Novartis presents data at ACTRIMS-ECTRIMS on the effects of treatment with Mayzent® (siponimod) studied on disability progression and cognitive processing speed in patients with progressing relapsing multiple sclerosis

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- *Subgroup post hoc analysis of EXPAND reported that Mayzent reduced the risk of cognitive worsening and improved the chance of cognitive improvement at 6 months versus placebo in patients with active and non-active SPMS*[1]
- *A separate open-label extension interim analysis of the EXPAND trial for up to five years observed the effects of early treatment initiation (disability progression, cognitive processing speed and annualized relapse rate) with Mayzent in patients with active SPMS*[2]

East Hanover, September 11, 2020 — Novartis announced today that new data were presented on Mayzent® (siponimod) from the Phase III EXPAND trial reporting that Mayzent reduced the risk of cognitive worsening and improved the chance of cognitive improvement at 6 months in patients with active and non-active secondary progressive multiple sclerosis (SPMS). The observations of a separate analysis were also presented on the effects of Mayzent on reducing disability progression, cognitive processing speed and annualized relapse rate (ARR) in patients with active SPMS. These data were presented at the MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting that is taking place September 11–13, 2020.

The subgroup post hoc analysis of EXPAND evaluated the effect of siponimod on the Symbol Digit Modalities Test (SDMT) in subgroups of patients with active SPMS (presence of relapses in 2 years before screening and/or ≥1 T1 gadolinium-enhancing lesions at baseline) and non-active SPMS (counterpart of active SPMS) from the core EXPAND study.[1] The analysis reported that in patients with active SPMS, siponimod reduced the risk of 6-month cognitive worsening by 27% and improved the chance of 6-month cognitive improvement by 62% versus placebo. Corresponding values in the non-active SPMS group were 6-month confirmed worsening (24%) and 6-month cognitive improvement (19%). In the active SPMS group, a lower proportion of patients worsened (27.3% vs 38.2%) and a higher proportion of patients improved (34.1% vs 22.9%) on SDMT versus placebo. Corresponding proportion for the non-active SPMS group were: worsened, 21.2% vs 23.7%; improved, 35.6% vs 31.2%.[1] This analysis has limitations, which were not included in this particular data presentation, and no conclusions can be made.

Patients who completed the core EXPAND study were able to enroll in the ongoing Open-label Extension (OLE) study. In this interim OLE analysis for up to five years presented at MSVirtual2020, time to 6-month CDP, SDMT, and ARR only were assessed. Of the 1,651 patients randomized in the EXPAND Core study, 779 were with active SPMS (Continuous group: N=516; Switch group: N=263), and 710 entered the Extension. The risk of 6-month CDP was reduced by 29% for the Continuous versus Switch group. Median time to 6-month CDP was 48 months for the Switch group and was not reached for the Continuous group. The risk of 6-month confirmed cognition worsening of ≥4-point on SDMT (6mCCW) for the Continuous versus Switch group

was reduced by 33%. In patients without active disease, a nonsignificant trend for reduced risk of disability progression and cognitive worsening was observed for the Continuous vs Switch groups. A reduction in ARR for the Continuous versus Switch groups was observed in patients with or without active disease (0.03 vs 0.08).[2] This analysis has limitations, which were not included in this particular data presentation, and no conclusions can be made.

About the EXPAND Study

The core EXPAND study was a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of siponimod versus placebo in 1,651 patients with SPMS with varying levels of disability.[3] Patients (age 18–60 years) with SPMS and an Expanded Disability Status Scale score of 3.0–6.5 were randomly assigned (2:1) to once daily oral siponimod 2 mg or placebo for up to 3 years or until the occurrence of a prespecified number of confirmed disability progression (CDP) events.[3] The primary endpoint of the EXPAND study was time to 3-month CDP. The two key secondary endpoints were time to 3-month confirmed worsening of at least 20% from baseline in the timed 25-foot walk test (T25-FW) and change from baseline in T2 lesion volume. Additional secondary endpoints were: time to 6-month CDP; ARR; time to first relapse; proportion of relapse-free patients; change in score on the patient-reported 12-item Multiple Sclerosis Walking Scale; number of new or enlarging T2 lesions; number of T1 gadolinium-enhancing lesions; and percentage change in brain volume from baseline.[3]

