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**Novartis data at AAN show Mayzent's® positive impact on cognitive processing speed, a core element of cognitive function, in people living with secondary progressive MS**

- *Data from EXPAND – the largest randomized controlled trial in a representative secondary progressive MS (SPMS) population – show Mayzent® (siponimod) had a meaningful benefit on cognitive processing speed (CPS) for these patients<sup>1</sup>*
- *Impairment in cognitive function, one of the most disabling aspects of MS, affects 50-70% of patients and is more severe in patients with SPMS<sup>2</sup>*
- *EXPAND findings demonstrate that SPMS patients treated earlier in the course of their disease benefited most, suggesting early treatment leads to better cognitive outcomes<sup>1</sup>*
- *Mayzent is the only FDA-approved treatment for active SPMS, with proven efficacy in a pivotal study of a typical SPMS population*

**Basel, May 08, 2019** – Novartis today announced a new analysis of the Phase III EXPAND study, demonstrating that treatment with Mayzent® (siponimod) had a clinically meaningful positive impact on cognitive processing speed (CPS) in patients with SPMS, an important element in cognitive function. The EXPAND data also show patients treated earlier in the course of their disease with less cognitive impairment – benefited most from Mayzent treatment vs. placebo, suggesting early treatment is important to ensure better cognitive outcomes<sup>1</sup> which is critical in helping patients maintain their independence for longer. These findings are being presented at the 2019 American Academy of Neurology Annual Meeting (AAN) in Philadelphia, Pennsylvania, USA. Mayzent is the only FDA-approved treatment for active SPMS based on a positive pivotal study of a typical SPMS patient population.

Impairment in cognitive function substantially impacts the lives of patients with MS and their families. Half to three-quarters of people with MS are unemployed within 10 years of diagnosis<sup>3</sup>, with cognitive impairment being the leading predictor of occupational disability<sup>4</sup>. Furthermore, patients who experience impaired cognitive function participate in social activities less frequently<sup>4</sup> which may have an impact on their overall wellbeing and relationships.

“Cognitive decline is a real fear among people with multiple sclerosis, a fear that can be even bigger in patients with SPMS,” said Ralph Benedict, PhD, Professor of Neuropsychology at Buffalo General Medical Center and an EXPAND study investigator. “The EXPAND study revealed exciting findings for SPMS patients and the scientific community. We are delighted to see Mayzent may protect against cognitive decline, as preserving cognitive function is a crucial aim of disease-modifying MS treatments.”

In EXPAND, Mayzent's effect on CPS was measured by a standard test (Symbol Digit Modalities Test, SDMT). CPS affects everyday activities of patients such as remembering

information learned in the past or recalling information to complete a task, finding words and holding conversations, processing information and responding as quickly as they once did. Its worsening is often the first noticeable sign of a decline in cognitive function in MS and it significantly affects patients' quality of life, as simple tasks become more and more difficult<sup>5</sup>. The data presented at AAN show that a significantly higher proportion of patients treated with Mayzent experienced sustained improvement in SDMT versus those on placebo ( $p=0.0131$ )<sup>1</sup>. Mayzent was superior to placebo across the entire spectrum of SPMS, and specifically:

- Patients treated earlier in their disease course with less cognitive impairment – benefited most from Mayzent treatment, with a significantly higher proportion experiencing meaningful improvement over the course of the study and follow up ( $p=0.0126$  for those with relapses and  $p=0.0094$  for those with an initial SDMT score  $\geq$  median)<sup>1</sup>.
- There was also a benefit from Mayzent treatment in delaying deterioration in SDMT ( $p=0.0269$  for those with cognitive impairment at baseline and  $p=0.0071$  for those with an initial SDMT score  $<$  median) for those with more advanced disease<sup>1</sup>.

However, treatment with Mayzent did not result in significant differences in tests such as the Brief Visuospatial Memory Test-Revised (BVM-T-R, assessing memory).

