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ECTRIMS 2019

Exclusive Coverage of the

35TH CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

September 11-13 | Stockholm, Sweden

Ofatumumab Impresses in Head-to-Head Phase 3 Trials in Patients With Relapsing Forms of Multiple Sclerosis

During the late-breaking news scientific sessions, Stephen Hauser, MD, Robert A. Fishman distinguished professor of neurology at the University of California, San Francisco, presented new data from the ASCLEPIOS I and II trials regarding the safety and efficacy of ofatumumab—the first fully human anti-CD20 monoclonal antibody for the treatment of multiple sclerosis (MS)—compared with teriflunomide in patients with relapsing forms of MS.

Prior to presentation of the data, Hauser noted that one of the advantages of targeting CD20 is that the earliest and latest B cells in the differentiation cycle, which lack CD20 expression, are not affected by treatment. "Preservation of stem and pro-B cells ensures that there will be a repopulation of mature B cells, and preexisting humoral immunity

(Continued on page 9)

Weighing the Impact of Comorbidities on Multiple Sclerosis Treatment Selection and Course

In recent years, early treatment has been shown to be critical in the management of patients with multiple sclerosis (MS).[1,2] Fortunately, the MS treatment landscape is expanding, with a number of disease-modifying therapies (DMTs) with varying mechanisms of action now available. Nevertheless, the selection of optimal treatments for a patient can be challenging. In a poster presentation, investigators reviewed real-world data with the goal of elucidating the impact of comorbidities, MS subtype, and prognostic profile on physicians' treatment recommendations for patients.[3]

Comorbidities and Treatment Selection

Researchers collected real-world data from US neurologists who have initiated a DMT in treatment-naïve patients with MS. Among the 1059 patients included in the study,

(Continued on page 11)

ALSO IN THIS ISSUE

Not actual patients.

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.

MAYZENT®
(siponimod) tablets
0.25 mg • 2 mg

FOR PATIENTS WITH ACTIVE SPMS

IT'S TIME TO SLOW DOWN SPMS WITH MAYZENT® (siponimod)

THE FIRST AND ONLY ORAL TREATMENT STUDIED AND PROVEN IN ACTIVE SPMS[1]

DEMONSTRATED 21% RELATIVE RISK REDUCTION

in 3-month confirmed disability progression in patients with SPMS (*P*=0.013)[2*]

LARGEST SPMS TRIAL TO DATE (N=1651)

EXPAND was powered to prospectively demonstrate the efficacy of MAYZENT[3†]

THE LOWEST-PRICED

daily administered oral DMT[4]

*Proportion of patients with 3-month confirmed disability progression for MAYZENT was 26% vs 32% for patients on placebo. Although MAYZENT had a significant effect on confirmed disability progression in patients with active SPMS (relapse in the 2 years prior to study entry), its effect in patients with nonactive SPMS was not statistically significant.[2,3]

†More information about the *EXPAND* trial in SPMS can be found at the bottom of the next page, following the Important Safety Information.

The mechanism by which siponimod exerts therapeutic effects on multiple sclerosis is unknown.[2]

CDP=confirmed disability progression; DMT=disease-modifying therapy; S1P=sphingosine 1-phosphate; SPMS=secondary progressive multiple sclerosis.

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IMPORTANT SAFETY INFORMATION (CONT)

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.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

IMPORTANT SAFETY INFORMATION (CONT)

Bradyarrhythmia and Atrioventricular Conduction Delays (cont):

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.

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 additional Important Safety Information on the previous pages, and Brief Summary of full Prescribing Information on adjacent pages.

Trial Design: *EXPAND* was a randomized, double-blind, placebo-controlled study in 1651 patients with SPMS. The inclusion criteria were: documented evidence of progression in the 2 years prior to enrollment, no evidence of relapse in the 3 months prior to study enrollment, and an expanded disability status scale (EDSS) score of 3.0-6.5 at study entry. Patients were randomized 2:1 to receive either once-daily MAYZENT 2 mg or placebo. Evaluations were performed at screening, every 3 months, and when relapses occurred. MRI evaluations were performed at screening and every 12 months. The follow-up duration was 37 months.

References: 1. DOF FirstOnlyOral SPMS July 2019. **2.** Mayzent [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; March 2019. **3.** Kappos L, Bar-Or A, Cree BAC, et al; for the EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391(10127):1263-1273. **4.** AnalySource data as of 7/12/2019.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

MAYZENT® (siponimod) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

MAYZENT 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.

4 CONTRAINDICATIONS

MAYZENT is contraindicated in patients who have:

- A CYP2C9*3/*3 genotype *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5) in the full prescribing information]*
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of Infections

MAYZENT causes a dose-dependent reduction in peripheral lymphocyte count to 20%-30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT may therefore increase the risk of infections, some serious in nature *[see Clinical Pharmacology (12.2) in the full prescribing information]*. Life-threatening and rare fatal infections have occurred in association with MAYZENT.

In Study 1 *[see Clinical Studies (14) in the full prescribing information]*, the overall rate of infections was comparable between the MAYZENT-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infection were more common in MAYZENT-treated patients. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT-treated patients compared to 2.5% of patients receiving placebo.

Before initiating treatment with MAYZENT, results from a recent complete blood count (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

Initiation of treatment with MAYZENT should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period *[see Warnings and Precautions (5.11)]*.

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT should be considered if a patient develops a serious infection.

Cryptococcal Infections

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have also occurred with MAYZENT. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. MAYZENT treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Herpes Viral Infections

Cases of herpes viral infection, including one case of reactivation of VZV infection leading to varicella zoster meningitis, have been reported in the development program of MAYZENT. In Study 1, the rate of herpetic infections was 4.6% in MAYZENT-treated patients compared to 3.0% of patients receiving placebo. In Study 1, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT-treated patients compared to 0.7% of patients receiving placebo. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT *(see Vaccinations below)*.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in MAYZENT-treated patients in the development program; however, PML has been reported in patients treated with a S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with MAYZENT should be suspended until PML has been excluded.

Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects during such therapy *[see Drug Interactions (7.1)]*.

Vaccinations

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with MAYZENT, following which initiation of treatment with MAYZENT should be postponed for 4 weeks to allow the full effect of vaccination to occur.

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT and for 4 weeks after stopping treatment *[see Drug Interactions (7.1)]*.

Vaccinations may be less effective if administered during MAYZENT treatment. MAYZENT treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema

Macular edema was reported in 1.8% of MAYZENT-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT.

Continuation of MAYZENT therapy in patients with macular edema has not been evaluated. A decision on whether or not MAYZENT should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during MAYZENT therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT, the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.3 Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of MAYZENT treatment results in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of MAYZENT *[see Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.2) in the full prescribing information]*.

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 *[see Drug Interactions (7.2)]*

Reduction in Heart Rate

After the first titration dose of MAYZENT, the heart rate decrease starts within an hour, and the Day 1 decline is maximal at approximately 3-4 hours. With continued up-titration, further heart rate decreases are

seen on subsequent days, with maximal decrease from Day 1-baseline reached on Day 5-6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on Day 1, with the pulse declining on average 5-6 bpm. Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after Day 6 and reaches placebo levels within 10 days after treatment initiation.

In Study 1, bradycardia occurred in 4.4% of MAYZENT-treated patients compared to 2.9% of patients receiving placebo. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, including dizziness or fatigue, and these symptoms resolved within 24 hours without intervention *[see Adverse Reactions (6.1)]*. Heart rates below 40 bpm were rarely observed.

Atrioventricular Conduction Delays

Initiation of MAYZENT treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The AV conduction delays manifested in most of the cases as first-degree AV block (prolonged PR interval on ECG), which occurred in 5.1% of MAYZENT-treated patients and in 1.9% of patients receiving placebo in Study 1. Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at the time of treatment initiation with MAYZENT in less than 1.7% of patients in clinical trials. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, rarely required treatment with atropine, and did not require discontinuation of MAYZENT treatment.

If treatment with MAYZENT is considered, advice from a cardiologist should be sought:

- In patients with significant QT prolongation (QTc greater than 500 msec)
- In patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs *[see Drug Interactions (7.2)]*
- In patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block *[see Contraindications (4)]*

Treatment-Initiation Recommendations

- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.
- In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects *[see Dosage and Administration (2.2, 2.3) in the full prescribing information]*.
- In patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset > 6 months prior to initiation, ECG testing and first-dose monitoring is recommended *[see Dosage and Administration (2.1, 2.4) in the full prescribing information]*.
- Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, MAYZENT is not recommended in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.
- Use of MAYZENT in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.
- Experience with MAYZENT is limited in patients receiving concurrent therapy with drugs that decrease heart-rate (e.g., beta-blockers, calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate, such as ivabradine and digoxin). Concomitant use of these drugs during MAYZENT initiation may be associated with severe bradycardia and heart block.
  - For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing MAYZENT treatment. If the resting heart rate is greater than 50 bpm under chronic beta-blocker treatment, MAYZENT can be introduced. If resting heart rate is less than or equal to 50 bpm, beta-blocker treatment should be interrupted until the baseline heart-rate is greater than 50 bpm. Treatment with MAYZENT can then be initiated and treatment with a beta-blocker can be reinitiated after MAYZENT has been up-titrated to the target maintenance dosage *[see Drug Interactions (7.3)]*.
  - For patients taking other drugs that decrease heart rate, treatment with MAYZENT should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate *[see Dosage and Administration (2.4) in the full prescribing information and Drug Interactions (7.2)]*.