In the core EXPAND study, Mayzent was superior to placebo in reducing the risk of 3-month confirmed disability progression, based on a time-to-event analysis (P<.0134).[4] Although Mayzent had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of Mayzent in patients with non-active SPMS was not statistically significant.[4] Mayzent did not significantly delay the time to 20% deterioration in the timed 25-foot walk, compared to placebo.[4] Patients treated with Mayzent had a reduced change from baseline in T2 lesion volume, compared to patients on placebo.[4] In EXPAND, a prespecified hierarchical analysis consisted of the primary endpoint and the 2 key secondary endpoints. The T25-FW test key endpoint was not significant; therefore, the T2 lesion volume key secondary endpoint was considered nominal. The remaining endpoints were not corrected for multiple comparisons.[4] In a previously presented core EXPAND study analysis, the effect of siponimod was assessed on the following exploratory cognitive endpoints: Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT) and the Brief Visuospatial Memory Test-Revised (BVMT-R). Siponimod showed a 21.3% overall reduction on cognitive processing speed as measured in the SDMT compared to placebo but did not show significant differences in the PASAT or BVMT-R.[5-8] These analyses have not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

Patients who completed the core EXPAND study were able to enroll in the ongoing Open-label Extension (OLE) Study. Patients either remained on Mayzent (continuous Mayzent group, n=824) or switched to Mayzent from placebo (placebo-switch group, n=400). The extension study endpoints differ from the core study and were predefined in the extension protocol. The mean exposure to Mayzent was 39.4 months, with 18.5% of all study patients reaching the 5-year Mayzent treatment milestone. Patients with SPMS continuously treated with Mayzent experienced 22% relative risk reduction of 6-month CDP, 23% overall reduction in cognitive processing speed and 52% relative reduction of ARR.[9] No conclusions of statistical or clinical significance can be drawn. Consider open-label extension study limitations when interpreting results. The open-label extension study was not blinded, not controlled, and included inherent self-selection bias for remaining in the trial.

About Mayzent® (siponimod)

Mayzent is a selective sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (RMS), to include 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 (CNS))[10], 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 MS. This is thought to lead to the anti-inflammatory effects of Mayzent.[3] Mayzent also enters the CNS and directly binds to the S1P5 and S1P1 sub-receptors on specific cells in the CNS (oligodendrocytes and astrocytes).[11] The mechanism by which siponimod exerts therapeutic effects on MS is unknown but may involve reduction of lymphocytes in the CNS.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by myelin destruction and axonal damage in the brain, optic nerves and spinal cord.[12] MS, which affects approximately 2.3 million people worldwide,[13] can be characterized into four main types of MS: clinically isolated syndrome (CIS), relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS).[14] 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.[12]

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.

MAYZENT US INDICATION

What is MAYZENT® (siponimod) tablets?
MAYZENT is a prescription medicine that is used to treat relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

It is not known if MAYZENT is safe and effective in children.

IMPORTANT SAFETY INFORMATION:

Do not take MAYZENT if you:

- have a CYP2C9*3/*3 genotype. Before starting treatment with MAYZENT, your CYP2C9 genotype should be determined by your health care provider. Ask your health care provider if you are not sure.
- have had a heart attack, chest pain called unstable angina, stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months
- have certain types of heart block or irregular or abnormal heartbeat (arrhythmia), unless you have a pacemaker

MAYZENT may cause serious side effects, including:

1. **Slow heart rate (bradycardia or bradyarrhythmia) when you start taking MAYZENT**. MAYZENT can cause your heart rate to slow down, especially after you take your first dose. You should have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of MAYZENT.

   During the initial updosing period (4 days for the 1-mg daily dose or 5 days for the 2-mg daily dose), if you miss 1 or more doses of MAYZENT, you need to restart the updosing. Call your health care provider if you miss a dose of MAYZENT.
2. **Infections.** MAYZENT can increase your risk of serious infections that can be life-threatening and cause death. MAYZENT lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 3 to 4 weeks of stopping treatment. Your health care provider should review a recent blood test of your white blood cells before you start taking MAYZENT.