Data previously published from EXPAND show Mayzent significantly slowed the rate of brain shrinkage in patients with SPMS by more than 20% (relative difference; mean across 12 and 24 months,  $p=0.0002$ )<sup>6</sup>. Brain shrinkage was found to be related to loss of cognitive function and disability progression<sup>6</sup>.

"The significant effects on cognitive impairment presented at AAN continue to build on the evidence that Mayzent can delay disability progression and positively impact patients' lives," said Danny Bar-Zohar, Global Head of Neuroscience Development, Novartis Pharmaceuticals. "With Mayzent, we finally have a therapy with proven efficacy in SPMS."

In March 2019, Novartis received approval by the US Food and Drug Administration (FDA) for Mayzent across the MS spectrum for clinically isolated syndrome (CIS\*), RRMS and active SPMS. Patients starting Mayzent treatment do not require a first dose observation (FDO, cardiac monitoring) unless they have certain pre-existing cardiac conditions. Regulatory action for Mayzent in the European Union is anticipated in late 2019, with additional regulatory action anticipated in Switzerland, Japan, Australia and Canada this year.

*\*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<sup>13</sup>.*

#### **About the EXPAND Study**

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, Expanded Disability Status Scale (EDSS) scores of 3.0 to 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 confirmed disability progression (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 to 5.0, or a 0.5-point increase, if the baseline score was 5.5 to 6.5. No significant differences were found in the T25FW, 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 gadolinium-enhancing lesions (89%) and from new or enlarging T2 lesions (57%)<sup>6</sup>.

#### **About Mayzent® (siponimod)**

Mayzent is a next generation, selective sphingosine 1-phosphate receptor modulator

indicated for the treatment of RMS, to include 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 central nervous system (CNS) of patients with MS. This leads to the anti-inflammatory effects of Mayzent<sup>6</sup>. Mayzent also enters the CNS and directly binds to the S1P5 and S1P1 sub-receptors on specific cells in the CNS (oligodendrocytes and astrocytes)<sup>7</sup> to promote re-myelination and prevent inflammation.

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### **About Multiple Sclerosis**

MS is a chronic disorder of the CNS that affects around 2.3 million people worldwide<sup>8</sup>. There are three main forms of MS: RRMS (the most common form of the condition at diagnosis), SPMS and primary progressive MS (PPMS)<sup>9</sup>. MS disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss<sup>10</sup>.

SPMS follows an initial form of RRMS, which accounts for approximately 85% of all MS diagnoses, and is characterized by gradual worsening of neurological function over time<sup>11</sup>. This leads to a progressive accumulation of neurological disability. 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)<sup>12</sup>.

### **Novartis in Multiple Sclerosis**

The Novartis multiple sclerosis portfolio includes Gilenya<sup>®</sup> (an S1P modulator), which is indicated for relapsing forms of MS. In the United States and the European Union, Gilenya is indicated for the treatment of adult patients and children and adolescents 10 years of age and older with relapsing multiple sclerosis.

In March 2019, Novartis received approval by FDA for the treatment of RMS, to include CIS\*, relapsing remitting disease, and active secondary progressive disease, in adults. The approval is based on the Phase III EXPAND trial, the largest controlled clinical study of SPMS patients, showing Mayzent significantly reduced the risk of disease progression, including impact on physical disability and cognitive decline<sup>6</sup>.

An investigational compound currently being investigated in two Phase III pivotal studies is ofatumumab (OMB157), a fully human monoclonal antibody which targets CD20 and is subcutaneously administered. Ofatumumab is in development for relapsing MS.

Extavia<sup>®</sup> (interferon beta-1b for subcutaneous injection) is approved in the US for the treatment of relapsing forms of MS. 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<sup>®</sup> (glatiramer acetate injection) 20mg/mL and 40mg/mL, generic versions of Teva's glatiramer acetate.

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### **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 105 000 people of more than 140 nationalities work at Novartis around the world. Find out more at [www.novartis.com](http://www.novartis.com).

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