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

If a titration dose is missed or if 4 or more consecutive daily doses are missed during maintenance treatment, reinitiate Day 1 of the dose titration and follow titration monitoring recommendations *[see Dosage and Administration (2.2, 2.3) in the full prescribing information]*.

5.4 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV_1) were observed in MAYZENT-treated patients as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV_1 from baseline compared to placebo was 88 mL [95% confidence interval (CI): 139, 37] at 2 years. The mean difference between MAYZENT-treated patients and patients receiving placebo in percent predicted FEV_1 at 2 years was 2.8% (95% CI: -4.5, -1.0). There is insufficient information to determine the reversibility of the decrease in FEV_1 after drug discontinuation. In Study 1, five patients discontinued MAYZENT because of decreases in pulmonary function testing. MAYZENT has been tested in MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The changes in FEV_1 were similar in this subgroup compared with the overall population. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated.

5.5 Liver Injury

Elevations of transaminases may occur in MAYZENT-treated patients. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of MAYZENT therapy.

In Study 1, elevations in transaminases and bilirubin were observed in 10.1% of MAYZENT-treated patients compared to 3.7% of patients receiving placebo, mainly because of transaminase [alanine aminotransferase/aspartate aminotransferase/gamma-glutamyltransferase (ALT/AST/GGT)] elevations.

In Study 1, ALT or AST increased to three and five times the upper limit of normal (ULN) in 5.6% and 1.4% of MAYZENT-treated patients, respectively, compared to 1.5% and 0.5% of patients receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of MAYZENT. In clinical trials, MAYZENT was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic dysfunction.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should have liver enzymes checked. MAYZENT should be discontinued if significant liver injury is confirmed.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking MAYZENT, caution should be exercised when using MAYZENT in patients with a history of significant liver disease.

5.6 Increased Blood Pressure

In Study 1, MAYZENT-treated patients had an average increase over placebo of approximately 3 mmHg in systolic pressure and 1.2 mmHg in diastolic pressure, which was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Hypertension was reported as an adverse reaction in 12.5% of MAYZENT-treated patients and in 9.2% of patients receiving placebo. Blood pressure should be monitored during treatment with MAYZENT and managed appropriately.

5.7 Fetal Risk

Based on animal studies, MAYZENT may cause fetal harm *[see Use in Specific Populations (8.1)]*. Because it takes approximately 10 days to eliminate MAYZENT from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT treatment.

5.8 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for MAYZENT-treated patients in the development program. However, should a MAYZENT-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical

visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider a MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, MAYZENT should be discontinued.

5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies
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 while at the same time minimizing risk of disease reactivation, when initiating MAYZENT.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended *[see Drug Interactions (7.1)]*.

5.10 Severe Increase in Disability After Stopping MAYZENT
Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment. Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping MAYZENT
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 *[see Clinical Pharmacology (12.2) in the full prescribing information]*. However, residual pharmacodynamics 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 *[see Drug Interactions (7.1)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Macular Edema *[see Warnings and Precautions (5.2)]*
- Bradyarrhytmia and Atrioventricular (AV) Conduction Delays *[see Warnings and Precautions (5.3)]*
- Respiratory Effects *[see Warnings and Precautions (5.4)]*
- Liver Injury *[see Warnings and Precautions (5.5)]*
- Increased Blood Pressure *[see Warnings and Precautions (5.6)]*
- Fetal Risk *[see Warnings and Precautions (5.7)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.8)]*
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies *[see Warnings and Precautions (5.9)]*
- Severe Increase in Disability After Stopping MAYZENT *[see Warnings and Precautions (5.10)]*
- Immune System Effects After Stopping MAYZENT *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1737 MS patients have received MAYZENT at doses of at least 2 mg daily. These patients were included in Study 1 *[see Clinical Studies (14) in the full prescribing information]* and in a Phase 2 placebo-controlled study in patients with MS. In Study 1, 67% of MAYZENT-treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of MAYZENT-treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in MAYZENT-treated patients in Study 1 were headache, hypertension, and transaminase increases.

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate at least 1% higher than in patients receiving placebo.

Table 3 Adverse Reactions Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate at Least 1% Higher Than in Patients Receiving Placebo)

Adverse Reaction	MAYZENT 2 mg (N = 1099) %	Placebo (N = 546) %
Headache[a]	15	14
Hypertension[b]	13	9
Transaminase increased[c]	11	3
Falls	11	10
Edema peripheral[d]	8	4
Nausea	7	4
Dizziness	7	5
Diarrhea	6	4
Bradycardia[e]	6	3
Pain in extremity[f]	6	4

Terms were combined as follows:
[a]headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.
[b]hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.
[c]alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.
[d]edema peripheral, joint swelling, fluid retention, swelling face.
[e]bradycardia, sinus bradycardia, heart rate decreased.
[f]pain in extremity and limb discomfort.

The following adverse reactions have occurred in less than 5% of MAYZENT-treated patients but at a rate at least 1% higher than in patients receiving placebo: herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block (1st and 2nd degree), asthenia, and pulmonary function test decreased *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)]*.

Seizures
In Study 1, cases of seizures were reported in 1.7% of MAYZENT-treated patients, compared to 0.4% in patients receiving placebo. It is not known whether these events were related to the effects of MS, to MAYZENT, or to a combination of both.

Respiratory Effects
Dose-dependent reductions in forced expiratory volume over 1 second (FEV_1) were observed in patients treated with MAYZENT *[see Warnings and Precautions (5.4)]*.

Vascular Events
Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.0% of MAYZENT-treated patients compared to 2.6% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

Malignancies
Malignancies such as malignant melanoma *in situ* and seminoma were reported in MAYZENT-treated patients in Study 1. An increased risk of cutaneous malignancies has been reported in association with another S1P modulator.

7 DRUG INTERACTIONS
7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies
MAYZENT has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration *[see Warnings and Precautions (5.1)]*.

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects *[see Warnings and Precautions (5.9)]*.

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with MAYZENT after alemtuzumab is not recommended.

MAYZENT can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate
MAYZENT has not been studied in patients taking QT prolonging drugs.

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with MAYZENT is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) *[see Warnings and Precautions (5.3) and Drug Interactions (7.3)]*. If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

7.3 Beta-Blockers
Caution should be applied when MAYZENT is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of MAYZENT *[see Warnings and Precautions (5.3)]*. Beta-blocker treatment can be initiated in patients receiving stable doses of MAYZENT *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

7.4 Vaccination
During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination *[see Warnings and Precautions (5.1)]*.

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT *[see Warnings and Precautions (5.1)]*.

7.5 CYP2C9 and CYP3A4 Inhibitors
Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inhibitors.

7.6 CYP2C9 and CYP3A4 Inducers
Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and*2/*3 genotype *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women. Based on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman *(see Data)*. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, the only dose with fetuses available for evaluation. A no-effect dose for adverse effects on embryo-fetal development in rats was not identified. Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose (RHD) of 2 mg/day.

When siponimod (0, 0.1, 1, or 5 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryolethality and increased incidences of fetal skeletal variations were observed at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose (0.1 mg/kg) for adverse effects on embryo-fetal development in rabbits is less that than in humans at the RHD.

When siponimod (0, 0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual maturation were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m^2 basis.

8.2 Lactation
Risk Summary
There are no data on the presence of siponimod in human milk, the effects of MAYZENT on the breastfed infant, or the effects of the drug on milk production. A study in lactating rats has shown excretion of siponimod and/or its metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAYZENT and any potential adverse effects on the breastfed infant from MAYZENT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Contraception
Females
Before initiation of MAYZENT treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with MAYZENT *[see Use in Specific Populations (8.1)]*. Since it takes approximately 10 days to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period *[see Warnings and Precautions (5.7)]*.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 CYP2C9 Genotype
Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.5) in the full prescribing information]*.

10 OVERDOSAGE

In patients with overdosage of MAYZENT, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed *[see Warnings and Precautions (5.3, 5.6) and Clinical Pharmacology (12.2) in the full prescribing information]*.

There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body. The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

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Ofatumumab Impresses (Continued from page 1)

can be protected in large part because late plasmablasts and long-lived memory cells are also CD20 negative," Hauser said in his presentation. CD20 targeting is very effective at nearly complete depletion of B cells in the blood but only partial depletion of lymph nodes, which may explain, in part, its safety profile.

