-ms/types-of-ms>. Accessed March 2019.
17. National Multiple Sclerosis Society. Secondary Progressive MS (SPMS). <https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS>. Accessed March, 2019.
18. Hauser S. Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. Oral presentation. ECTRIMS 2019.
19. National MS Society. Clinically Isolated Syndrome (CIS). [https://www.nationalmssociety.org/Symptoms-Diagnosis/Clinically-Isolated-Syndrome-\(CIS\)](https://www.nationalmssociety.org/Symptoms-Diagnosis/Clinically-Isolated-Syndrome-(CIS)). Accessed March 2019.

###

Novartis Media Relations

E-mail: media.relations@novartis.com

Antonio Ligi
 Novartis External Communications
 + 41 61 324 1374 (direct)
antonio.ligi@novartis.com

Mark Chakravarty
 Novartis Global Pharma Communications
 +41 61 324 0990 (direct)
 +41 79 540 3775 (mobile)
mark.chakravarty@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
 Samir Shah +41 61 324 7944
 Pierre-Michel Bringer +41 61 324 1065
 Thomas Hungerbuehler +41 61 324 8425
 Isabella Zinck +41 61 324 7188

North America
 Sloan Simpson +1 862 778 5052
 Cory Twining +1 862 778 3258