Transcript Details
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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Staying Ahead of Progression in RMS

Announcer:
Welcome to ReachMD. This medical industry feature titled, “Staying Ahead of Progression in RMS,” is sponsored by Novartis Pharmaceuticals Corporation, and the presenter has been compensated for his time.

Dr. West:
Hello, everyone. I’m Dr. Timothy West from the Rocky Mountain MS Clinic in Salt Lake City, Utah. In today’s program, we will first be learning about progression in relapsing multiple sclerosis, or RMS.

To start things off, let’s introduce ourselves to a hypothetical progressing relapsing MS patient.

Jess is a 41-year-old science teacher with an eight-year history of relapsing MS. She has tried two treatments since her MS diagnosis and is currently on an oral medication she started two years ago. In terms of her MS activity, Jess has not had a relapse in the past year but her last MRI did reveal one new gadolinium enhanced T1 lesion and an increase in her overall T2 lesion volume. She has recently experienced mild motor deficits, such as weakness in her right leg, and has trouble concentrating when organizing lesson plans for her class.

Let’s take a look at why Jess may be experiencing increasing disability.

As MS progresses, disease activity such as relapses or MRI lesions become less frequent while disability level continues to increase in between relapses or MRI activities.[1 - 3] Neurodegeneration becomes more prominent as the peripherally driven inflammation declines.[4] Thus, treatment goals in relapsing MS may change as the disease progresses.[5]

Looking back at Jess’s MS history and the changes including her increasing disability and cognitive difficulties, we find that her disability level is a score of 3.5 using the Expanded Disability Status Scale or EDSS. A score of 3.5 might seem low but for patients like Jess, it’s never too early to stay ahead of progression.

Now let’s talk about MAYZENT®, siponimod, the first and only oral disease-modifying therapy studied and proven to delay disability progression in a more progressed relapsing MS population.[6,7]

Announcer:
MAYZENT®(siponimod) indication and important safety information.

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

Dr. West:
Please see additional Important Safety Information throughout this podcast and full Prescribing Information on ReachMD.com/relapsingMS.

Now let's take a closer look at MAYZENT®.

The dual mechanism of action of MAYZENT targets $S1P_1$ and $S1P_5$, two key receptors thought to play a role in relapsing multiple sclerosis inflammation and neurodegeneration.[6,8-11] MAYZENT reduces the migration of lymphocytes into the central nervous system by sequestering the lymphocytes in the lymph nodes.[6] This sequestration of lymphocytes is reversible. Within the *EXPAND* trial, lymphocyte counts typically returned to the normal range in 90% of patients within 10 days of stopping therapy.[6]

Announcer:
The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment. Patients should be monitored upon discontinuation.

Dr. West:
The elimination half-life of MAYZENT is approximately 30 hours.[6] The mechanism by which MAYZENT exerts therapeutic effects on MS is unknown but may involve reduction of lymphocyte migration into the central nervous system.[6]

Next, we can look at MAYZENT within the central nervous system. MAYZENT is a small molecule that readily crosses the blood-brain barrier and may have direct effects in the central nervous system independent of its effects on peripheral lymphocytes.[6,8,9,12-14]

Now let's review the clinical data of MAYZENT in *EXPAND* which was the Phase III trial. This actually is the largest clinical trial to date in progressing relapsing MS patients.[15,16] *EXPAND* enrolled 1651 patients with a mean age of 48 years and an average of 13 years since their diagnosis of multiple sclerosis.[6,15] 36% of the patients had one or more relapses in the two years prior to the study and at baseline 21% of the patients with available imaging had one or more gadolinium-enhancing lesions.[6,15] The average EDSS score in *EXPAND* was 5.4 and 56% of the patients did require a walking aid upon entering to the study.[6,15]

MAYZENT was proven to significantly delay relative risk of time to 3-month confirmed disability progression or CDP by 21% in the *EXPAND* trial.[6,13] The effect of MAYZENT was not statistically significant in patients with nonactive secondary progressive MS although MAYZENT had a significant effect in SPMS patients with disease activity.[6,15]

A separate post hoc analysis evaluated the efficacy of MAYZENT in delaying disability progression in the active subgroup of *EXPAND*.[17] Within that active subgroup, MAYZENT reduced the relative risk in time to 3-month confirmed disability progression by 31% as compared to placebo.[17] Disease activity was defined as the presence of relapses in the 2 years before screening with no relapses within 3 months before randomization and/or one or more T1 gadolinium-enhancing lesions.[17] It's important to remember that this analysis was not corrected for multiple comparisons and therefore no conclusions of statistical or clinical significance can be made. So, please keep that in mind when viewing data from this post hoc analysis of *EXPAND*.