Study Design and Methods

Ofatumumab binds to CD20, resulting in B-cell depletion, as well as reduced B-cell and T-cell interactions, which may reduce inflammation in the central nervous system (CNS).[1] ASCLEPIOS I and II are parallel, double-blind, double-dummy, multicenter trials with identical study designs, which evaluated the safety and efficacy of subcutaneous ofatumumab compared with oral teriflunomide for the treatment of patients with relapsing MS.[2] Patients in the ofatumumab group received ofatumumab 20 mg subcutaneously every week for 3 weeks at 0.4 mL under observation; patients in this group were also taking a once-daily oral placebo pill. At week 4, patients self-administered ofatumumab every 4 weeks. Patients in the teriflunomide group were randomized to receive a full 14-mg dose of the agent once daily and subcutaneous placebo injections. Following completion of the study, patients were entered into open-label screening and an ongoing open-label extension study.

"This trial was designed in an adaptive and flexible way, which means that the number of events would determine the ultimate duration and also the size of the study," said Hauser. Discussing the rationale for the head-to-head study design during the Q&A portion of the presentation, Hauser pointed out that the investigators wanted to have effects that would be present not only against focal disease activity but potentially against progression as well. Considering the latter, the investigators thought that teriflunomide was a very good comparator.

The primary endpoint within each study was the annualized relapse rate (ARR), which is defined as the number of confirmed MS relapses in 1 year. Among key secondary clinical endpoints in the prespecified pooled analysis were 3- and 6-month confirmed disability worsening (CDW) and 6-month confirmed disability improvement (CDI). Other secondary magnetic resonance imaging (MRI)/biomarker endpoints included gadolinium-enhancing (Gd+) T1 lesions, new or enlarging T2 lesions, serum neurofilament light (NfL) chain levels, and brain volume loss—all of which were analyzed in individual studies.

Eligible patients were aged 18 to 55 years; had an Expanded Disability Status Scale (EDSS) score of 0 to 5.5; and needed to have experienced 1 of the following: (1) ≥1 relapses in the year prior to screening, (2) ≥2 relapses in the 2 years prior to screening, or (3) a positive Gd+ T1 scan in the year prior to randomization (**FIGURE**).[2] Patients also needed to have been neurologically stable

FIGURE. ASCLEPIOS I and II Inclusion Criteria[2]

- Male or female patients aged 18 to 55 years
- Diagnosis of MS according to the 2010 Revised McDonald Criteria
- Relapsing-remitting MS or secondary progressive MS
- EDSS score of 0 to 5.5
- Documented occurrence of 1 of the following:
  - ≥1 relapses in the year prior to screening
  - ≥2 relapses in the 2 years prior to screening
  - A positive Gd+ T1 scan in the year prior to randomization
- Neurologically stable within 1 month prior to enrollment

EDSS indicates Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis.

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in the month prior to enrollment. "This was a typical active MS relapsing population," Hauser said. "About 5% of patients would qualify as having secondary progressive MS. [Individuals in this population] have very active disease.... The criteria are not very different from [those in] other studies of this type."

A total of 927 patients were enrolled in ASCLEPIOS I, and 955 were enrolled in ASCLEPIOS II. Countries with the highest enrollment were the United States, Russia, Poland, the Czech Republic, Croatia, Germany, Spain, and India. In each of the 2 studies, all enrolled patients were randomized to treatment in a 1:1 ratio. Hauser observed that dropout rates were relatively low across all 4 arms of the 2 studies. "The dropout rates were low because of a lack of AEs [adverse effects] or obvious lack of efficacy during the treatment trial."

> "There was a quite impressive, greater than 50% decrease in ARR in ASCLEPIOS I and [greater than] 58% [decrease] in ASCLEPIOS II, favoring ofatumumab over teriflunomide."
>
> —Stephen Hauser, MD

Patient demographics and baseline characteristics were similar between the 2 studies. For example, the duration of MS since initial symptoms (approximately 8 years), the percentage of patients treated with disease-modifying therapies (approximately 60%), the number of relapses in the past 12 months (approximately 1.3), and the EDSS score (approximately 2.9) were consistent across all groups, Hauser said.

Efficacy Findings

Results showed that ofatumumab therapy was associated with significant reductions in ARR. In ASCLEPIOS I, the ARR in teriflunomide-treated patients was 0.22 compared with 0.11 in ofatumumab-treated patients (P <.001). In ASCLEPIOS II, the ARR in patients treated with teriflunomide was 0.25 compared with 0.10 in patients treated with ofatumumab (P <.001). "There was a quite impressive, greater than 50% decrease in ARR in ASCLEPIOS I and [greater than] 58% [decrease] in ASCLEPIOS II, favoring ofatumumab over teriflunomide," Hauser said. "The absolute numbers of relapses, about 1 in 10 years, may come close to the floor that we're going to be able to see in a population of this type."

In the prespecified pooled analysis, ofatumumab showed significant reductions in CDW. At 3 months, the cumulative event rate for patients in the teriflunomide group was 15%, compared with 10.9% in the ofatumumab group—a risk reduction of 34.4% (hazard ratio [HR], 0.656; 95% CI, 0.499-0.862; P = .002). At 6 months, the cumulative event rate for patients in the teriflunomide group was 12%, compared with 8.1% in the ofatumumab group—a risk reduction of 32.5% (HR, 0.675; 95% CI, 0.498-0.916; P = .012). In the 6-month pooled analysis of CDI, ofatumumab demonstrated a favorable trend but failed to achieve statistical significance. Teriflunomide demonstrated an 8.1% cumulative event rate compared with 11.0% with ofatumumab—a 35.2% increase in the risk for CDI (HR, 1.352; 95% CI, 0.950-1.924; P = .094).

Regarding secondary endpoints, ofatumumab demonstrated a statistically significant 97.5% relative reduction in the number of Gd+ T1 lesions versus teriflunomide in ASCLEPIOS I (P <.001) and a significant 93.8% relative reduction versus teriflunomide in ASCLEPIOS II (P <.001). Ofatumumab also showed a significant reduction in the number of new or enlarging T2 lesions, with a significant 82.0% relative reduction compared with teriflunomide in ASCLEPIOS I (P <.001) and a significant 84.5% relative reduction compared with teriflunomide in ASCLEPIOS II (P <.001).

Ofatumumab also demonstrated a significant and consistent reduction over teriflunomide in serum NfL levels at 3 months, with a 7% relative reduction in ASCLEPIOS I (P <.011) and an 11% relative reduction in ASCLEPIOS II (P <.001). At 12 months, the relative reduction in serum NfL levels with ofatumumab versus teriflunomide was 27% in ASCLEPIOS I and 26% in ASCLEPIOS II. Moreover, at 24 months, the relative reduction in NfL levels with ofatumumab versus teriflunomide was 23% in ASCLEPIOS I (P <.001) and 24% in ASCLEPIOS II (P <.001).

Regarding brain volume change, there was no difference in slope from baseline between ofatumumab and teriflunomide. According to Hauser, the similarities in brain volume loss are not surprising because earlier trial findings have shown that teriflunomide has a fairly remarkable effect on halting brain volume loss. "It's very interesting to contemplate the discordant results between NfL and brain atrophy data; it suggests that preserving brain volume is not always the same thing clinically or biologically," said Hauser.

Safety Findings

AEs were balanced between the groups, with no unexpected safety findings reported. Nasopharyngitis (16.7%), injection-related reactions (15.3%), and alopecia (14.7%) were the most often reported AEs. Overall, 83.6% of patients experienced AEs in the ofatumumab group, with the most common AEs in that treatment arm being injection-related reaction (20.6%), nasopharyngitis (18.0%), and headache (13.3%).

In the teriflunomide group, 7.9% of patients experienced serious AEs, with the most common serious AEs being infections and infestations (1.8%); CNS disorders (1.6%); and injury, poisoning, and procedural complications (1.0%). In the ofatumumab group, 9.1% of patients experienced serious AEs, with the most common serious AEs being infections and infestations

(2.5%); injury, poisoning, and procedural complications (1.4%); and psychiatric disorders (1.1%).

During the 2 trials, 1 death occurred in the teriflunomide group because of a fatal aortic hemorrhage. Overall, 3 malignancies were reported in the teriflunomide arm compared with 5 malignancies in the ofatumumab arm. Among the 5 malignancies in the ofatumumab arm, Hauser noted that 2 of the malignancies were basal cell carcinomas, 1 was a melanoma that was discovered at study entry, and another was a preexisting non-Hodgkin lymphoma that was thought to be in remission.

In patients who reported injection-site reactions, 99% of the events were mild to moderate. Moreover, Hauser explained that imbalance in injection reactions with ofatumumab appears to be limited to the first injection. He also noted that only 1 patient in the ofatumumab group with a nonserious injection-site reaction discontinued the study as a result.

Summary and Implications

"ASCLEPIOS I and II, in this broad, active, somewhat advanced relapsing MS population, successfully demonstrated that ofatumumab [with a 20-mg subcutaneous dosing regimen] showed superior efficacy to teriflunomide in lowering relapse rates and MRI activity; substantial, significant reductions in 3- and 6- month disability worsening; lower levels of NfL already present at month 3; and a favorable safety profile with no unexpected safety signals," Hauser concluded.

Discussing the implications of the data within the context of the current landscape of MS therapies, particularly ocrelizumab, Hauser explained that "at a 35,000-foot level, we are looking at similar efficacy." He also observed that both agents offer attractive features and mechanisms of action. "Young people who may not be compliant might do well with treatment under observation/infusion, [while] others may prefer a home-based solution." ●

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The Impact of Comorbidities (Continued from page 1)

79 received a diagnosis of clinically isolated syndrome, 758 had relapsing-remitting MS, 142 had secondary progressive MS, and 80 had primary progressive MS (PPMS).[3] In addition to collecting data on comorbid conditions, the investigators categorized the prognostic profiles of patients as "favorable" or "concerning," based on the physician's subjective assessment. The investigators found that 18% of patients with MS had a concerning prognostic profile, and patients with PPMS were significantly more likely to be categorized as concerning (45%) versus favorable (16%; $P < .05$).[3]

Approximately 62% of patients were shown to have comorbidities. The most common comorbid conditions reported included depression (24%), anxiety (23%), hypertension (13%), migraines (12%), smoking or history of smoking (10%), and obesity (9%).[3] Patients with a concerning prognostic profile were significantly more likely than those with a favorable prognostic profile to have comorbidities (82% vs 57%, respectively; $P < .05$), including a body mass index indicating overweight/obese, hypertension, and a history of smoking.[3]

Regarding therapeutic selection, patients with a concerning prognostic profile were significantly more likely than those with a favorable prognostic profile to be recommended treatment with ocrelizumab (33% vs 8%, respectively; $P < .05$) or natalizumab (10% vs 3%, respectively; $P < .05$).[3] Among patients with PPMS, ocrelizumab was recommended significantly more often to patients with a concerning versus a favorable prognostic profile (48% vs 26%, respectively; $P < .05$).[3] Among patients with specific comorbidities, overweight/obese patients were less likely to be recommended an interferon beta agent. In addition, patients with hypertension were significantly less likely to be recommended treatment with an oral DMT (26% vs 38%, respectively; $P < .05$) and significantly more likely to be recommended treatment with a monoclonal antibody DMT (34% vs 18%; $P < .05$).[3] Despite the impact of obesity and hypertension on DMT recommendation, the study findings showed that smoking had no influence on treatment recommendation.[3]

> "Patients don't go on these drugs and feel better, necessarily, and they don't expect to improve. Our goal with DMTs is to stop something that hasn't ocurred yet."
>
> —Patricia K. Coyle, MD

These observational findings underscore the need to increase awareness regarding the importance of comorbid conditions in MS, according to lead author Patricia K. Coyle, MD, professor and interim chair of Neurology at Stony Brook University in Stony Brook, New York. In an interview with *The American*

Journal of Managed Care®, Coyle observed that "comorbidities do play a role in DMT selection." Specifically, she explained, "if a comorbid condition is going to be potentially worsened by a DMT, or if adverse events are more likely in patients with certain comorbidities, physicians would correctly avoid that agent." Thus, comorbidities should be recognized as important in MS, not only for identifying and optimally managing these patients but also for influencing treatment selection.

The Importance of Shared Decision Making

Among the notable findings from this study is the acceptance rate by patients of recommendations from clinicians. The investigators noted that top recommended DMTs were communicated to 93% of patients and that 78% of patients accepted those recommendations, suggesting that roughly 1 of 5 patients may want to pursue therapeutic paths other than their recommended regimen.[3] One of the challenges associated with recommending DMTs for the treatment of MS is that they are "invisible therapies," Coyle noted. "Patients don't go on these drugs and feel better, necessarily, and they don't expect to improve. Our goal with DMTs is to stop something that hasn't occurred yet," which includes a relapse that can cause significant disability. "There is no biomarker that tells us the ideal treatment for each patient," said Coyle. Thus, several factors beyond DMT mechanisms of action and prognostic profile should enter into the treatment selection process, according to Coyle. "In addition to DMT drug factors and disease activity, we should be considering patient factors, such as tolerability, risk tolerance, and preferences," she observed. "Ideally, patients are coming to physicians for their expertise and want meaningful recommendations. We need to partner with the patient and elicit important requirements when discussing and recommending drugs. Patients generally follow that but not always. We are presenting our best opinion, but this is really shared decision making. The patient has to be a partner," Coyle said.

The association among comorbidities, prognostic profile, and MS subtype has important implications for DMT selection. Given the availability of multiple DMTs for patients with MS, Coyle noted that the shared decision making between the patient and the physician, accounting for the range of disease-, drug-, and patient-related factors, should be the guiding principle in securing third-party approval for treatment. "If a physician and patient decide that a particular agent is the best one for that patient, in my opinion, it should be funded," Coyle said. Moreover, she observed, "if physicians can make a rational, cogent case for why a particular agent is in the best interest of the patient, as opposed to other DMTs, it should be reimbursed." ●

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Age is Linked With Disability Risk in Patients With Multiple Sclerosis

Patients older than 40 years with multiple sclerosis (MS) who start disease-modifying therapy (DMT) appear to have a higher risk of disability progression versus younger patients, according to new findings.[1] Viktor von Wyl, PhD, of the University of Zurich, and other investigators used age at start of DMT, not age at symptom onset, because the time between symptom onset and start of DMT can span several years.[1]

The Impact of Age on MS

The research objectives of the study encompassed 2 primary areas. The first was to determine whether patient age at the start of DMT affects the time to first relapse and the time to the first Expanded Disability Status Scale (EDSS) progression.[1] Data were controlled for gender, age of DMT start, type of DMT, pre-DMT relapses, time since first MS symptoms, and MS Severity Score.[1] The second objective addressed whether the age-dependent risk score differed by DMT type.[1] DMT types included platform agents (eg, interferon beta, glatiramer acetate) and higher-efficacy agents (eg, fingolimod, teriflunomide, dimethyl fumarate, natalizumab).[1]

Investigators analyzed data from 9705 patients who received a diagnosis of relapsing-remitting MS between 1995 and 2017, with at least 2 years of follow-up and no gaps in treatment.[1] Complete data regarding EDSS and documentation of relapses, including 2 years prior to DMT, were required.[1]

Patients' mean age at first symptom onset was 32 years, and their mean age at DMT onset was 37 years.[1] Of the 3522 relapses included in the study, the MS relapse rate was higher at earlier ages and decreased with aging, with a plateau noted between 40 and 42 years.[1]

Additionally, the age at DMT start for first confirmed disability progression peaked at approximately 38 years, then remained stable.[1] Disability progression was defined as a 1.0-score increase since DMT start, confirmed in the

following visit (1.5-score increase if pretreatment EDSS was 0, or 0.5-score increase if pretreatment EDSS was 5.5).[1] Disability progression did not appear to differ by DMT type,[1] with no measurable difference between platform DMT and higher-efficacy DMT in this study.[1]

According to von Wyl, "The most relevant question from a clinical standpoint is, 'Can we shift the high-risk phase toward later ages with more efficacious drugs?'" He recommended collaboration and additional studies to this end.[1] He further explained that age at start of DMT is an important factor that affects relapse and confirmed disability progression.[1] The age at the start of DMT is independent of other disease characteristics and is possibly also independent of DMT.[1] Study findings also indicate that the age at first symptom onset and MS duration are relevant and correlate with initiating DMT.[1]

Conclusions

The investigators concluded that in patients aged between 37 and 40 years, the weakened central nervous system is no longer able to compensate for the damage caused by MS.[1] Also, patients 40 years and older starting DMT have a higher risk of disability progression.[1] "It's not to say that DMTs are ineffective, but the risk for the first event drastically increases," noted von Wyl. Initiating DMT early after symptom onset and noting the age-related risks in the population with MS can guide care and future research, von Wyl suggested. ●

> "The age at the start of DMT is independent of other disease characteristics and is possibly also independent of DMT. Study findings also indicate that the age at first symptom onset and MS duration are relevant and correlate with initiating DMT."

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Ocrelizumab Reduces Disability Progression in Primary Progressive Multiple Sclerosis

New long-term open-label extension data presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Stockholm, Sweden, suggest that ocrelizumab reduces disability progression in the long term for patients with primary progressive multiple sclerosis (PPMS). Jerry S. Wolinsky, MD, Bartels Family and Opal C. Rankin professor of neurology at the University of Texas Health Science Center in Houston, presented results of the open-label extension period of the phase 3 ORATORIO trial (NCT01194570), which assessed the efficacy and safety of ocrelizumab in PPMS.[1] Ocrelizumab is a humanized monoclonal antibody that targets and selectively depletes CD20-positive B cells. It is the only drug on the market approved for both relapsing-remitting and primary progressive disease.

Study Details

The ORATORIO study was a phase 3, randomized, parallel-group, double-blind, placebo-controlled trial, and the results of the study demonstrated the efficacy and safety of ocrelizumab in the disability progression of PPMS compared with placebo. The ORATORIO trial consisted of 3 treatment periods: the double-blind period, the extended controlled period, and the open-label extension phase.

For 24 weeks, trial investigators assessed the efficacy of ocrelizumab on measures of disability progression confirmed at 24 weeks in patients switching to or maintaining ocrelizumab therapy in the open-label extension phase of ORATORIO. In his presentation, Wolinsky noted that "[this] allows us to look for the 6.5 years of follow-up." To measure the time to the onset of 24-week confirmed disability progression (CDP) from baseline that is sustained for at least 24 weeks, multiple efficacy assessments needed to be met. These included the following:

- CDP–Expanded Disability Status Scale (EDSS), defined as an increase in the EDSS score from the baseline of the double-blind period of at least 1.0 point (increase of at least 0.5 point if baseline EDSS score >5.5)
- CDP–9-Hole Peg Test (9HPT), defined as at least a 20% increase in timed 9HPT from baseline
- CDP–Timed 25-Foot Walk (T25FW), defined as at least a 20% increase in T25FW from baseline

- Composite CDP, defined as the time to first onset of either CDP or at least a 20% increase in T25FW or 9HPT
- Time to wheelchair analysis (confirmed EDSS at least 7.0 for at least 24 weeks)

Investigators also measured statistical analysis; CDP at 24 weeks was assessed using Kaplan-Meier and Cox survival analysis in the intent-to-treat population, and hazard ratios were estimated by a stratified Cox regression.

In the double-blind portion of the study, which randomized 732 patients 2:1 to either ocrelizumab or placebo, ocrelizumab was associated with lower rates of clinical and magnetic resonance imaging progression compared with placebo. The patients were followed for 120 weeks or longer until a prespecified number of CDP events occurred. At the end of the double-blind portion of the study, patients remained on blinded treatment until the trial outcome was reached; this was the extended controlled period.

> "This is the first study to share positive results in any controlled trial of PPMS, let alone durability of those results for up to 6.5 years. It will be some time before these results can be challenged."
>
> —Jerry S. Wolinsky, MD

"This study had an adaptive design, in that it was to run until we had projected that there would be enough events of progression that was confirmed for 12 weeks, and at that time, the study data would be closed. The patients would continue in a controlled portion of the trial until the data [were] analyzed," Wolinsky said of ORATORIO. "Once we understood whether or not we had a successful study, all patients would be offered to continue on ocrelizumab [wh had been initially randomized to it or to be switched from placebo to active therapy." During the open-label extension phase, patients who received ocrelizumab in the double-blind period continued with ocrelizumab (OCR/OCR) treatment, and patients from the placebo group were switched to ocrelizumab (PBO/OCR). In fact, 95% of patients who completed the double-blind period entered the open-label extension phase. "In many ways, this could be seen as a delayed-start trial," said Wolinsky.

The last patient entered the extension phase by week 240. All patients had approximately 3 years of open-label extension phase follow-up; up to week 312, investigators analyzed time to onset of 12- and 24-week CDP (increase from baseline EDSS score of ≥1 point if baseline EDSS ≤5.5 or ≥0.5 point if baseline EDSS >5.5) and time to 24-week CDP on the 9HPT (CDP-9HPT; ≥20% increase from baseline in the timed 9HPT).

In the open-label extension phase, some patients withdrew from treatment. In the OCR/OCR group (n = 367), reasons for withdrawal included discontinuation (n = 54), adverse event (n = 7), death (n = 6), lack of efficacy (n = 4), lost to follow-up (n = 3), other (n = 14), physician decision (n = 4), and patient withdrawal (n = 16). In the PBO/OCR group (n = 160), reasons included discontinuation (n = 22), adverse event (n = 3), death (n = 2), lack of efficacy (n = 4), protocol violation (n = 1), other (n = 3), physician decision (n = 1), and patient withdrawal (n = 9).

Findings and Implications

Overall, 72% of patients entered the open-label extension phase. In the double-blind period, OCR reduced the risk of 24-week CDP by 25% ($P = .037$) and 24-week CDP-9HPT by 45% ($P < .001$) compared with placebo. Twelve weeks after the first patients entered the open-label extension phase (week 168), the percentage of patients with 24-week CDP-EDSS in the PBO/OCR and OCR/OCR groups was 44.7% versus 33.3% ($P = .005$), respectively. At week 192, the percentage was 49.3% versus 37.8% ($P = .006$), respectively; at week 264, 58.7% versus 48.0% ($P = .011$); and week 312, 64.8% versus 51.7% ($P = .002$). At week 168, the proportion of patients with 24-week CDP-9HPT in the PBO/OCR group was 29.7% and 17.9% in the OCR/OCR group ($P = .001$). At weeks 192, 264 and 312, the percentages were as follows: 32.5% versus 21.6% ($P = .005$), 39.4% versus 26.9% ($P = .003$), and 43.1% versus 30.6% ($P = .004$), respectively. The safety profiles of the open-label extension and the double-blind period were generally consistent.

After 312 weeks of follow-up, disability progression outcomes favored early treatment with ocrelizumab compared with delayed initiation. Moreover, the risk of becoming wheelchair confined was significantly reduced (42%) for those who began earlier initiation of ocrelizumab versus those who switched from placebo to ocrelizumab. "This is the first study to share positive results in any controlled trial of PPMS, let alone durability of those results for up to 6.5 years," Wolinsky said. "It will be some time before these results can be challenged." ●

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New EXPAND Trial Analyses Show Positive Effects of Siponimod on Disability, Brain Volume, and Disease Progression

The EXPAND trial was a randomized, double-blind, placebo-controlled study that investigated the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis (SPMS).[1] Siponimod, the only oral disease-modifying therapy approved in the past 15 years, selectively modulates the sphingosine 1-phospate (S1P) receptors S1P1 and S1P5, which are expressed on peripheral lymphocytes and within the central nervous system on neurons and glial cells.[1] With a total of 1645 patients, EXPAND was conducted across 292 hospital clinics and MS centers in 31 countries.[1] Results published in the *Lancet* in 2018 showed that siponimod reduced disability progression and had a similar safety profile to that of other S1P modulators.[1]

Several new data analyses from the EXPAND trial were presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, exploring the effect of siponimod on brain volume loss, progressive disability, and cognitive decline in patients with SPMS.[2-5] This article reviews key findings from these analyses.

Effect on Disability

Gary Cutter, PhD, professor of biostatistics at the School of Public Health at the University of Alabama in Birmingham, shared results showing that treatment with siponimod improved Expanded Disability Status Scale (EDSS) and other subscales in patients with SPMS.[2] Researchers evaluated the effects of siponimod on the Motor Integration subscale, encompassing ambulation, cerebellar (ataxia, balance, coordination, or tremor), and pyramidal measure (muscle weakness or difficulty moving limbs); and the Collateral subscale, measuring bowel/bladder function, brainstem function (dysphasia, dysphagia, nystagmus), and cerebral components (memory and brain processing).[2]

Data were analyzed in patients with SPMS with or without relapses in 24 months before enrollment, and in patients with or without gadolinium-enhancing (Gd+) lesions at baseline.[2] EDSS data from 1645 patients (siponimod, 1099; placebo, 546) were allocated to Motor Integration (55.2%) and Collateral (44.8%) subscales.[2] Siponimod efficacy was shown in EDSS ($P = .02$), Motor Integration ($P = .014$), and Collateral ($P = .021$) scores in the overall population.[2] Marked improvement in EDSS and Motor Integration scores were observed at months 9, 15, and 18, while Collateral disability changes were noted later, at 18 and 27 months.[2]

Subgroup evaluation revealed improved Motor Integration subscale scores in relapsing patients and those with Gd+ lesions versus those with stable disease at baseline.[2] Marked effects on the Motor Integration subscale occurred at months 9 ($P < .01$) and 18 ($P < .05$) for relapsing patients, at month 12 ($P < .05$) for those with Gd+ lesions, and at months 9 ($P < .05$), 15 ($P < .05$), and 18 ($P < .05$) for those with no Gd+ lesions at baseline.[2]

The authors concluded that siponimod is efficacious, according to EDSS data and Motor Integration and Collateral disability subscales.[2] Whereas positive patient effects were evident earlier on the Motor Integration subscale in patients experiencing relapse and with Gd+ lesions, Collateral disability scores improved later in these groups.[2]

Effect on Brain Volume

Siponimod may also lower total brain volume loss, reduce progressive disability, and slow cognitive decline in patients with SPMS, according to results from another EXPAND poster.[3] Douglas L. Arnold, MD, of NeuroRx Research in Montreal, Quebec, Canada, presented data evaluating the comparative effects of siponimod versus placebo on cortical gray matter (cGM) and thalamic volume loss in patients with SPMS participating in the EXPAND trial.[3] Notably, cGM atrophy has been associated with progressive disability and cognitive decline in patients with MS.[3]

Data from 583 patients who had high-resolution T1-weighted magnetic resonance imaging (MRI) scans and 1062 patients who underwent standard-resolution MRI (post hoc analysis) were combined.[3] A total of 1645 intention-to-treat patients were included in the analysis, including those who received at least 1 dose of siponimod (full analysis set [FAS]) and a 1560 per-protocol patient set (PPS; which excluded patients with major protocol deviations and efficacy data after drug continuation).[3] The pooled study population (FAS/PPS) consisted of 1315/1029 patients for analysis of cGM volume, 1329/1038 patients analyzed for thalamic volume, and 1333/1036 patients analyzed for total brain volume.[3]

Changes in cGM and thalamic volume were analyzed using a mixed model for related measures adjusted for baseline volume.[3] Then cGM and thalamic adjusted mean volume percentages were reported at months 12 and 24.[3]

Siponimod significantly slowed cGM, thalamic, and total brain atrophy progression compared with placebo.[3] The cGM volume reports showed an 88% reduction versus placebo ($P < .0001$) at month 12 and a 43% reduction versus placebo ($P < .0001$) at month 24 in the pooled FAS population.[3] Similarly, in the pooled PPS population, there was significant cGM volume reduction of 102% versus placebo ($P < .001$) and 63% versus placebo at months 12 and 24, respectively.[3]

Siponimod also slowed thalamic atrophy progression versus placebo.[3] In the pooled FAS data set, there was a 47% thalamic

volume reduction (P <.0001) and a 31% reduction (P = .0001) at months 12 and 24, respectively.[3] The pooled PPS population showed a 50% and 42% reduction (P <.0001 for both) in thalamic volume loss versus placebo at months 12 and 24, respectively.[3]

Finally, siponimod also slowed progression of total brain atrophy versus placebo.[3] In the pooled FAS population, researchers noted a 40% reduction in total brain atrophy versus placebo (P <.0001) at month 12 and a 17% reduction versus placebo (P = .0562) at week 24.[3] In the pooled PPS data set, researchers noted a 49% reduction versus placebo in total brain atrophy at month 12 and a 31% reduction versus placebo at month 24 (P <.0001 for both).[3]

The authors concluded that siponimod significantly reduced cGM and thalamic volume loss and therefore positively affects neuroaxonal damage in patients with SPMS.[3] MRI data verified biologic changes to support the marked cognitive and disability improvements in those taking siponimod, indicating the value of siponimod treatment in patients with SPMS.[3]

Gray Matter Atrophy, Disability, and Cognition

A second poster presented by Arnold examined how cGM and thalamic atrophy contribute to long-term disability and cognitive impairment in patients with MS.[4] Investigators explored the predictive qualities of baseline cGM, thalamic, and normalized brain volumes in patients with SPMS who were part of the core EXPAND analysis who received at least 1 dose of siponimod (n = 1645). They evaluated disability progression using EDSS scores and cognitive processing speed using the symbol digit modality test (SDMT).[4] Participants were separated into 4 quartiles (Q1-Q4) based on cGM, thalamic volume, and normalized measures of brain volume (NBV): Q1 (worst; lowest NBV), Q2 (Q1 to <median), Q3 (median to <Q3) and Q4 (best; highest NBV).[4] The predictive values of baseline cGM, thalamic, and NBVs were assessed for time to 6-month confirmed disability progression (6m-CDP) on the EDSS and 6-month confirmed worsening on the SDMT.[4]

Findings showed that patients in Q1 (vs Q4) of cGM had a higher risk for both 6m-CDP (hazard ratio [HR], 1.52; P = .0210) and SDMT worsening (HR, 1.63; P = .0165), respectively. SDMT scores declined (–1.75 vs 1.52; P = .0002) at month 24.[4] Patients with thalamic volume and NBV in the lowest quartile had lower SDMT scores (–2.65 vs 2.16; –1.81 vs 1.07, respectively; both P <.001). Patients with Q1 thalamic volume had twice the risk of SDMT worsening compared with Q4 (1.94; P = .0036) and Q1 NBV patients were also likely to have SDMT worsening compared with Q4 (1.62; P = .0132).[4]

This analysis revealed that cGM atrophy was predictive of both 6m-CDP and SDMT worsening, while thalamic volume and NBV predicted declines in cognitive processing speed.[4] The researchers concluded that for patients with SPMS, GM atrophy measures have predictive relevance for physical and cognitive disability.[4]

Effect on Disability Progression

Another poster presentation based on results of EXPAND evaluated the efficacy of siponimod in CDP in a subgroup of patients with active SPMS.[5] Investigators conducted post hoc subgroup analyses that included patients with active SPMS and/or more than 1 T1 Gd+ lesion at baseline.[5]

Clinical outcome measures included the following: time to 3-month CDP, as measured by EDSS; time to 6m-CDP, as measured by EDS; annualized relapse rate; time to 3-month confirmed 20% worsening in Timed 25 foot walk test; and time to 6-month confirmed 4-point worsening in the SDMT.[4] MRI outcomes included the number of T1 Gd+/new enlarging T2 lesions and change from baseline in T2 lesion volume (T2LV) and in percent brain volume change (PBVC).[5]

> “Although patients in the core EXPAND study showed improvement on disability progression, cognitive speed, and disease activity on MRI, a more pronounced effect was observed in this subgroup of patients with active SPMS.”

The analysis included 779 patients with active SPMS (siponimod [n = 516], placebo [n = 263]). Approximately 76% of patients had experienced relapse in the 2 years prior to the study and 45% had Gd+ lesions on MRI at baseline.[5] Data analysis revealed that siponimod reduced 3-month CDP risk by 31% and 6-month CDP risk by 37% versus placebo.[4] Additionally, the risk of 6-month SDMT worsening was reduced by 27%, and annualized relapse rate was reduced by 46% versus placebo.[5]

On MRI, the numbers of T1 Gd+ lesions and new/enlarging T2 lesions decreased significantly (85% [P <.0001] and 80% [P <.0001], respectively) compared with placebo.[5] Finally, the adjusted mean difference in T2LV over months 12 and 24 (siponimod vs placebo) was –1161.5 mm^3 (P <.0001) and 0.128 (P = .1153), respectively, for PBVC.[5]

Although patients in the core EXPAND study showed improvement on disability progression, cognitive speed, and disease activity on MRI, a more pronounced effect was observed in this subgroup of patients with active SPMS.[5] The investigators concluded that siponimod significantly reduced cGM, thalamic, and total brain atrophy in patients with active SPMS.[5]

Conclusions

These analyses provide support findings from the EXPAND trial regarding the efficacy of siponimod in patients with SPMS. For

a population with few treatment choices, these data show that siponimod may lower brain volume loss and reduce cognitive decline and physical disability. ●

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Preliminary Findings from a North American Multiple Sclerosis Registry Show the Economic Impact on Patients

New data show that the debilitating effects of multiple sclerosis (MS) have a significant impact on patients' quality of life, not only on physical ability but on economics as well. At the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Yang Mao-Draayer, MD, PhD, clinical professor of neurology at the University of Michigan, Ann Arbor, presented preliminary findings from the North American Registry for Care and Research in Multiple Sclerosis (NARCRMS).[1]

> "Of the 92% of individuals who were scheduled to work during the week prior to reporting, 14% missed work because of MS and 34% reported that MS affected their work output. When asked if patients were underemployed and unemployed because of MS, 137 of participants responded yes."

NARCRMS is the first physician-based database to link MS centers in the United States and Canada, gathering information on the impact of healthcare economics on the daily lives of patients with MS, in addition to clinical and imaging data. The goal of the economic impact analysis is to allow for resource allocation to patients, providers, payers, and society, to care for patients with MS. There are 22 enrollment sites for NARCRMS, with a plan to recruit several additional centers, for a total of 25 to 30 sites.

Registry Details

Participants completed 2 questionnaires, in addition to existent case report forms (CRFs). The Health-Related Productivity Questionnaire evaluated employment status (part time vs full time), household chores, and insurance changes. The Health Resource Utilization Questionnaire evaluated living situation; disability income; number of healthcare providers/visits; and use of aids, home care, and other variables in the prior 3 months. Questionnaires were incorporated into CRFs and completed at enrollment, as well as during annual and exacerbation visits.

Preliminary Findings

Enrollment and Demographic Data

Of the 535 patients, 517 participants completed the health economics and outcomes research (HEOR) CRFs, which comprised 126 men, 383 women, 2 transgender men, and 6 individuals with no information. The median age at diagnosis was 33 years, and the median Extended Disability Status Scale (EDSS) score at enrollment was 1.5. "The EDSS is very mild because the enrollment criteria are CIS [clinically isolated syndrome] and RMS [relapsing MS] at age 18 to 65, so you can see the spectrum," Mao-Draayer said in her presentation. One of the limitations of the analysis, said Mao-Draayer, is that the population does not include patients in the later stages of MS. "This is meant to follow them for 10 years longitude, to look at other outcomes," she noted.

Employment Data

Overall, 61% of patients reported being employed full-time, whereas 11% reported working part-time, 24% were unemployed,

3% did not specify full-time or part-time employment, and 1% provided no information. "Since the EDSS is mild at 1.5, the employment rate status is pretty striking," Mao-Draayer said.

Of the 92% of individuals who were scheduled to work during the week prior to reporting, 14% missed work because of MS and 34% reported that MS affected their work output. When asked if patients were underemployed and unemployed because of MS, 137 of participants responded yes. The most commonly reported symptoms that affected work included fatigue (n = 75), weakness (n = 17), and pain (n = 15). Patients reported an average of 7.5 hours of work missed due to MS or treatment for MS in the week prior to reporting.

Household Chores Data

When asked about their ability to complete household chores, 86% of patients planned to complete household chores in the week prior to reporting, but 65% missed household chores because of MS or treatment for MS. Overall, 45% of patients reported that MS affected their ability to complete household chores. The most commonly reported symptoms that affected their ability to perform household chores were fatigue (n = 160), weakness (n = 32), and pain (n = 20).

Healthcare Resource Utilization

Investigators looked at specialty healthcare visits among patients within the 3 months prior to reporting. A total of 546 visits to a neurologist were reported, which was the most common of the unique healthcare providers with whom the patients consulted. Other common visits included those to psychiatrists (n = 250), massage therapists (n = 176), general practitioners (n = 148), and psychologists (n = 86). NARCRMS also analyzed the number of hospital visits per patient population, with findings showing 45 emergency department visits, 15 inpatient hospitalizations, and 2 rehabilitation center admissions. Those who required inpatient hospitalization recorded an average 4.2 days of hospital stays.

Key Takeaways

In summary, 74.6% of the initial 517 patients who completed HEOR CRFs and are enrolled in NARCRMS are employed, whereas 26.5% reported underemployment or unemployment because of MS. Mao-Draayer concluded her presentation by noting that MS prevents patients from completing necessary at-home tasks and from working at their full potential, which, she emphasized, can be attributed primarily to fatigue. ●

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Astrocyte Research Unlocks Genetic Code to Siponimod Efficacy in Secondary Progressive Multiple Sclerosis

The recent identification of secondary progressive multiple sclerosis (SPMS) gene expression in astrocytes helps to explain differences in MS clinical outcomes, pharmacological activity, and astrocyte modulation between 2 sphingosine-1-phosphate receptor (S1P) inhibitors: fingolimod and siponimod.[1] Although it was previously unclear how the biochemistry of S1P inhibitors affects patients with relapsing-remitting MS (RRMS) versus SPMS, single-nucleus transcriptomics have revealed genetic alterations in astrocytes critical to the pharmacotherapeutics of fingolimod and siponimod.[2] Changes in gene regulation and expression in astrocytes resulting from specific S1P inhibitors support biochemical specialization with these agents.[2] New research presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis explores the differential central nervous system (CNS) effects of siponimod versus fingolimod and suggests possible directions for future scientific inquiries into S1P inhibition.[1]

Siponimod Versus Fingolimod and the Role of Astrocytes

Siponimod selectively modulates the S1P1 and S1P5 receptors expressed on peripheral lymphocytes and within the CNS on neurons and glial cells.[2] Fingolimod, a nonspecific S1P receptor antagonist, reduces relapse occurrence in RRMS, does not reduce brain volume loss, and has shown no efficacy in progressive forms of MS.[3] In clinical outcomes, siponimod is efficacious in SPMS, whereas fingolimod is ineffective in progressive forms of MS.[1] Siponimod has been found to decrease brain atrophy and slow disability in progressive MS.[3] Fingolimod reduced relapse rate in patients with RRMS but had no effects on brain atrophy or disability.[3]

Although both fingolimod and siponimod antagonize astrocyte S1P receptors, there are pharmacological distinctions. It is now known that siponimod selectively binds to both S1P1 and S1P5 astrocyte receptors.[1] In contrast, fingolimod requires phosphorylation (fingolimod-P) to have nonselective affinity to S1P1 and S1P5 astrocyte receptors.[1]

Astrocytes were once thought to contribute only to glial scarring later in the MS process, but now astrocytes are known to be essential to the development of lesions and progression of MS through proinflammatory mechanisms.[3] Reactive astrocytes, present on the periphery of demyelinating lesions, extend into normal-appearing white matter.[3] The reactive astrocytes release cytokines and other proinflammatory substances, activating inflammation.[3] This mechanism may cause MS lesions and volume loss.[3]

“Astrocytes were once thought to contribute only to glial scarring later in the MS process, but now astrocytes are known to be essential to the development of lesions and progression of MS through proinflammatory mechanisms.”

Single-Cell Nuclear Transcriptome Analysis

Investigators exposed human astrocytes to siponimod, fingolimod-P, or vehicle, revealing 9 distinct cell clusters.[1] Within these cell clusters, siponimod caused up- or downregulation of 56 genes, the majority of the mutations occurring in a specific cluster (cluster 8).[1] By contrast, fingolimod-P affected approximately 450 genes across 7 clusters, with a nonspecific and general response.[1] Thus, siponimod may modulate a subset of astrocytes that fingolimod-P does not, possibly explaining clinical outcome differences between the 2 agents.[1]

Sphingosine kinase gene expression (SPHK-1/2), responsible for the production of S1P, is dysregulated in MS.[1] Kihara and colleagues relayed findings of reduced SPHK1/2 expression in cells from patients with RRMS versus SPMS.[1] Although further research is warranted, this finding might explain the lack of efficacy of fingolimod in progressive forms of MS.[1]

Kihara and colleagues also effectively demonstrated the differential CNS effects of siponimod versus fingolimod in patients with MS.[1] The impact of inflammatory astrocytes in MS lesion proliferation is observed through the response in RRMS and SPMS to fingolimod and siponimod, respectively.[1] The specialization of siponimod to S1P1 and S1P5 receptors, as well as the generalization of fingolimod to S1P receptors, adds to the understanding of the role of astrocyte gene expression and its sequelae in MS.[1] According to the investigators, continued research into the pharmacological understanding of MS treatments will enhance disease understanding and future treatment, especially in progressive MS, for which there are limited pharmaceutical treatment options. ●

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Evidence Supports Safety and Efficacy of Cladribine

New studies aim to bolster support for the use of cladribine,[1,2] an oral disease-modifying therapy (DMT), for the treatment of multiple sclerosis (MS). Approved by the FDA in March 2019, cladribine is a deoxyadenosine analogue that selectively impairs DNA synthesis of T and B lymphocytes, depleting lymphocytes and essentially reprogramming the immune system.[1] Controversy surrounding cladribine's safety and efficacy is rooted in adverse events (AEs) reported from the double-blind, placebo-controlled CLARITY trial, originally reported in 2010, which overshadowed robust clinical benefits and delayed approval for almost a decade.[3] Ongoing analyses of subgroup safety and efficacy of CLARITY and patient treatment satisfaction and quality of life (QOL) measures presented at the 35th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS) in Stockholm, Sweden, support the use of cladribine in patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).[1]

New CLARITY Analyses

In the CLARITY trial, cladribine was administered in a 3.5 mg/kg oral dose over 2 years.[1] The study included patients previously treated with 0 to2 DMTs prior to the clinical trial.[1] After the 96-week trial period, participants showed reduced relapse rates, lower risk of disability progression, and less magnetic resonance imaging (MRI) evidence of disease.[1] AEs were similar to those of other DMTs, except for a small group of individuals who developed solid tumors, prompting the European Medicines Agency and the FDA to deny approval of the drug.[3] Approval was

given after a meta-analysis of trial data revealed no increased risk with cladribine versus other DMTs.[3]

At ECTRIMS 2019, investigators presented additional corroborating data regarding patient safety and efficacy in the CLARITY trial, as well as plans for reporting patients' perceived treatment satisfaction and QOL since cladribine approval.[1,2] Patrick Vermersch, MD, with the University of Lille, France, presented an analysis of efficacy, annualized relapse rate (ARR), and time to 3- and 6-month Expanded Disability Status Score (EDSS) progression.[1] Prior DMTs included interferon beta-1a, interferon beta-1b, glatiramer acetate, and natalizumab.[1] In this subgroup, 110 subjects were randomized to cladribine tables 3.5 mg/kg, and 132 were randomized to placebo.[1] Compared with patients receiving placebo, patients receiving cladribine tablets had reduced ARR (0.22 vs 0.42, $P < .005$), a higher relapse-free rate (70.4% vs 55.9%, $P = .0204$), a lower risk of 3- and 6-month confirmed disability progression (CDP) (HR, 0.64; $P = .1589$; and HR, 0.62; $P = .2071$, respectively), and reduced brain lesions on MRI ($P < .001$).[1] Results from this pretreated group of patients with RRMS showed similar efficacy to those of the full CLARITY population.[1]

CLEVER and CLADQoL

In addition to the new data based on the CLARITY trial, 2 noninterventional ongoing studies presented at ECTRIMS are evaluating treatment satisfaction (CLEVER) and QOL (CLADQoL) in patients with MS treated with cladribine.[2] During recruitment, investigators gathered safety data, citing sparse post-study safety data.[2] The primary goal of CLEVER is to evaluate treatment satisfaction over a 6-month period.[2] Recruitment for CLEVER began November 2017 and will end December 2019, with final reporting planned for December 2020.[2] In contrast, the objective of CLADQoL is to observe patient QOL over 24 months.[2] Recruitment began January 2018 and will end April 2020, with the final report planned for December 2024.[2] Investigatorsshared their current analysis of safety data for the 2 studies combined.[2] Of the 405 patients enrolled, 119 had AEs, including headache, fatigue, and alopecia.[2] Of these, 10 were serious AEs (SAEs): allergic dermatitis, general body pain, herpes zoster, and 1 anterior myocardial infarction (in a patient with preexisting conditions).[2] The investigators concluded that these AEs and SAEs are similar to those reported with initial CLARITY data, supporting the safety of cladribine.

Conclusions

Despite previous concerns regarding the approval of cladribine for the treatment of RRMS and SPMS, the latest findings suggest that cladribine is safe.[1,2] According to the investigators, cladribine is comparable to other DMT options, even in patients previously treated with DMTs.[1] The benefits of cladribine include the fact that it is an oral treatment, it can be given as pulse therapy over 2 years, and it has well-documented efficacy (decreased ARR, higher relapse-free rate, lower risk of 3- and 6-month CDP, and reduction in lesions on MRI). Future results from CLEVER and CLADQoL will provide more information on treatment satisfaction and patient-perceived QOL to guide future treatment strategies. ●

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Long-Term Data Offer Insights Into Benefits of Induction Therapy

Many disease-modifying therapies (DMTs) are available for the treatment of relapsing forms of multiple sclerosis (MS), yet the selection of an optimal treatment regimen can be difficult, given the lack of biomarkers for diagnosis. Alasdair Coles, of the University of Cambridge in England, discussed new long-term data that suggest induction therapy is the preferred mode of treatment over escalation therapy for relapsing forms of MS.

The Basics of Induction Therapy in MS

The concept of induction therapy originated in the 1950s and has been attempted in various disease states since then, according to Coles. It is a single treatment that leads to long-lasting immunologic tolerance and disease control, with a very limited duration of risk.

In MS, 3 therapies can be considered induction therapy: autologous hematopoietic stem cell therapy, alemtuzumab (approved by the FDA in 2014), and cladribine (approved by the FDA in 2019). Importantly, Coles noted that not all high-efficacy therapies are induction therapies. Although natalizumab and ocrelizumab can be considered high-efficacy therapies, because they are continuously delivered, they cannot be considered induction therapies.

Coles further observed that demonstrating immunological tolerance in the treatment of MS is not possible. "We do not know

what the pathogenic autoimmune process is; we have to infer the induction of tolerance by disease suppression," he observed.

Induction Therapy With Alemtuzumab

Coles presented findings from long-term studies that support the use of alemtuzumab as an induction therapy. As a matter of background, Coles shared several studies that have been designed to explore the potential benefits of the high-efficacy intervention approach. Two ongoing trials testing early high efficacy versus escalation approaches are the TREAT-MS trial[1] and the DELIVER-MS trial.[2] Coles pointed out that natalizumab and ocrelizumab were included in these trials as early and intensive therapies. Additionally, published findings show that early treatment with high-efficacy drugs slows the rate of secondary progression.[3]

> "I would argue that the goal of an induction therapy is the best goal in the treatment of MS. We are somewhere, but not a long way there, to achieving it."
>
> —Alasdair Coles

Coles also discussed new phase 2 findings presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in individuals (N = 60) who were treated with alemtuzumab as an induction therapy after 12 years of follow-up.[4] Patients had a mean age of 32 years and a median 1.3 years since onset. Patients were given 3 cycles of interferon beta therapy or 2 cycles of alemtuzumab. At 12 years, 33% of patients did not need further therapy, 38% needed an extra 3 days of additional therapy, and 29% needed more cycles of therapy. "[The data show] prolonged suppression of relapse activity and that 12 years after starting this induction therapy, [approximately] 70% of patients either have stable or improved disability compared to baseline," Coles said. This suggests prolonged suppression following induction therapy.

Nine-year follow up data from 2 phase 3 trials were also shared at the ECTRIMS meeting. In the phase 3 CARE-MS1 trial, investigators evaluated patients with untreated MS (N = 581) for less than 2 years who were given either 2 cycles of interferon beta therapy or alemtuzumab.[5] Patients had a median age of 33 years and a median 1.7 years since onset. The CARE-MS2 evaluated patients (N = 628) who had been on injectable DMTs and had disease activity breakthrough.[6] Patients had a mean age of 35 years and a median 4 years since onset. Patients who received interferon beta were automatically switched to 2 cycles of alemtuzumab, if they wished.

At 9 years' follow-up, in the CARE-MS1 alemtuzumab-only arm, 58% of patients did not need further therapy, 22% needed another 3 days of therapy, and 20% needed more than 1 cycle.[5] In CARE-MS2 alemtuzumab-only arm, 46% of patients needed no further therapy, 30% needed another 3 days of therapy, and 24% needed more than 1 cycle.[6]

"In terms of disability, these 9-year data tell us that if [treatment-naïve patients] started with alemtuzumab treatment very early on or [had] beta interferon and automatically switched, there is no difference in outcome. However, if you have a patient for 2 more years and give beta interferon, and they have disease breakthrough, and then put them on [interferon beta] for another 2 years, those patients, even though they are automatically switched to alemtuzumab 2 years later, never recover disability advantage," Coles noted. "That's a very extreme example of how early treatment in the treatment-experienced group is advantageous compared with most dramatic forms of escalation at 2 years on an automatic basis."

Regarding brain volume, Coles observed that treatment with interferon beta leads to greater brain volume loss than alemtuzumab in the first 2 years in treatment-naïve patients, but over 9 years, that difference no longer exists. "If you switch aggressively and early, you recover the loss from early interferon exposure. However, if you are 2 years older and have had exposure to interferon beta [therapy], you haven't recovered brain volume that has been lost," Coles said.

Regarding adverse events, Coles noted that at the time of treatment, there are serious risks from infusion reactions and infections for about a month associated with alemtuzumab. Then there is a window of risk of about 4 years [for] autoimmune disease after each cycle. Patients were advised not to become pregnant for 4 months after each cycle of therapy. "We do have, in the ideal scenario, the possibility that from years 5 to 10, you just have benefit of treatment, that is disease suppression and no longer any risks. You also have windows of opportunity where you have disease suppression and can get pregnant," said Coles. "Of course, if you need a further cycle of therapy, as in the case of about 50% of patients at 10 years, all of these risks recur and the window of disease suppression with no risk is reduced."

Implications and Future Directions

According to Coles, these data suggest that prolonged disease control can be achieved with induction therapy but only with repeated cycles. These prolonged windows of risk give limited periods when patients have control of their disease and are free of risk. Coles also suggested the possibility of improving the safety and efficacy profiles of induction therapies through combination regimens with lower-efficacy, lower-risk agents. Other strategies for optimal use of induction therapies may emerge, and it is important that the implications of treatment

are considered. "As we consider the consequences of these very powerful induction therapies, we have to recognize the ignorance of what we're doing and how we best manipulate it," Coles said. "I would argue that the goal of an induction therapy is the best goal in the treatment of MS. We are somewhere, but not a long way there, to achieving it." ●

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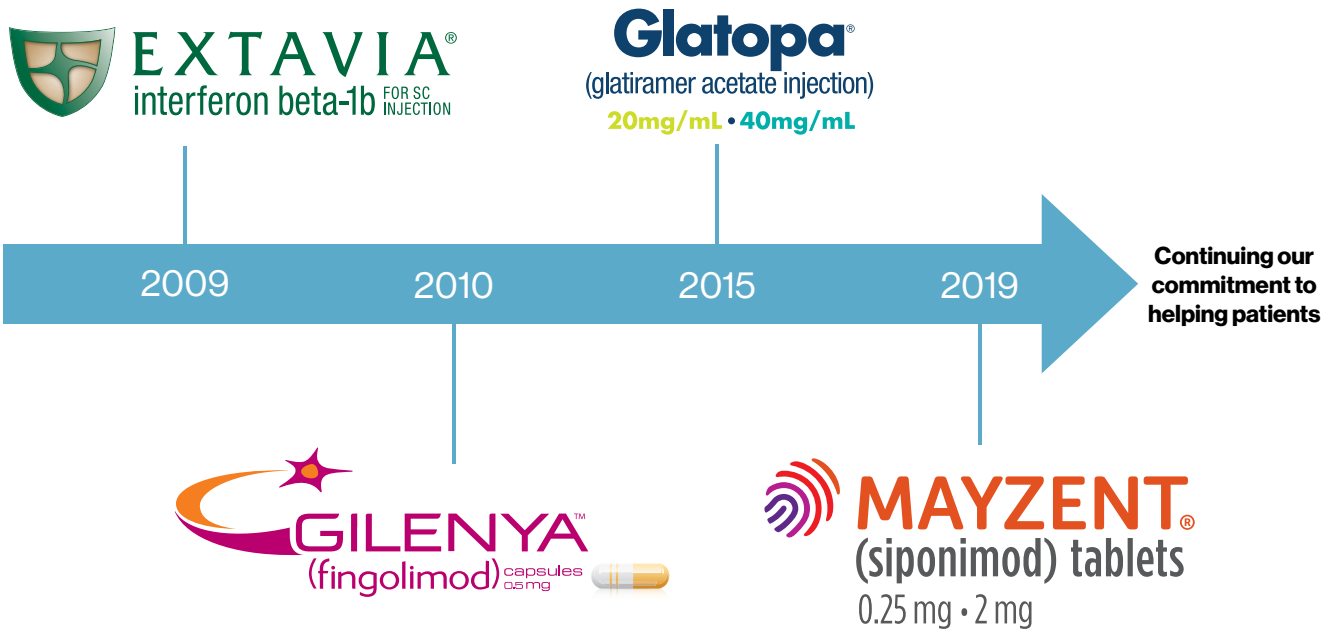

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