   Call your health care provider right away if you have any of these symptoms of an infection during treatment with MAYZENT and for 3 to 4 weeks after your last dose of MAYZENT:
   - fever
   - tiredness
   - body aches
   - chills
   - nausea
   - vomiting
   - headache with fever, neck stiffness, sensitivity to light, nausea, confusion (these may be symptoms of meningitis, an infection of the lining around your brain and spine)
3. A problem with your vision called macular edema. Macular edema can cause some of the same vision symptoms as a multiple sclerosis (MS) attack (optic neuritis). You may not notice any symptoms with macular edema. If macular edema happens, it usually starts in the first 1 to 4 months after your start taking MAYZENT. Your health care provider should test your vision before you start taking MAYZENT and any time you notice vision changes during treatment with MAYZENT. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis.

   Call your health care provider right away if you have any of the following: blurriness or shadows in the center of your vision, a blind spot in the center of your vision, sensitivity to light, or unusually colored (tinted) vision.

Before taking MAYZENT, tell your health care provider about all of your medical conditions, including if you:

- have an irregular or abnormal heartbeat
- have a history of stroke or other diseases related to blood vessels in the brain
- have breathing problems, including during your sleep
- have a fever or infection, or you are unable to fight infections due to a disease or are taking medicines that lower your immune system. Tell your health care provider if you have had chicken pox or have received the vaccine for chicken pox. Your health care provider may do a blood test for chicken pox virus. You may need to get the full course of vaccine for chicken pox and then wait 1 month before you start taking MAYZENT.
- have slow heart rate
- have liver problems
- have diabetes
- have eye problems, especially an inflammation of the eye called uveitis

- have high blood pressure
- are pregnant or plan to become pregnant. MAYZENT may harm your unborn baby. Talk to your health care provider right away if you become pregnant while taking MAYZENT or if you become pregnant within 10 days after you stop taking MAYZENT.
    - If you are a woman who can become pregnant, you should use effective birth control during your treatment with MAYZENT and for at least 10 days after you stop taking MAYZENT.
- are breastfeeding or plan to breastfeed. It is not known if MAYZENT passes into your breast milk. Talk to your health care provider about the best way to feed your baby if you take MAYZENT.

Tell your doctor about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Especially tell your health care provider if you take medicines to control your heart rhythm (antiarrhythmics), or blood pressure (antihypertensives), or heart beat (such as calcium channel blockers or beta-blockers); take medicines that affect your immune system, such as beta-interferon or glatiramer acetate, or any of these medicines that you took in the past.

Tell your doctor if have recently received a live vaccine. You should avoid receiving live vaccines during treatment with MAYZENT. MAYZENT should be stopped 1 week before and for 4 weeks after receiving a live vaccine. If you receive a live vaccine, you may get the infection the vaccine was meant to prevent. Vaccines may not work as well when given during treatment with MAYZENT.

MAYZENT may cause possible side effects, including:

- **increased blood pressure**. Your health care provider should check your blood pressure during treatment with MAYZENT.
- **liver problems**. MAYZENT may cause liver problems. Your health care provider should do blood tests to check your liver before you start taking MAYZENT. Call your health care provider right away if you have any of the following symptoms of liver problems:
    - nausea
    - vomiting
    - stomach pain
    - tiredness
    - loss of appetite
    - your skin or the white of your eyes turn yellow
    - dark urine
- **breathing problems.** Some people who take MAYZENT have shortness of breath. Call your health care provider right away if you have new or worsening breathing problems.
- **swelling and narrowing of the blood vessels in your brain.** A condition called PRES (Posterior Reversible Encephalopathy Syndrome) has happened with drugs in the same class. Symptoms of PRES usually get better when you stop taking MAYZENT. However, if left untreated, it may lead to a stroke. Call your health care provider right away if you have any of the following symptoms: sudden severe headache, sudden confusion, sudden loss of vision or other changes in vision, seizure.
- **severe worsening of multiple sclerosis after stopping MAYZENT**. When MAYZENT is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your doctor before you stop taking MAYZENT for any reason. Tell your health care provider if you have worsening symptoms of MS after stopping MAYZENT.

The most common side effects of MAYZENT include: headache, high blood pressure (hypertension), and abnormal liver tests.

These are not all of the possible side effects of MAYZENT. Call your doctor for medical advice about side

effects.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full Prescribing Information, including Medication Guide.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of 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 employs about 15,000 people in the United States. For more information, please visit https://www.novartis.us.

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2. Giovannoni G, Kappos L, Fox RJ, et al. Sustained reduction of disability and cognitive decline with long-term siponimod treatment in patients with active SPMS: EXPAND data up to 5 years. ePoster presentation at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 2020.
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