Looking at the 2 key secondary end points, MAYZENT® did not significantly delay the time of confirmed 20% deterioration in the timed 25-foot walk test end point.[6,15] MAYZENT reduced the expansion of T2 lesion volume at 12 and 24 months vs placebo, but in the *EXPAND* trial, a prespecified hierarchical analysis consisted of the primary end point and the 2 key secondary end points. Because the timed 25-foot walk test was not significant, all end points analyzed after this end point were not corrected for multiple comparisons and no conclusions of statistical or clinical significance can be made. Please keep this in mind when viewing this data from the *EXPAND* clinical trial.[6,15]

The time to 6-month confirmed disability progression was studied as an additional secondary end point of *EXPAND*.[15] Treatment with MAYZENT resulted in a 26% relative risk reduction in time to 6-month confirmed disability progression versus those patients on placebo.[15] No conclusions of statistical or clinical significance can be made.

In terms of additional secondary relapse and MRI activity end points, treatment with MAYZENT resulted in a 55% relative reduction in annualized relapse rate, an 81% reduction in the number of new or enlarging T2 lesions, and an 86% reduction in the number of new gadolinium-enhanced T1 lesions.[15]

MAYZENT was also studied across exploratory cognitive end points.[18] Treatment with MAYZENT resulted in a 21.3% overall reduction in the risk of having a sustained decrease in the symbol digit modalities test score of at least 4 points. At 24 months, a 2.48-point difference was seen between the MAYZENT and placebo groups.[18] MAYZENT did not show clinically meaningful differences from placebo in the brief visuospatial memory test revised score and the paced auditory serial addition test score.[18]

Announcer:
IMPORTANT SAFETY INFORMATION (continued)

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.

Dr. West:
At the end of the *EXPAND* core study, patients had the option to roll over into an open-label extension, or OLE. In this study, MAYZENT patients could continue their MAYZENT therapy whereas placebo patients in the core study would switch over to MAYZENT therapy as

well.[19]

In an interim analysis of the OLE study, time to 6-month confirmed disability progression, SDMT and annualized relapse rate only were assessed.[15,19] 75% of MAYZENT patients, which is 824 patients, continued on MAYZENT, and 73% of the placebo patients, with a number of 400 patients, switched over to MAYZENT.[19] The mean exposure of MAYZENT for all patients was 39.4 months and 18.5% of all study patients reached the five-year MAYZENT milestone.[19]

Please remember that the analyses in this section have not been adjusted for multiple comparisons and no conclusions of statistical or clinical significance can be made. Consider open-label extension study limitations when interpreting these results as well. The open-label extension study was not blinded, not controlled, and included inherent self-selection bias for remaining in the trial. Please keep this in mind when viewing this data from the *EXPAND* extension study.[15,19]

An interim analysis of the *EXPAND* extension study of up to 5 years showed sustained benefits of early treatment with MAYZENT.[6,19] Patients who started earlier on MAYZENT showed a 22% relative risk reduction in the time to 6-month confirmed disability progression versus the placebo switch group.[19]

Additional extension study results showed sustained benefits of treatment for up to 5 years.[19] Patients who started earlier on MAYZENT showed a 23% overall reduction in risk of decrease in SDMT score versus the placebo-switch group. The symbol digit modalities test was the only cognitive assessment conducted in the extension study.[19] A 52% relative reduction in annualized relapse rate for the continuous MAYZENT group was also observed as compared to the placebo-switch group, and patients who started treatment on MAYZENT earlier saw a reduction in annualized relapse rates versus patients who switched to MAYZENT later from placebo.[19]

This visual is displaying adverse reactions that occurred in 5% or more of the patients taking MAYZENT® and at a rate of 1% or more higher than in the patients receiving placebo.[6] In the *EXPAND* core study, the most common adverse reactions with an incidence of 10% or more were headache, hypertension, and transaminase increases.[6]

Adverse events led to discontinuation of treatment in 8.5% of patients treated with MAYZENT and 5.1% of patients receiving placebo.[6]

The adverse events displayed in this visual here were those that occurred in 3% or more of the patients taking MAYZENT in the core and extension studies.[19] The *EXPAND* extension study showed a safety profile consistent with the core study based on the listed criteria.[19]

In summary, MAYZENT has a dual mechanism of action in multiple sclerosis by targeting S1P receptors 1 and 5, two key receptors thought to play a role in relapsing multiple sclerosis inflammation and neurodegeneration.[6,8-11] The mechanism by which MAYZENT exerts therapeutic effects in multiple sclerosis is unknown.[6] MAYZENT is the first and only oral disease-modifying therapy studied and proven to delay disability progression in a progressed patient population in relapsing multiple sclerosis.[6,7]

Announcer:
IMPORTANT SAFETY INFORMATION (continued)

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.

Dr. West:
Please see additional Important Safety Information throughout this podcast and full Prescribing Information on ReachMD.com/relapsingMS.

Thank you for joining me.

Announcer:
This program was sponsored by Novartis Pharmaceuticals Corporation. If you missed any part of this discussion, visit ReachMD.com. This is ReachMD. Be part of the knowledge.

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