Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

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

Novartis announces new Mayzent® (siponimod) data show sustained effect in delaying disability for up to five years in patients with secondary progressive multiple sclerosis (SPMS)

- *New long-term data from EXPAND show patients with SPMS continuously treated with Mayzent® (siponimod) experienced lower risk of disability progression and cognitive decline than patients who delayed Mayzent treatment*[1]
- *Separate post-hoc analysis from EXPAND demonstrated Mayzent reduced cortical grey matter (cGM) and thalamic atrophy in patients with SPMS*[2]*, outcomes associated with long-term irreversible disability accumulation*[3]
- *Mayzent is the first and only oral disease modifying therapy (DMT) studied and proven to delay disability progression in a broad range of SPMS patients*

Basel, April 21, 2020 — Novartis announced today new Mayzent® (siponimod) data in the April supplemental issue of *Neurology®,* the medical journal of the American Academy of Neurology. The data build on existing clinical evidence that Mayzent has proven to slow physical disability progression and provide cognitive benefits in people living with secondary progressive multiple sclerosis (SPMS)[1]. Although every patient's multiple sclerosis (MS) journey is unique, 1 in 4 relapsing-remitting MS (RRMS) patients on treatment transition to SPMS within 10 years of RRMS onset*[4].

Data released from the five-year EXPAND open-label extension trial assessed the long-term efficacy and safety of Mayzent in patients with SPMS who on entering the extension trial either continued on Mayzent treatment (Mayzent group) or switched from placebo to Mayzent (placebo switch group). Patients in the Mayzent group were significantly less likely to experience both three- and six-month confirmed disability progression (CDP) (p=0.0064 and p=0.0048, respectively) compared with the placebo switch group, which underscores advantages of early treatment initiation[1]. These data were included in the April supplemental issue of *Neurology* after the 2020 American Academy of Neurology Annual Meeting was cancelled due to COVID-19.

"The data continue to show that Mayzent has the ability to help patients maintain independence for longer through its long-term effect on delaying progression and cognitive impairment," said Norman Putzki, MD, Global Head of Development Neuroscience. "Novartis is committed to reimagining medicine for patients with progressive diseases and with Mayzent, Novartis offers patients hope for improved health outcomes."

The new data also show a 52% reduction in the annualized relapse rate (ARR) observed in the Mayzent group compared to the placebo switch group (p<0.0001). Risk of confirmed worsening of cognitive impairment (according to the Symbol Digit Modalities Test) at six-months was reduced by 23% for the Mayzent group compared with placebo switch group (p=0.0014). The benefits seen in the Mayzent group were sustained for up to five years, underscoring the advantages of early treatment initiation with Mayzent. The incidence of adverse events was consistent with the controlled treatment period[1]. This EXPAND open-label extension is ongoing for up to a total of seven years.

Additional Mayzent data shared in the same *Neurology* issue includes a new post-hoc analysis from EXPAND, which showed Mayzent consistently reduced cortical grey matter (cGM) and thalamic atrophy in patients with SPMS, including those with less active and more advanced disease. Across the subgroups studied, Mayzent reduced cGM atrophy versus placebo by 48–116% (p<0.01 at both M12 and M24) and thalamic atrophy by 30– 68% (p<0.05 at both M12 and M24; except for 'disease duration >15 years' p=0.1029 at M12)[2]. Combined with other analyses, these findings could translate into a favorable impact on long-term clinical outcomes including disability progression and cognitive decline.

Further analysis from EXPAND, evaluating Mayzent's effect on magnetization transfer ratio (MTR) changes in patients with SPMS, builds on existing pre-clinical evidence that suggests Mayzent may promote repair mechanisms in the central nervous system (CNS). MTR is a technique widely used for estimating myelin content in the brain. MTR results show that Mayzent significantly reduces de-myelination and substantiate previous pre-clinical findings on remyelination[5].

"These data highlight the critical importance of early treatment intervention with a disease-modifying treatment, such as Mayzent, to ensure the best possible long-term outcomes for patients with MS who are experiencing progression," said Bruce Cree, MD, PhD, MAS, Clinical Research Director and George A. Zimmermann Endowed Professor in Multiple Sclerosis, University of California, San Francisco, School of Medicine. "It's never too early to stay ahead of progression in multiple sclerosis, since the early identification of physical and cognitive changes – even subtle ones – can indicate MS disease progression and therefore allow for timely intervention."

**For specific indications of Mayzent approved in each country, see the section "About Mayzent® (siponimod)" below.*

†*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 system[6].*

About the EXPAND Study[7]

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 (Core Part), EDSS scores of 3·0–6·5, followed by extended treatment with open-label BAF312 to obtain data on long-term safety, tolerability and efficacy (Extension Part)[8]. 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. 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). Additional exploratory analyses presented at the 35th Congress of the European Committee for Treatment and Research in

Multiple Sclerosis (ECTRIMS), demonstrated Mayzent can help patients keep their mobility for over four years longer on average[9†].

About Mayzent® (siponimod)
Mayzent is a sphingosine 1-phosphate receptor modulator that 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 MS[7]. This leads to the anti-inflammatory effects of Mayzent[10]. Mayzent also enters the CNS and binds to the S1P5 sub-receptor on specific cells in the CNS[11,12,13], including astrocytes and oligodendrocytes and has shown pro-remyelinating and neuroprotective effects in preclinical models of MS[14,15,16].

In the European Union (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 the US, Mayzent is approved for the treatment of relapsing forms of MS, to include clinically isolated syndrome (CIS‡), relapsing remitting disease and active secondary progressive disease in adults. The approvals are based on the Phase III EXPAND trial, the largest controlled clinical study of a broad range of SPMS patients, showing Mayzent significantly reduced the risk of disease progression, including impact on physical disability and cognitive decline[7]. Mayzent is also approved in Australia and Albania for adult patients with SPMS and in Canada and United Arab Emirates for adult patients with active SPMS. Novartis is committed to bringing Mayzent to patients worldwide, and additional regulatory filings are currently underway in Switzerland, Japan, China, and elsewhere.

About Multiple Sclerosis
MS disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss[17]. MS, which affects approximately 2.3 million people worldwide[18], is often characterized into three forms: primary progressive MS (PPMS)[19], 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 disability[20]. Approximately 85% of patients initially present with relapsing forms of MS[18]. 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)[20].

About Novartis in MS
In addition to Mayzent, the Novartis MS portfolio includes also 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 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.

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 RMS[21]. 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.

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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 145 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
Pierre-Michel Bringer	+41 61 324 1065	Cory Twining	+1 862 778 3258
Thomas Hungerbuehler	+41 61 324 8425		

Isabella Zinck +41 61 324 7188