Novartis presents data at AAN on novel combination biomarker that may predict disability worsening in secondary progressive multiple sclerosis

Apr 16, 2021

- *New post hoc data from the Phase III EXPAND trial showed combined high levels of plasma neurofilament light chain (NfL) and plasma glial fibrillary acidic protein (GFAP) were consistently associated with a higher risk of disability worsening detection in non-active secondary progressive multiple sclerosis (SPMS)*[1]
- *These data may suggest the addition of GFAP to NfL as a novel, combined biomarker could have the potential to better identify or predict the risk of disease progression in people with SPMS*[1]
- *While people with non-active SPMS do not show signs of relapse or changes in MRI activity, they may be experiencing underlying disability worsening that will likely continue to progress*[2]
- *The Phase III EXPAND trial – the largest randomized, controlled study of SPMS patients to date – evaluated Mayzent, the first and only pill studied and proven to delay disability progression in a more progressed RMS population, including active SPMS*[3,4]

East Hanover, April 16, 2021 — Novartis announced today new post hoc data from the Phase III EXPAND trial (core and ongoing extension) on Mayzent® (siponimod), which demonstrated that combined high levels of plasma neurofilament light chain (NfL) and plasma glial fibrillary acidic protein (GFAP) were consistently associated with a higher risk of disability worsening detection in non-active secondary progressive multiple sclerosis (SPMS).[1] The findings, which may suggest that this novel biomarker combination could ultimately help identify people with SPMS at risk for disease progression, will be presented along with other Mayzent data at the American Academy of Neurology (AAN) Annual Meeting being held virtually on April 17-22, 2021.

“In people with non-active SPMS, identifying those with a higher risk of progression who might benefit from treatment is especially difficult because by definition, they are lacking the established signs of relapse and MRI activity seen in active SPMS, while still experiencing disability worsening,” said Professor Ludwig Kappos, University Hospital Basel. “These encouraging data indicate that a combination of blood biomarkers may increase sensitivity in detecting the early signs of progression in non-active SPMS, allowing for intervention when treatment could be most effective in delaying further progression.”

The EXPAND trial is the largest randomized, controlled Phase III study to date assessing a broad SPMS population and the impact of Mayzent on delaying disability progression in these patients.[3,4] Mayzent was superior to placebo in reducing the risk of confirmed disability progression (CDP), based on a time-to-event analysis in the overall population. Although Mayzent had a significant effect on CDP in patients with active SPMS, its effect in patients with non-active SPMS was not statistically significant.

All abstracts will be published in the journal *Neurology* following the meeting.

MAYZENT

INDICATION

MAYZENT® (siponimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Contraindications

- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

Infections: MAYZENT may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred.

Before starting MAYZENT, review a recent complete blood count (CBC) (ie, within 6 months or after discontinuation of prior therapy). Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy. Consider discontinuing treatment if patient develops a serious infection.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with MAYZENT. If CM is suspected, MAYZENT should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) were reported in MAYZENT clinical trials; however, they have been observed in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, MAYZENT should be discontinued.

Cases of herpes viral infection, including one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, have been reported. Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting MAYZENT. If VZV antibodies are not present or detected, then VZV immunization is recommended and MAYZENT should be initiated 4 weeks after vaccination.

Use of live vaccines should be avoided while taking MAYZENT and for 4 weeks after stopping treatment.

Caution should be used when combining treatment (ie, anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.

Bradyarrhythmia and Atrioventricular Conduction Delays: Prior to initiation of MAYZENT, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose

titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects.

MAYZENT was not studied in patients who had:

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs

Reinitiation of treatment (initial dose titration, monitoring effects on heart rate and AV conduction [ie, ECG]) should apply if ≥4 consecutive daily doses are missed.

Respiratory Effects: MAYZENT may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy if clinically warranted.

Liver Injury: Elevation of transaminases may occur in patients taking MAYZENT. Before starting treatment, obtain liver transaminase and bilirubin levels. Closely monitor patients with severe hepatic impairment. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked, and MAYZENT should be discontinued if significant liver injury is confirmed.

Cutaneous Malignancies: Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended. Monitor for suspicious skin lesions and promptly evaluate any that are observed. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended.

Increased Blood Pressure: Increase in systolic and diastolic pressure was observed about 1 month after initiation of treatment and persisted with continued treatment. During therapy, blood pressure should be monitored and managed appropriately.

Fetal Risk: Based on animal studies, MAYZENT may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT therapy.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for patients treated with MAYZENT in clinical trials. If patients develop any unexpected neurological or psychiatric symptoms, a prompt evaluation should be considered. If PRES is suspected, MAYZENT should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Treatment or After Stopping MAYZENT: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended.

After stopping MAYZENT therapy, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. However, residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore, caution should be applied 3-4 weeks after the last dose of MAYZENT.

Severe Increase in Disability After Stopping MAYZENT: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of an S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment, thus patients should be monitored upon discontinuation.

Most Common Adverse Reactions: Most common adverse reactions (>10%) are headache, hypertension, and transaminase increases.

Please see accompanying 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 nearly than 16,000 people in the United States. For more information, please visit https://www.novartis.us.

Novartis and Novartis US is on Twitter. Sign up to follow @Novartis at https://twitter.com/novartisnews and @NovartisUS at https://twitter.com/NovartisUS.

For Novartis multimedia content, please visit https://www.novartis.com/news/media-library.

For questions about the site or required registration, please contact media.relations@novartis.com.

# # #

Novartis Media Relations
E-mail: media.relations@novartis.com

Julie Masow	**Jamie Bennett**
Head, US External Engagement	Director, US External Engagement
+1 862 579 8456	+1 862 217 3976
julie.masow@novartis.com	jamie.bennett@novartis.com

Novartis Investor Relations
E-mail: investor.relations@novartis.com

North America	
Sloan Simpson	+1 862 778 5052

References

1. Kuhle J, Maceski AM, Meinert R, et al. Plasma neurofilament light chain and glial fibrillary acidic protein levels are prognostic of disability worsening: a biosignature that helps differentiating active from non-active SPMS. ePoster presentation at Virtual AAN Meeting; April 2021.
2. National Multiple Sclerosis Society. Secondary progressive MS (SPMS). Accessed April 1, 2021. https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS
3. Mayzent [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; January 2021.
4. Data on file. First and only progressing RMS treatment. Novartis pharmaceuticals Corp; January 2021.

Disclaimer

This media update 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,” “may,” “could,” “would,” “expect,” “anticipate,” “seek,” “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 media update, 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 media update 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, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity 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 media update as of this date and does not undertake any obligation to update any forward-looking statements contained in this media update as a result of new information, future events or otherwise.

List of links present in page

- https://www.novartis.com/us-en/us-en/news/media-releases/novartis-presents-data-aan-novel-combination-biomarker-may-predict-disability-worsening-secondary-progressive-multiple-sclerosis
- https://www.novartis.com/us-en/us-en/sites/novartis_us/files/2022-03/mayzent_0.pdf
- https://www.novartis.com/us-en/us-en/sites/novartis_us/files/2022-03/mayzent_pmg_0.pdf
- https://www.novartis.com/us-en/us-en/home
- https://twitter.com/novartisnews

- https://twitter.com/NovartisUS
- https://www.novartis.com/news/media-library
- mailto:media.relations@novartis.com
- mailto:julie.masow@novartis.com
- mailto:jamie.bennett@novartis.com
- mailto:investor.relations@novartis.com
- https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS