Phase III data in *The Lancet* show Novartis siponimod significantly improves outcomes in patients with secondary progressive MS

- **EXPAND** shows oral siponimod (BAF312) is the first potential therapy to meaningfully delay disability progression in typical secondary progressive MS (SPMS) patients.

- Results demonstrate siponimod also had beneficial effects on clinical relapses and MRI disease activity, including brain volume loss (brain shrinkage).

- Novartis plans to file siponimod for US approval in SPMS in early 2018. Filing for EU approval planned for later in 2018, pending scientific consultation with EMA.

Basel, March 23, 2018 – Novartis today announced that the full results from the Phase III EXPAND study of oral, once-daily siponimod (BAF312) in secondary progressive multiple sclerosis (SPMS) were published in the peer-reviewed journal *The Lancet*. These pivotal results show significant reductions in the risk of three- (primary endpoint) and six-month confirmed disability progression with siponimod versus placebo and favorable outcomes in other relevant measures of MS disease activity. If approved, siponimod would be the first disease-modifying therapy to delay disability progression in typical SPMS patients, including many who had reached a non-relapsing stage and high level of disability.

SPMS is a form of MS that leads to progressive, irreversible disability, largely independent of relapses. Patients transition to SPMS after an initial phase of relapsing-remitting MS (RRMS), the most commonly diagnosed type of MS. There is a high unmet medical need for new treatments that are safe and effective for patients with SPMS.

“Today’s published, full EXPAND results show that siponimod can delay disability progression in typical established SPMS patients, where other approaches tested so far have been unsuccessful,” said Professor Ludwig Kappos, University Hospital Basel and Principal Investigator of EXPAND. “These data are all the more impressive when considering that the majority of patients already had advanced disability when starting treatment in EXPAND.”

Siponimod is an oral selective modulator of sphingosine-1-phosphate (S1P) receptor subtypes one and five (S1P1 and S1P5). Full data from EXPAND show that siponimod reduced the risk of three-month confirmed disability progression by a statistically significant 21% versus placebo (p=0.013; primary endpoint); efficacy was consistent across many pre-defined subgroups. Other clinically relevant endpoint data show that siponimod, when compared to placebo:

- Reduced the risk of six-month confirmed disability progression by 26% (p=0.0058)\(^1\)
- Slowed the rate of brain volume loss by 23% (relative difference; mean across 12 and 24 months, p=0.0002)\(^1,\,8\)
- Limited the increase of T2 lesion volume by approximately 80% (mean over 12 and 24 months, p<0.0001)\(^1,\,8\)
- Reduced annualized relapse rate (ARR) by 55% (p<0.0001)\(^1\)
- Did not show a significant difference in the Timed 25-Foot Walk test and MS Walking Scale.\(^1\)
• Demonstrated a safety profile that was overall consistent with the known effects of S1P receptor modulation

“Novartis is dedicated to advancing MS research and pioneering solutions for people living with SPMS—a complex, debilitating disease,” said Danny Bar-Zohar, Global Head, Neuroscience Development for Novartis. “The pivotal EXPAND data provides patients, and the medical community alike, with hope that a much needed, safe and effective treatment option is on the horizon for SPMS, for which treatment options are scarce. We look forward to continuing to work with regulatory agencies to make siponimod available for these patients as fast as possible.”

Novartis plans to file for regulatory approval of siponimod for SPMS with the US Food and Drug Administration (FDA) in early 2018. Novartis has initiated a scientific advice consultation with the European Medicines Agency (EMA) and, pending its outcome, plans to file in Q3 2018. The EXPAND results have previously been presented at scientific congresses.

**About the EXPAND study**

The EXPAND study is a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of siponimod versus placebo in people with secondary progressive multiple sclerosis (SPMS). It is the largest randomized, controlled study in SPMS to date, including 1,651 people with SPMS from 31 countries. At the time of the study, individuals enrolled in EXPAND had a mean age of 48 years and had been living with MS for approximately 17 years. Patients had received a diagnosis of SPMS, and also demonstrated progression of disability in the two years prior to study. They also had an Expanded Disability Status Scale (EDSS) score between 3.0 and 6.5 inclusive, with a median score of 6.0, which corresponds to the use of a unilateral walking aid (e.g. a cane or a crutch). Patients were randomized to receive either 2mg siponimod once-daily or placebo.

**About siponimod (BAF312)**

Siponimod is an investigational, selective modulator of specific subtypes of the sphingosine-1-phosphate (S1P) receptor. Siponimod binds to the S1P1 sub-receptor on lymphocytes, which prevents them from entering the central nervous system (CNS) of patients with multiple sclerosis. This leads to the anti-inflammatory effects of siponimod.

Siponimod also enters the CNS and binds to the S1P5 sub-receptor on specific cells in the CNS (oligodendrocytes and astrocytes). By binding to these specific receptors, siponimod has the potential to modulate damaging cell activity and helps to reduce the loss of neurological function associated with SPMS. The receptor specificity and pharmacokinetic properties (e.g. the faster elimination compared with first-generation S1P modulators) of siponimod facilitate treatment initiation, while improving its safety and convenience profile.

**About Multiple Sclerosis**

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) that disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss. The evolution of MS results in an increasing loss of both physical (e.g. walking) and cognitive (e.g. memory) function. There are three main types of MS: relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS).

SPMS is characterized by gradual worsening of neurological function over time. This leads to a progressive accumulation of disability, largely independent of relapses, which can severely affect patients’ abilities to carry out everyday activities. It follows an initial phase of RRMS, which accounts for approximately 85% of all MS diagnoses; a quarter of people with RRMS
will eventually go on to develop SPMS within 10 years of their initial RRMS diagnosis, rising to more than three-quarters after 30 years\textsuperscript{3,16}. There remains a high unmet need for effective and safe treatments to help delay disability progression in SPMS\textsuperscript{3}.

MS affects approximately 2.3 million people worldwide\textsuperscript{3}.

**About Novartis in Multiple Sclerosis**

The Novartis multiple sclerosis (MS) portfolio includes Gilenya\textsuperscript{®} (fingolimod, an S1P modulator), which is indicated for relapsing forms of MS and is also in development for pediatric MS. Extavia\textsuperscript{®} (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 relapsing-remitting MS, secondary progressive MS (SPMS) with active disease and people who have had a single clinical event suggestive of MS.

Investigational compounds include siponimod (BAF312), under investigation in MS, and ofatumumab (OMB157), a fully human monoclonal antibody in development for relapsing MS. Ofatumumab targets CD20, and is currently being investigated in two Phase III pivotal studies.

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

*Copaxone\textsuperscript{®} is a registered trademark of Teva Pharmaceutical Industries Ltd.

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About Novartis
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 122,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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