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AMERICAN ACADEMY OF NEUROLOGY®

Visit *AAN.com/Covid19* for the latest pandemic information and resources to support you and your crucial work.

CALL FOR ABSTRACTS: 2022 ANNUAL MEETING

AAN 2022 Annual Meeting

April 2–7 • Seattle
In-person and Virtual

Mark your calendar!

Abstract submission for the 2022 Annual Meeting—taking place both virtually and in-person in Seattle—opens in early September. Visit *AAN.com/22Abstracts* to learn more and submit your breakthrough research.

Abstracts will be accepted until October 11 in all subspecialties and career levels. The submission fee is $100 for AAN members and $200 for nonmembers. Submission is free for residents and medical students. For more information, contact Laura Southwick at *science@aan.com*. ■

Registration Open for Hybrid 2021 Fall Conference

The Fall Conference is returning this year—in person and virtual— and registration opens early August! The AAN is excited to welcome attendees to Chicago on November 5–7 where you can reconnect with colleagues and friends in a safe, in-person environment. We'll also have an online component to the conference to ensure convenient access to a broad range of members, given the popularity of virtual conferences over the past year. Stay tuned for more information about programming, registration, and more at *AAN.com/Fall*. ■

AAN FALL CONFERENCE
Chicago 2021

AAN Advocacy Pays Off!

CMS proposals to include:

- Updates to telehealth policies for coverage through 2023
- 1% increase depending on individual neurology practice
- More!

› *Read all about it on page 15*

Not representative of a patient.

INDICATION

KESIMPTA 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

Contraindication: KESIMPTA is contraindicated in patients with active hepatitis B virus infection.

WARNINGS AND PRECAUTIONS

Infections: An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections; some have been fatal in patients treated with other anti-CD20 antibodies. The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until resolved.

Consider the potential increased immunosuppressive effects when initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA.

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

Kesimpta® (ofatumumab) 20 mg injection

Make KESIMPTA your 1st choice for RMS

POWER

In two Phase 3 pivotal clinical trials vs teriflunomide, KESIMPTA demonstrated:

- Significant reduction in ARR of up to nearly 60% vs teriflunomide (*P*<0.001)[1,2*]
- Profound reduction in mean number of Gd+ T1 lesions per scan of up to 98% (*P*<0.001)[1†]
- Superior reduction in mean number of new or enlarging T2 lesions per year of up to 85% (*P*<0.001)[1†]
- Significant risk reduction in 3-month CDP of 34% (*P*=0.002) and 6-month CDP of 32% (*P*=0.01)[1,2†]

PRECISION

- A targeted and precisely delivered B-cell therapy[1,3‡]

Safety

- Favorable safety profile similar to teriflunomide as demonstrated in 2 pivotal trials[1]

FLEXIBILITY

- The first once-monthly (20 mg), SC, B-cell therapy administered at home or anywhere[1§‖]

Learn more at **KesimptaHCP.com**

Study Design: ASCLEPIOS I and II were 2 identical randomized, active-controlled, double-blind Phase 3 studies in patients with RMS, approximately 40% of whom were DMT treatment naïve. Patients were randomized to double-dummy subcutaneous KESIMPTA (20 mg every 4 weeks) or oral teriflunomide (14 mg daily) for up to 30 months. Primary endpoint was ARR. Key MRI endpoints were number of Gd+ T1 lesions, and annualized rate of new or enlarging T2 lesions. A key clinical endpoint was reduction in risk of 3-month CDP. Treatment duration was variable based on end of study criteria. Maximum duration 120 weeks, median duration 85 weeks.

ARR=annualized relapse rate; CDP=confirmed disability progression; DMT=disease-modifying therapy; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging; RMS=relapsing multiple sclerosis; SC=subcutaneous.

*Primary endpoint: relative reduction in adjusted ARR vs teriflunomide of 51% (0.11 vs 0.22) in ASCLEPIOS I and 59% (0.10 vs 0.25) in ASCLEPIOS II.

†Key clinical and MRI endpoints: reduction in mean number of Gd+ T1 lesions per scan vs teriflunomide of 98% (0.01 vs 0.45) in ASCLEPIOS I and 94% (0.03 vs 0.51) in ASCLEPIOS II; reductions in T2 lesions vs teriflunomide of 82% (0.72 vs 4.00) in ASCLEPIOS I and 85% (0.64 vs 4.15) in ASCLEPIOS II; reduced risk in 3-month CDP vs teriflunomide of 34% (15.0 vs 10.9) and 6-month CDP of 32% (8.1 vs 12.0) in pooled populations from both trials.

‡The precise mechanism by which KESIMPTA exerts its therapeutic effects is unknown.

§The initial dose period consists of 20 mg SC doses at Weeks 0, 1, and 2.

‖KESIMPTA Sensoready® Pens must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming, do not shake.

References: 1. Kesimpta [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020. **2.** Hauser SL, Bar-Or A, Cohen JA, et al; for the ASCLEPIOS I and ASCLEPIOS II trial groups. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med*. 2020;383(6):546-557. **3.** Huck C, Leppert D, Wegert V, et al. Low-dose subcutaneous anti-CD20 treatment depletes disease relevant B cell subsets and attenuates neuroinflammation. *J Neuroimmune Pharmacol*. 2019;14(4):709-719.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Hepatitis B Virus: *Reactivation:* No reports of hepatitis B virus (HBV) reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with ofatumumab at higher intravenous doses for chronic lymphocytic leukemia (CLL) than the recommended dose in MS and in patients treated with other anti-CD20 antibodies.

Infection: KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. Perform HBV screening in all patients before initiation of KESIMPTA. Patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], should consult liver disease experts before starting and during KESIMPTA treatment.

Progressive Multifocal Leukoencephalopathy: No cases of progressive multifocal leukoencephalopathy (PML) have been reported for KESIMPTA in RMS clinical studies; however, PML resulting in death has occurred in patients being treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. In addition, JC virus infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. If PML is suspected, withhold KESIMPTA and perform an appropriate diagnostic evaluation. If PML is confirmed, KESIMPTA should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to starting KESIMPTA for inactivated vaccines. The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy. For infants whose mother was treated with KESIMPTA during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines. If the B-cell count has not recovered in the infant, do not administer the vaccine as having depleted B-cells may pose an increased risk in these infants.

Injection-Related Reactions: Injection-related reactions with systemic symptoms occurred most commonly within 24 hours of the first injection, but were also observed with later injections. There were no life-threatening injection reactions in RMS clinical studies.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If injection-related reactions occur, symptomatic treatment is recommended.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Fetal Risk: Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose.

Most common adverse reactions (>10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions.

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

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

KESIMPTA® (ofatumumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

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

1 INDICATIONS AND USAGE

KESIMPTA 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

KESIMPTA is contraindicated in patients with:

- Active HBV infection *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies.

KESIMPTA has the potential for an increased risk of infections, including serious bacterial, fungal, and new or reactivated viral infections; some of these infections have been fatal in patients treated with other anti-CD20 antibodies. In Study 1 and Study 2 *[see Clinical Studies (14) in the full prescribing information]*, the overall rate of infections and serious infections in patients treated with KESIMPTA was similar to patients who were treated with teriflunomide (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in the randomized clinical relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until the infection is resolved.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2) in the full prescribing information]*. KESIMPTA has not been studied in combination with other MS therapies.

Hepatitis B Virus

Reactivation

There were no reports of HBV reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment) and in patients treated with other anti-CD20 antibodies.

Infection

KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients being treated with ofatumumab for CLL (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). HBV screening should be performed in all patients before initiation of treatment with KESIMPTA. At a minimum, screening should include Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with KESIMPTA. These patients should be monitored and managed following local medical standards to prevent HBV infection or reactivation.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

Although no cases of PML have been reported for KESIMPTA in the RMS clinical studies, PML resulting in death has occurred in patients being treated with ofatumumab for CLL (at substantially higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). In addition, JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. At the first sign or symptom suggestive of PML, withhold KESIMPTA and perform an appropriate diagnostic evaluation. Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms. 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.

If PML is confirmed, treatment with KESIMPTA should be discontinued.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of KESIMPTA for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines.

KESIMPTA may interfere with the effectiveness of inactivated vaccines.

The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy

In infants of mothers treated with KESIMPTA during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered, as indicated, prior to recovery from B-cell depletion, but an assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted.

5.2 Injection-Related Reactions

In Study 1 and Study 2, systemic and local injection reactions were reported in 21% and 11% of patients treated with KESIMPTA compared to 15% and 6% of patients treated with teriflunomide who received matching placebo injections, respectively *[see Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information]*.

Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection, but were also observed with later injections. Symptoms observed included fever, headache, myalgia, chills, and fatigue, and were predominantly (99.8%) mild to moderate in severity. There were no life-threatening injection reactions in RMS clinical studies.

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain.

Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical studies. The first injection of KESIMPTA should be performed under the guidance of an appropriately trained healthcare professional. If injection-related reactions occur, symptomatic treatment is recommended.

5.3 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 7.7% of patients treated with KESIMPTA compared to 3.1% of patients treated with teriflunomide in RMS clinical trials *[see Adverse Reactions (6.1)]*. Treatment was discontinued because of decreased immunoglobulins in 3.4% of patients treated with KESIMPTA and in 0.8% of patients treated with teriflunomide. No decline in immunoglobulin G (IgG) was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

5.4 Fetal Risk

Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA *in utero*. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Injection-Related Reactions *[see Warnings and Precautions (5.2)]*
- Reduction in Immunoglobulins *[see Warnings and Precautions (5.3)]*

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 clinical practice.

Approximately 1500 patients with RMS received KESIMPTA in clinical studies. In Study 1 and Study 2, 1882 patients with RMS were randomized, 946 of whom were treated with KESIMPTA for a median duration of 85 weeks; 33% of patients receiving KESIMPTA were treated for up to 120 weeks *[see Clinical Studies (14.1) in the full prescribing information]*. The most common adverse reactions occurring in greater than 10% of patients treated

with KESIMPTA and more frequently than in patients treated with teriflunomide were upper respiratory tract infections, injection-related reactions (systemic), headache, and injection-site reactions (local). The most common cause of discontinuation in patients treated with KESIMPTA was low immunoglobulin M (3.3%), defined in trial protocols as IgM at 10% below the lower limit of normal (LLN).

Table 1 summarizes the adverse drug reactions that occurred in Study 1 and Study 2.

Table 1: Adverse Reactions in Patients with RMS with an Incidence of at Least 5% with KESIMPTA and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

Adverse Reactions	KESIMPTA 20 mg N = 946 %	Teriflunomide 14 mg N = 936 %
Upper respiratory tract infections[a]	39	38
Injection-related reactions (systemic)	21	15
Headache	13	12
Injection-site reactions (local)	11	6
Urinary tract infection	10	8
Back pain	8	6
Blood immunoglobulin M decreased	6	2

[a]Includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.

Injection-Related Reactions and Injection-Site Reactions

The incidence of injection-related reactions (systemic) was highest with the first injection (14.4%), decreasing with subsequent injections (4.4% with second, less than 3% with third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) patients treated with KESIMPTA reported serious injection-related reactions. There were no life-threatening injection-related reactions. Most frequently reported symptoms (2% or greater) included fever, headache, myalgia, chills, and fatigue.

In addition to systemic injection-related reactions, local reactions at the administration site were very common. Local injection-site reactions were all mild to moderate in severity. The most frequently reported symptoms (2% or greater) included erythema, pain, itching, and swelling *[see Warnings and Precautions (5.2)]*.

Laboratory Abnormalities

Immunoglobulins

In Study 1 and Study 2, a decrease in the mean level of IgM was observed in KESIMPTA-treated patients but was not associated with an increased risk of infections *[see Warnings and Precautions (5.3)]*. In 14.3% of patients in Study 1 and Study 2, treatment with KESIMPTA resulted in a decrease in a serum IgM that reached a value below 0.34 g/dL. KESIMPTA was associated with a decrease of 4.3% in mean IgG levels after 48 weeks of treatment and an increase of 2.2% after 96 weeks.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ofatumumab products may be misleading.

Treatment induced anti-drug antibodies (ADAs) were detected in 2 of 914 (0.2%) KESIMPTA-treated patients; no patients with treatment enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient; however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of KESIMPTA.

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

Concomitant usage of KESIMPTA with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with KESIMPTA.

When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of potential additive immunosuppressive effects when initiating KESIMPTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies *(see Data)*.

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to ofatumumab *in utero*, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA *in utero* until B-cell recovery occurs *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2) in the full prescribing information]*.

Following administration of ofatumumab to pregnant monkeys, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans *(see Data)*.

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

Data

Animal Data

Intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestations days 20 to 50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was observed in fetuses at both doses when assessed on gestation day 100. Plasma exposure (C_{ave}) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (C_{ave}) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.

Intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys throughout pregnancy resulted in no adverse effects on the development of the offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the high dose. The deaths at the high dose were considered secondary to B-cell depletion. Plasma exposure (C_{ave}) in dams at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose.

8.2 Lactation

Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3) in the full prescribing information]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of KESIMPTA did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger subjects.

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
U.S. License No.: 1244

T2020-112

AMERICAN ACADEMY OF NEUROLOGY®

The Mission *of the AAN is to promote the highest quality patient-centered neurologic care and enhance member career satisfaction.*

The Vision *of the AAN is to be indispensable to our members.*

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August Highlights

14 AAN Publishes Position Statement on Ethics in Dementia Diagnosis and Care

"Ethical Considerations in Dementia Diagnosis and Care: AAN Position Statement" was published in the *Neurology*® journal online on July 12, 2021. The position statement, approved by the AAN/AANI Board of Directors in January 2021, was developed before FDA approval of the new medication aducanumab and does not address that drug.

27 Diversity Leadership Graduate Discovers Entrepreneurial Spirit, Opens New Headache Clinic

When headache medicine specialist Hope O'Brien, MD, MBA, FAHS, FAAN, entered the 2016 class of the AAN's Diversity Leadership Program, she already knew there was an unmet need in the management of patients with headache and had long envisioned opportunities to address those needs through a unique space that considers the equally unique aspects of headache and migraine.

28 Paper Examines Mentoring Women in Neurology

The research paper "Current Status and Future Strategies for Mentoring Women in Neurology" was published in the June 4, 2021, online issue of *Neurology.*

News Briefs

Aducanumab Resources

Following the FDA's June announcement of the approval of the Alzheimer's drug aducanumab, the AAN has begun to provide members with resources and education to know who should be receiving the drug, when to prescribe the drug, how to treat any side effects, and tools to help patients and families. Learn more at *AAN.com/aducanumab*. Under the direction of the AAN Aducanumab Workgroup, the AAN provided brief public comments at the July 15 Institute for Clinical and Economic Review public meeting. Congress has also announced an investigation of the drug's price, set at $56,000/year.

CEO Post Interviewed

AAN CEO Mary E. Post, MBA, CAE, was interviewed by Stacey Clardy, MD, PhD, FAAN, in a two-part series on the *Neurology*® Podcast at *Neurology.org/podcast*. Post discusses her background and experience, the challenges—and successes—experienced by the AAN and neurology due to the pandemic, and her determination to continue to deliver value to Academy members.

New NeuroSAE Available

The NeuroSAE 15th Edition self-assessment exam includes 100 questions to help physicians assess areas of strength and weakness and educational resources for self-education and improvement. Learn more at *Learning.AAN.com.* ■

In Memoriam

Join us in remembering members of the AAN and neurology community who have perished from COVID-19:

- Michael P. Krieger, MD, FAAN

Welcome Back

Avitzur

As this nation returned to pre-pandemic activities with cautious optimism this summer, so too has the American Academy of Neurology. While its mission has not changed—to promote the highest quality patient-centered neurologic care and enhance member career satisfaction—its methods of delivering value to members have been revitalized to keep pace with the insights borne of COVID-19. As Winston Churchill famously said as he was working to form the United Nations after WWII, "Never let a good crisis go to waste." Your organization has taken that sentiment to heart, and as a result, what you will experience in the upcoming year will be an AAN which is more sophisticated technologically, more mindful to your needs, and more accommodating to your preferences.

This summer, AAN staff began to head back to its headquarters in Minneapolis. After working remotely for 15 months, the return of its workforce will be phased in over several months. Many employees are looking forward to the liveliness and creative spark of exchanging ideas face-to-face. Proper precautions will be taken as they return with the health and safety of our staff, members, and guests top of mind. Our CEO, Mary E. Post, MBA, CAE, has already moved into her office, and to her delight, has finally begun to meet her staff in person after working with them virtually since her arrival in March of 2020.

Our 700+ volunteers will also be resuming in-person meetings. I am looking forward to joining those who will be attending the Meeting Management Committee meeting in Seattle later this August as we move ahead with innovative plans for both a virtual and in-person Annual Meeting in 2022. For our first live Annual Meeting since 2019, we plan to surprise and thrill you with dynamic science and educational programming and unmissable networking opportunities that will reunite you with friends and colleagues. We are now in the midst of planning the 2021 Fall Conference as well, scheduled for Chicago on November 5–7 in person and with a virtual encore soon to follow.

I will be traveling to Minneapolis for the next board of directors meeting next month and my first visit to the AAN office in Minneapolis' Mill District in two years. We will simultaneously be conducting those upcoming committee meetings on Zoom, so that colleagues who are unable to travel can join us in this new hybrid future. Towards that end, our committee composition expanded at the start of my term. We have added an all-virtual category of volunteer so that private practitioners who are unable to leave their practices; parents of young children or those with elderly parents who need to stay home for family reasons; members with disabilities for whom travel is unduly burdensome; and our international members from afar can all join in on the work that sustains and invigorates our organization.

More practice, demographic, and geographic diversity means better representation of our more than 36,000 members, more inclusiveness, and more new ideas. With the pandemic as a catalyst, we have also added a new Telemedicine Subcommittee dedicated to advocating for regulatory change beyond the public health emergency; a new Wellness Subcommittee focusing on our members' emotional health and fortitude; a new Academic Initiatives Committee to address growing needs of our members in academia; a new Inclusion, Diversity, Equity, Anti-racism, and Social Justice (IDEAS) Subcommittee to ensure the AAN and its actions reflect the breadth and diversity of its members; and a new Patient and Public Initiatives Committee committed to delivering information and education to those stakeholders. One of its new initiatives, currently in the planning stage, is a video series demonstrating the value neurologists bring to patients. On a new video platform, I plan on interviewing people with neurologic conditions about their diagnosis and care together with their neurologists addressing the science and latest treatment of their disorders. If you have a fascinating story to tell, please let me know.

For our members at large, we will have more educational opportunities than ever, tailored to your learning preference and cognitive style: audio, video, in-person, and virtual offerings. The most popular are the Neurology Question of the Day mobile app and NeuroBytes videos. In addition, our virtual 2021 Annual Meeting is available through Annual Meeting On Demand, and thanks to a generous grant from the ABPN, Academy members as well as ABPN diplomates can access the 2020 Fall Conference on Demand at no charge. We've also launched registration for the virtual AAN Advanced Practice Provider Neurology Education Series as well as the return to in-person meetings with the 2021 Fall Conference.

We will also continue to provide the resources you request, just as we did in June when the FDA approval of aducanumab was announced, when drug and device alerts occur, such as the June recall of certain Philips CPAP devices, and as we did via the COVID-19 Neurology Resource Center throughout the pandemic to date.

Finally, know that I do not underestimate the toll that this pandemic has inflicted on your practices, your departments, your communities, your families, and yourselves. In welcoming you back, I also want to acknowledge your dedication and sacrifice to neurology during those difficult times. As we unfold these transformations, your feedback is important to me. Is this organization serving you the way you need, and is there anything essential that we have missed?

I would also like to learn what you are most excited about. So, when this publication appears online, I will also release a Twitter poll. Look for it under my handle, *@OrlyA*—it will be live for seven days. And if any of you are not yet on Twitter and interested in starting, let us know and the AAN will be happy to assist you. *#NeuroTwitter* is thriving and growing and the *@AANMember* will be there to greet you as well.

Looking forward to seeing you soon. ■

Orly Avitzur, MD, MBA, FAAN
President, AAN
oavitzur@aan.com
@OrlyA on Twitter

After we went to press, news of breakthrough infections, illness in the unvaccinated, and hospitalizations due to the delta variant caused us to re-evaluate our late summer/early fall in-person committee meetings and convert them to virtual meetings in order to ensure the safety and well-being of our volunteer members.

Meet Your New Board Member: Lily Jung Henson, MD, MMM, FAAN

Henson

Lily Jung Henson, MD, MMM, FAAN, is the chief executive officer of Piedmont Henry Hospital in Stockbridge, GA. She formerly served as the chief medical officer at Piedmont Henry as well as the former chief of neurology of the Piedmont Healthcare System in Atlanta, GA. Prior to her move to Atlanta in 2015, Henson served as the vice president of medical affairs of Swedish Ballard Hospital in Seattle, WA, after her tenure as the inaugural chief of staff of Swedish Issaquah Hospital. Henson has been a neurologist with 30 years of practice with a focus on multiple sclerosis and a principal investigator in many clinical trials involving MS disease-modifying therapies. She was an associate professor of neurology at the University of Washington Medical School.

How did you first get involved as a volunteer on committees/subcommittees and what moved you to participate?

I volunteered to represent the AAN at the National MS Society's Hill event, where I met AAN Chief Health Policy Officer Rod Larson and Dr. Mark Yerby. I enjoyed my advocacy work so much I ended up joining the Legislative Affairs Committee and ultimately became vice chair. I joined the BrainPAC board and also became *AAN.com's* advocacy editor as a result of that meeting.

Why did you wish to be on the Board of Directors?

I wanted to serve my profession, and the AAN truly represents the field of neurology. I feel as though I've been blessed with a lot of experiences professionally including clinical practice, teaching residents and med students, doing clinical trials, being active in advocacy, and my leadership roles both within neurology and outside. Those varied experiences give me a perspective which I think would be useful on the Board and allow me to serve the field.

What experiences and viewpoints do you bring to this role?

I have practiced neurology for 30 years and understand the joys and the struggles that practicing clinicians have. I was involved with training residents and medical students for years and feel as I've helped develop the next generation of physicians (as a matter of fact, one of my former medical students became the medical director of the neurohospitalist team that I helped create and became my boss!!). I've served in many leadership roles including chief of neurology, chief of staff, chief medical officer, and most recently chief executive officer, and feel that I can use those experiences and skills on the Board.

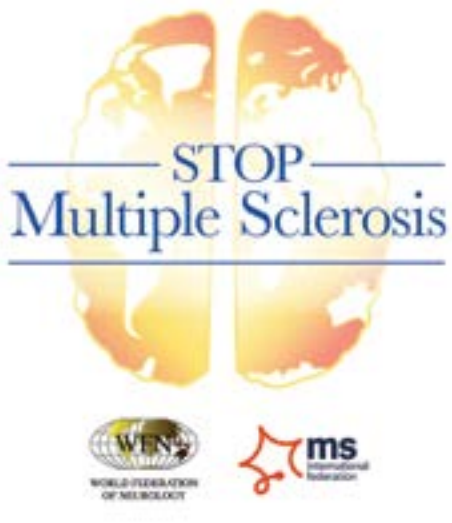
In your view, how does the AAN benefit the field of neurology most?

I am proud that the AAN really does represent the field of neurology. When I read about all the things that are going on within the Academy, I see the emphasis on all the issues that are relevant to neurologists, whether they be independent or employed or in academics. It really is an organization that focuses on what's important to its members and the patients we care for. ■

AAN Shows Support for World Brain Day 2021

The AAN showed its support for the World Federation of Neurology's Stop Multiple Sclerosis: World Brain Day 2021 on July 22 through a number of promotions. *BrainandLife.org* helped build awareness around the day through social media. The AAN participated in a Tweet chat and AAN President Orly Avitzur, MD, MBA, FAAN, and CEO Mary E. Post, CAE, created inspiring video messages to reinforce the importance of the day and the need for continued research into treatment and prevention of multiple sclerosis, which affects 2.8 million people worldwide.

For more information about World Brain Day 2021 and to view the videos, visit *WFNeurology.org/world-brain-day-2021*. ■



YOU GIVE YOUR BEST WHEN YOU . . .

FEEL YOUR **BEST!**

Take time for yourself. We can help with wellness resources to help you improve your physical, emotional, and mental health.

Learn more at *AAN.com/LiveWell*

AMERICAN ACADEMY OF NEUROLOGY.

Neurology Compensation and Productivity Data Now Available

The 2021 Neurology Compensation and Productivity Survey broke records with more than 4,000 AAN participants. The Academy thanks the thousands of members who completed the survey, because without you, we could not maintain the survey's status as the largest and most robust source of neurology data available. With this essential resource, neurologists, advanced practice providers, and business administrators can find the data needed to make informed decisions, analyze gaps, and identify opportunities.

The dashboard is now open and members who completed the survey have FREE access to the data via a dashboard (a $500 AAN member value). Easy to use filters and new data points allow you to

- Filter **neurologist compensation** data by **subspecialty**, geographic region, and more
- View benchmarking for **advanced practice providers**
- See how the **COVID-19** pandemic affected practices across the country
- Find out average **on-call** rates and duties

Participants may access the dashboard at *AAN.com/Benchmark*.

Members and nonmembers who did not participate in the survey may access the data for $500 ($1,500 for nonmembers). A complimentary executive summary is available at *AAN.com/Benchmark* to obtain a sneak peek at the insightful information you can use. ■

Grant Applications Available for Axon Registry Participants

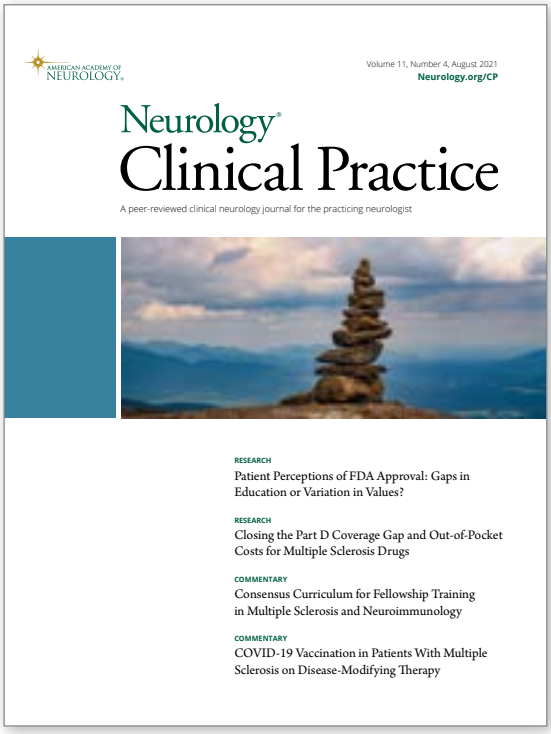
The Axon Registry® is a tool that extracts and analyzes practice medical record data for quality improvement. The AAN can help Axon Registry participants maximize the potential for their data despite limited time, resources, and staff. To help overcome these issues, the Axon Registry, through generous support from the American Board of Psychiatry and Neurology, is offering two types of grants to its current practices. The first grant offered is a quality improvement grant to help with the costs related to implementing quality improvement initiatives into the practice. The second grant is an IT grant to help practices integrate into the Axon Registry. Either type of grant can be worth up to $20,000 per practice.

The Axon Registry is currently transitioning its practices over to its new technical and ingestion vendor Verana Health. For current practices that need assistance with the transition process, applying for the IT grant is recommended. The IT grants are currently being offered to all practices that complete their onboarding with Verana Health by 2022. The Axon Registry is currently onboarding practices from several EHR systems. During the introduction call between the registry, Verana Health, and the practice, the IT grant will be offered to participating practices. For current participants, the introduction call allows them the opportunity to ask any questions regarding the IT grant application and discuss any requirements that are needed.

Both grants the Axon Registry offers provide the opportunity to close the gap with administrative costs and help members improve the quality of care. To apply for the grants or receive more information on the Axon Registry, please contact *registry@aan.com*. ■

axon REGISTRY®

Explore Latest Research in New *Neurology: Clinical Practice* Issue



The August issue of *Neurology® Clinical Practice* highlights multiple sclerosis, leading with an editorial from Marc R. Nuwer, MD, PhD, FAAN, on "Medication Costs Harm Patients with Multiple Sclerosis," and the research report "Closing the Part D Coverage Gap and Out-of-pocket Costs for Multiple Sclerosis Drugs," by Daniel M. Hartung, PharmD, MPH.

Related research includes "Pregnancy-related and Perinatal Outcomes in Women with MS: A Nationwide Danish Cross-sectional Study," by Johanna Balslev Andersen; "eFIT: RCT of a Telehealth Group-based Intervention to Increase Physical Activity in MS," by Victoria M. Leavitt, PhD, FAAN; and "Electronic Health Record Technology Designed for the Clinical Encounter: MS neuroSHARE," by Riley Bove, MD.

Online-only case studies examine spontaneous intracranial hemorrhage, cerebral vasoconstriction, Guillain-Barré syndrome following COVID-19 infection, reversible cognitive impairment in a patient with brain-sagging syndrome, and more.

Published continuously online and in print six times a year, *Neurology: Clinical Practice* is free to AAN members via the website (and available in print for US members only) who have a current subscription to *Neurology®*. Visit *Neurology.org/cp* for more information. ■

Actor Shares Inspiration for His Support for Wounded Vets

In the August/September cover story for *Brain & Life®*, actor Gary Sinise describes how he has dedicated his life to supporting members of the armed services. The Gary Sinise Foundation provides a variety of programs, services, and events for wounded veterans, including support for dealing with traumatic brain injury and posttraumatic stress disorder and mortgage-free specially adapted smart homes. Sinise talks about how portraying Lt. Dan in *Forrest Gump* inspired him to establish his foundation.

A second feature, about aducanumab, the first disease-modifying drug for Alzheimer's disease approved by the US Food and Drug Administration, looks at data that led to approval and talks to the experts about the drug's advantages and disadvantages.

The third feature explores the Compassionate Drug Use program, which allows patients with life-limiting diseases to take experimental drugs that may extend their lives.

Brain & Life magazine is free for AAN members in the United States to distribute to patients, who also can subscribe for free. If you would like to adjust the number of copies you receive for your patients or update your clinic address, email *BeGreen@WasteFreeMail.com*. All members have online access to the magazine articles and additional resources at *BrainandLife.org*. Please share the website with your patients! ■

Improve Quality with Updated MS Quality Measurement Set

The AAN has published the Multiple Sclerosis Quality Measurement Set 2020 Update, in the July 19, 2021 online issue of *Neurology*® journal at *n.Neurology.org*.

The updated MS measurement set has six measures:

- Magnetic Resonance Imaging (MRI) Monitoring for Patients with MS
- Disease Modifying Therapies (DMT) Monitoring for Patients with MS
- Bladder, Bowel, and Sexual Dysfunction Screening and Follow-up for Patients with MS
- Cognitive Impairment Screening and Follow-up for Patients with MS
- Fatigue Screening and Follow-up for Patients with MS
- Exercise and Appropriate Physical Activity Counseling for Patients with MS

This is the first update for the measurement set, and updates will be undertaken as needed by the standing work group, which has also been tasked with creating quality improvement tools to support implementation. The measures focus on collection of meaningful data for patients with MS and allow for treatment teams to benchmark and then drive quality improvement projects for their patients. There is no expectation that treatment teams will use every measure in the set, and treatment teams are encouraged to identify the one or two measures most important for their practices. Practices may prioritize areas where there are known gaps or areas where improvement can occur as screening may not be done frequently in practice or if it is being done it is not standardized. By establishing an initial performance rate during a timeframe, a treatment team can then drive improvement in future performance periods.

View the executive summary and the full measure set and tools on *AAN.com/MSMeasures*.

You may also be interested in the AAN resource "Top Tips for Planning a Quality Telehealth Visit for Patients with MS" at *AAN.com/Telehealth*. ■

AAN Publishes Position Statement on Ethics in Dementia Diagnosis and Care

"Ethical Considerations in Dementia Diagnosis and Care: AAN Position Statement" was published in the *Neurology*® journal online on July 12, 2021. The position statement, developed by the Ethics, Law and Humanities Committee, was approved by the AAN/AANI Board of Directors in January 2021. The position statement was developed and approved before FDA approval of the new medication aducanumab and does not address that drug.

This revision to the AAN's 1996 position statement summarizes ethical considerations that often arise in caring for patients with dementia. While it addresses how such considerations influence patient management, it is not a clinical practice guideline. The position statement first considers the diagnosis of dementia, then problems in decision-making are addressed, symptom and behavioral management, and concludes with the relationship between dementia care and society.

As stated in the abstract, "Alzheimer's disease and other dementias present unique practical challenges for patients, their families, clinicians, and health systems. These challenges reflect not only the growing public health impact of dementia in an aging global population, but also more specific ethical complexities including early loss of patients' capacity to make decisions regarding their own care, the stigma often associated with a dementia diagnosis, the difficulty of balancing concern for patients' welfare with respect for patients' remaining independence, and the impact on the physical, emotional, and financial well-being of family caregivers.

"Caring for patients with dementia requires respecting patient autonomy while acknowledging progressively diminishing decisional capacity, and continuing to provide care in accordance with other core ethical principles (beneficence, justice, and nonmaleficence). While these ethical principles remain unchanged, neurologists must reconsider how to apply them given changes across multiple domains including our understanding of disease, clinical and legal tools for addressing manifestations of illness, our expanding awareness of the crucial role of family caregivers in providing care and maintaining patient quality of life, and societal conceptions of dementia and individuals' personal expectations for aging."

To read the complete position statement, visit *n.Neurology.org*. ■

Capitol Hill Report

Capitol Hill Report presents regular updates on legislative and regulatory actions and how the Academy ensures that the voice of neurology is heard on Capitol Hill. It is emailed to US members twice monthly and is posted at *AAN.com/view/HillReport*. Below are some recent highlights.

Medicare Releases Proposed 2022 Physician Fee Schedule

The AAN works every day to develop a proactive relationship with officials at the Centers for Medicare & Medicaid Services (CMS). Over the past year, AAN staff have met regularly with leadership at CMS, submitted comment letters, and joined with stakeholder groups to amplify the voice of neurologists before federal officials. This work will continue with the release of the 2022 proposed Medicare Physician Fee Schedule.

According to its proposals issued on July 13, 2021, CMS has suggested these changes impacting the practice of neurology:

- Updating telehealth policies with proposals to cover all currently covered services through 2023
- A one-percent increase with variations depending on individual neurology practice
- An ongoing review of evaluation and management codes, including refinements to current policies for split or shared visits
- New Quality Payment Program policies updating the Merit-based Incentive Payment System (MIPS) and Alternative Payment Models (APMs)
- Creation of a stroke-related MIPS Value Pathway (MVP) featuring AAN feedback

Learn how additional provisions affect neurology at *AAN.com/view/Medicarenews*.

More Advocacy News

- On July 8, the FDA announced an updated label for the new Alzheimer's drug aducanumab (Aduhelm), approving the drug only for people with mild cognitive impairment or mild dementia. The AAN is pleased with this change as it aligns with the recommendation provided in our comment letter sent to the FDA. Congress has also announced an investigation of the drug's price, set at $56,000/year. The AAN continues to work to provide resources for members on the drug.
- Sens. Dick Durbin (D-IL), Chuck Grassley (R-IA), and Angus King (I-ME) introduced the Drug-price Transparency for Competition (DTC) Act, a bill that would require price disclosures on prescription drug advertisements. The AAN was listed as an endorsing organization of this bill on the Senate press release.
- Reps. Brian Babin (R-TX) and Chrissy Houlahan (D-PA) introduced the Resident Education Deferred Interest (REDI) Act, a bill to allow borrowers to qualify for interest-free deferment on their student loans while serving in a medical or dental internship or residency program. The AAN was listed as an endorsing organization of this bill on the press release.

Issue in Focus

The House Appropriations Committee approved the FY22 Military Construction, Veterans Affairs, and Related Agencies appropriations bill, which includes language to support Neurology Centers of Excellence within the Veterans Health Administration, including Epilepsy, Headache, Multiple Sclerosis, and Parkinson's Centers. The Multiple Sclerosis and Parkinson's Centers were created by Congress in the early 2000s, and the AAN championed the creation of the Epilepsy Centers in 2007, an effort that was motivated by a surge in veterans experiencing seizures and being diagnosed with epilepsy in connection with traumatic brain injuries from the wars in Iraq and Afghanistan. The Headache Centers were created by Congress in 2018, due to the advocacy of many AAN members and people with headache disorders.

The funding for these centers has been stagnant since they were established. The erosion of their funding due to inflation has been problematic, resulting in a reduction of capacity and staff. The AAN led this most recent advocacy effort to renew support for all the centers by sharing draft language aimed at accomplishing this objective with dozens of congressional offices and coordinating 15 meetings that were supported by allied patient groups, including the Alliance for Headache Disorders Advocacy, the Epilepsy Foundation, The Michael J. Fox Foundation for Parkinson's Research, and the National MS Society.

The AAN is optimistic that the Senate will also include this priority in their appropriations bill, which once passed would be enacted at the start of the fiscal year on October 1, 2021. ■

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.

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.

MAYZENT®
(siponimod) tablets
0.25 mg • 2 mg

FOR PATIENTS WITH FIRST SIGNS OF PROGRESSION IN RMS AND ACTIVE SPMS[1]

STAY AHEAD OF PROGRESSION WITH MAYZENT® (siponimod)

MAYZENT IS THE FIRST AND ONLY

oral DMT studied and proven to delay disability progression in a more progressed RMS population, including active SPMS[1,2]*

THE DUAL MOA OF MAYZENT

targets $S1P_{1,5}$—2 key receptors thought to play a role in RMS inflammation and neurodegeneration[1,3-6]

WITH INTERIM EXPLORATORY DATA UP TO 5 YEARS

from an open-label extension study aiming to evaluate long-term safety and tolerability, as well as efficacy measures; patients who completed the core part of the study either continued on MAYZENT or switched from placebo to MAYZENT[7,8†‡]

*Patients in *EXPAND* had a mean EDSS score of 5.4.[8]
†From a preplanned interim analysis of an open-label extension study.[8]
‡6-month CDP, ARR, and SDMT were exploratory end points and assessments of efficacy measurements, respectively, in the *EXPAND* extension study.[9]

The mechanism by which siponimod exerts therapeutic effects on MS is unknown but may involve reduction of lymphocytes in the CNS.[1]

ARR=annualized relapse rate; CDP=confirmed disability progression; CNS=central nervous system; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; MOA=mechanism of action; MS=multiple sclerosis; RMS=relapsing MS; S1P=sphingosine 1-phosphate; SDMT=Symbol Digit Modalities Test; SPMS=secondary progressive MS.

DISCOVER UP TO 5 YEARS OF INTERIM DATA AT mayzenthcp.com

IMPORTANT SAFETY INFORMATION (CONT)

Bradyarrhythmia and Atrioventricular Conduction Delays: Prior to initiation of MAYZENT, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects.

MAYZENT was not studied in patients who had:

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus

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):

syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker

- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References: 1. Mayzent [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; January 2021. **2.** Data on file. First and only progressing RMS treatment. Novartis Pharmaceuticals Corp; January 2020. **3.** O'Sullivan C, Schubart A, Mir AK, Dev KK. The dual S1PR1/S1PR5 drug BAF312 (siponimod) attenuates demyelination in organotypic slice cultures. *J Neuroinflammation*. 2016;13:31. **4.** Gergely P, Nuesslein-Hildesheim B, Guerini D, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Br J Pharmacol*. 2012;167(5):1035-1037. **5.** Mannioui A, Vauzanges Q, Fini JB, et al. The Xenopus tadpole: An in vivo model to screen drugs favoring remyelination. *Mult Scler.* 2018;24(11):1421-1432. **6.** Choi JW, Chun J. Lysophospholipids and their receptors in the central nervous system. *Biochim Biophys Acta*. 2013;1831(1):20-32. **7.** Data on file. Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis up to 5 Years. Novartis Pharmaceuticals Corp; May 2020. **8.** 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. **9.** Data on file. A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312. Novartis Pharmaceuticals Corp; July 2020.

NOVARTIS

MAYZENT®
(siponimod) tablets
0.25 mg • 2 mg

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% to 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 CBC (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 to 4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period *[see Warnings and Precautions (5.12)]*.

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 an 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 magnetic resonance imaging (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, transient ischemic attack (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, if not contraindicated, ECG testing and first-dose monitoring is recommended *[see Dosage and Administration (2.1, 2.4) in the full prescribing information and Contraindications (4)]*.
- 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 Cutaneous Malignancies

Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). In Study 1, the incidence of BCC was 1.0% in MAYZENT-treated patients. Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended in patients taking MAYZENT.

5.7 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.

5.8 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.

5.9 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an 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 an 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.

5.10 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)]*.

5.11 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. Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required.

5.12 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 to 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 to 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)]*
- Bradyarrhythmia and Atrioventricular Conduction Delays *[see Warnings and Precautions (5.3)]*
- Respiratory Effects *[see Warnings and Precautions (5.4)]*
- Liver Injury *[see Warnings and Precautions (5.5)]*
- Cutaneous Malignancies *[see Warnings and Precautions (5.6)]*
- Increased Blood Pressure *[see Warnings and Precautions (5.7)]*
- Fetal Risk *[see Warnings and Precautions (5.8)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.9)]*
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies *[see Warnings and Precautions (5.10)]*
- Severe Increase in Disability After Stopping MAYZENT *[see Warnings and Precautions (5.11)]*
- Immune System Effects After Stopping MAYZENT *[see Warnings and Precautions (5.12)]*

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 basal cell carcinoma, squamous cell carcinoma, malignant melanoma, and seminoma were reported in MAYZENT-treated patients in Study 1 (in the core or extension parts). The risk of basal cell carcinoma is increased in MAYZENT-treated patients, and an increased risk of cutaneous malignancies has also been reported in association with another S1P modulator *[see Warnings and Precautions (5.6)]*.

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 (5.10)]*.

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) antiarrhythmic 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% to 4% and 15% to 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 (5.8)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Oral administration of siponimod (0, 5, 15, or 50 mg/kg/day) to young rats from postnatal day 25 to 70 resulted in mortality, lung histopathology (alveolar/interstitial edema, fibrin, interstitial mixed cell infiltration) and decrease in body weight gain at the mid and high doses. Neurobehavioral impairment (decreased acoustic startle response) was observed at the high dose but was reversible by the end of the recovery period. Decrease in immune function (T-cell dependent antibody response) was observed at all doses and had not fully recovered by 4 weeks after the end of dosing. A no-effect dose for adverse effects in juvenile animals was not identified.

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% to 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, 5.7) 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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T2021-04

AAN Pushes Back on Regulatory Burdens

Physicians, including neurologists, face growing administrative requirements from the federal government, insurers, and their institutions. Despite the medical community constantly working toward providing more efficient, high-quality patient care, physicians are forced to adhere to many redundant and ineffective processes. Neurologists need relief from overwhelming regulatory requirements, so they may prioritize caring for patients with complex diseases of the brain and nervous system.

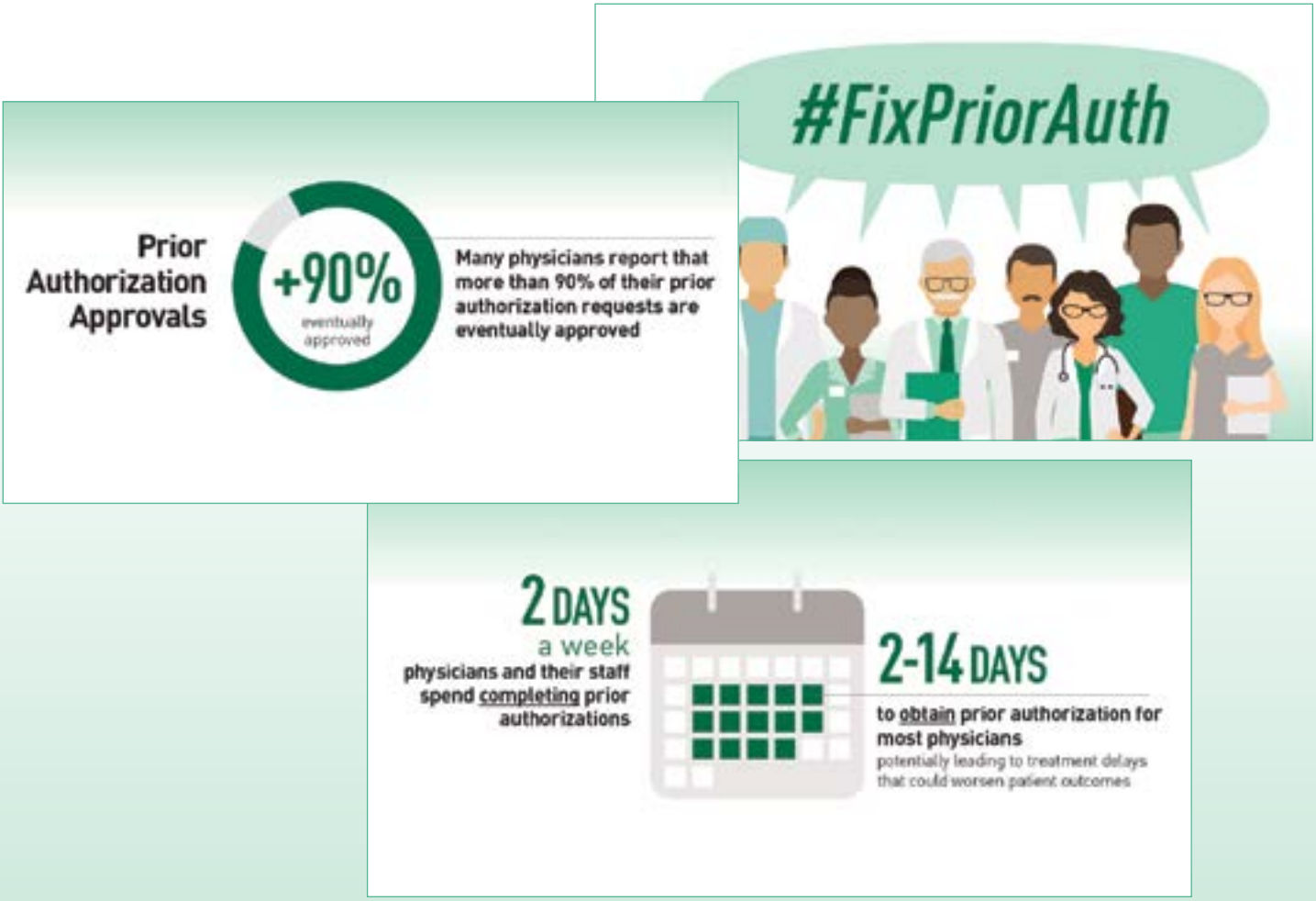
At the federal level, the AAN supports:

- **Policies to alleviate burden** associated with prior authorization, step therapy, quality reporting, and other administrative tasks
- **Repeal of the Medicare Appropriate Use Criteria program,** as new Medicare payment and delivery models that hold clinicians accountable for health care resource use have evolved and, when coupled with repeated implementation delays, this program is now outdated
- **The Safe Step Act,** which establishes commonsense exceptions to step therapy in group health plans
- **The Improving Seniors' Timely Access to Care Act,** which increases transparency and streamlines prior authorization in Medicare Advantage

The Academy has also advocated to reinstate step therapy prohibitions in Medicare Advantage for Part B drugs and commented on regulatory review and prior authorization in Medicaid, the Children's Health Insurance Program (CHIP), and qualified health plans.

Health insurance regulation is complicated and primarily determined at a state level, therefore limiting the power of congressional action. Since Medicare is a federal health care plan, the AAN often focuses on policy changes that affect Medicare administrative requirements. Medicare is frequently the model for private insurance coverage policies, therefore many of the federal policy changes are adopted by states as well.

In addition to advocacy efforts on a federal and state level, the AAN also engages with private payers regarding coverage policies and reimbursement. ■



Applications Open This Month for 2022 Resident Research Scholarship

Applications will be accepted beginning August 17 for one of three highly competitive $3,000 Resident Research Scholarships to be awarded in early 2022. Now in its third year, the program was designed to support AAN member neurology residents who are just getting started in their careers in neuroscience research and is intended as a springboard into the AAN's Research Program or other programs focused on early-career investigators.

Qualifying projects are those at a US or Canadian hospital, clinic, or private practice setting where there are ongoing programs of research, service, or training and where the project is jointly designed by the resident and a mentoring physician.

For more information about application requirements, project criteria, and expectations, contact Michelle Maxwell at *mmaxwell@aan.com*. ■

2022 RESIDENT RESEARCH SCHOLARSHIP

Get Updated on Neuroinfectious Disease in August *Continuum*

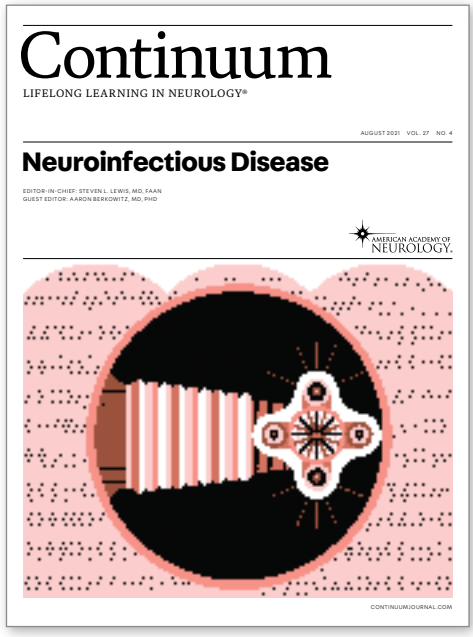
The latest issue of *Continuum*: *Lifelong Learning in Neurology*® provides neurologists with new insights on neuroinfectious disease.

Berkowitz

Guest Editor Aaron L. Berkowitz, MD, PhD, explained, "Some articles in this issue focus on clinical syndromes (e.g., meningitis, spinal disorder), others on particular infections (e.g., HIV, Lyme disease, COVID-19), and others on particular populations (e.g., patients on immunomodulatory therapy, neonates with congenital infections). Our hope is that these articles will prove useful in diagnosis and treatment of both common and rare neurologic infections in a wide variety of clinical contexts."

Topics covered in this issue include:

- Approach to Neurologic Infections / Aaron L. Berkowitz, MD, PhD
- Meningitis / Allen J. Aksamit Jr, MD, FAAN; Aaron L. Berkowitz, MD, PhD
- Encephalitis and Brain Abscess / Arun Venkatesan, MD, PhD
- Infections of the Spine and Spinal Cord / Shamik Bhattacharyya, MD, MS; Michael J. Bradshaw, MD
- Infections of the Peripheral Nervous System / Samantha LoRusso, MD
- Parasitic Infections of the Nervous System / Hector H. Garcia, MD, PhD
- Neurologic Complications of Human Immunodeficiency Virus / Marie F. Grill, MD
- Neurologic Complications of Tuberculosis / Deanna Saylor, MD, MHS
- Neurosyphilis / Felicia Chow, MD, MAS
- Neurologic Complications of Lyme Disease / Karen L. Roos, MD, FAAN
- Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 Infection / Avindra Nath, MD
- Neurologic Infections in Patients on Immunomodulatory and Immunosuppressive Therapies / Pria Anand, MD
- Congenital Infections of the Nervous System / Payal Patel, MD



The issue includes a postreading self-assessment and test with the opportunity to earn up to 20 *AMA PRA Category 1 Credits*™ toward Self-assessment CME.

Upcoming topics for 2021 include:

- October: Neurocritical Care
- December: Behavioral Neurology and Psychiatry

AAN members pay only $399 per year for a subscription to *Continuum*® and *Continuum*® Audio. Subscribe now by contacting Wolters Kluwer at (800) 361-0633 or (301) 223-2300 (international) or visit *shop.LWW.com/continuum*. AAN Junior members who are transitioning to neurologist memberships are eligible to receive a 60-percent discount on the already low member rate for the *Continuum* and *Continuum* Audio subscription. ■

Neurology Journal's Resident & Fellow Section Offers Opportunities

The Resident & Fellow Section (RFS) of the *Neurology*® journal seeks authors and reviewers from around the globe to contribute to the most widely read and highly cited peer-reviewed neurology journal. Residents and fellows can participate by:

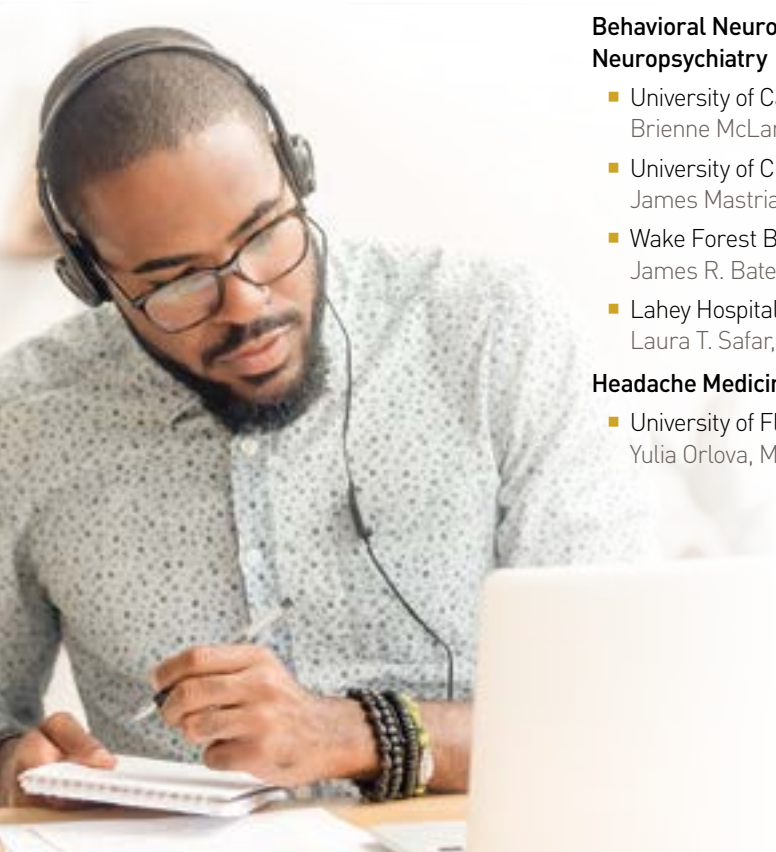
- **Authoring a manuscript.** Submit, publish, and share work with students, residents, fellows, and educators worldwide. Residents benefit from the prestige of publishing in the premier clinical neurology journal.
- **Submitting commentary.** The RFS website provides an outlet for blog posts and commentary on published articles and trending topics for trainees.
- **Being a reviewer.** Residents and fellows can either work independently or with a local faculty mentor to peer review manuscripts and contribute to scientific peer review. Trainees who sign up to review will be added to the pool of potential reviewers.

This is a unique opportunity to enhance a growing career. If you are interested in receiving more information, please complete the form at *NPub.org/rfsform*. ■

More information and a wealth of resources are available at *Neurology.org/residents_fellows*.

Eight Training Programs Achieve UCNS Accreditation

Eight training programs have achieved accreditation status from the United Council for Neurologic Subspecialties, making for a total of 218 UCNS-accredited programs in eight recognized subspecialties. These programs offer the core curriculum established by the subspecialty and meet required quality standards established by the UCNS.



The programs and directors are:

Behavioral Neurology & Neuropsychiatry

- University of Calgary
  Brienne McLane, MD, FRCPC, MSC
- University of Chicago
  James Mastrianni, MD, PhD
- Wake Forest Baptist Medical Center
  James R. Bateman, III, MD, MPH
- Lahey Hospital and Medical Center
  Laura T. Safar, MD

Headache Medicine

- University of Florida Health Shands
  Yulia Orlova, MD

Neurocritical Care

- University of Nebraska Medical Center
  Daryl R. Gress, MD
- Westchester Medical Center
  Stephan A. Mayer, MD

Neuro-oncology

- Cedars-Sinai Medical Center
  Jethro L. Hu, MD

Visit *UCNS.org* for more information about training program accreditation and requirements. ■

UNITED COUNCIL FOR NEUROLOGIC SUBSPECIALTIES®

Diversity Leadership Graduate Discovers Entrepreneurial Spirit, Opens New Headache Clinic

When headache medicine specialist Hope O'Brien, MD, MBA, FAHS, FAAN, entered the 2016 class of the AAN's Diversity Leadership Program, she already knew there was an unmet need in the management of patients with headache and had long envisioned opportunities to address those needs through a unique space that considers the equally unique aspects of headache and migraine. She just hadn't yet landed on how to turn the vision into reality.

"During my involvement in the leadership program, executive consultant Dr. Joanne Smikle introduced the term 'self-awareness,'" explained O'Brien. "I learned how to identify and analyze strengths, weaknesses, and how I am perceived by others."

To do this, O'Brien had to spend time self-reflecting, which she says challenged her beliefs about her role in medicine. "For instance, where did I see myself in five years if I were to continue in this academic pathway of medicine? Is becoming a department chair or dean where I want to end my career?"

She also learned the importance of being a part of an organization that makes use of and finds value in her strengths and talents. "One of the takeaways from the program was hearing [past AAN President] Dr. Terry Cascino express how important it is for a neurologist to be at the table of every industry, not just health care. I agree that we need to infiltrate where decisions are made in policy, education, technology, construction, and so forth. All industries are affected by neurologic disease."

As the program progressed, O'Brien discovered that she had the characteristics of an entrepreneur, but recognized that there were areas she first wanted to develop around business, such as process improvement, marketing, and strategic planning. "Therefore, I made the decision to go back to school and obtain an Executive MBA degree," she said. "Doing so gave me the confidence I needed to pursue my dream of owning my own business."

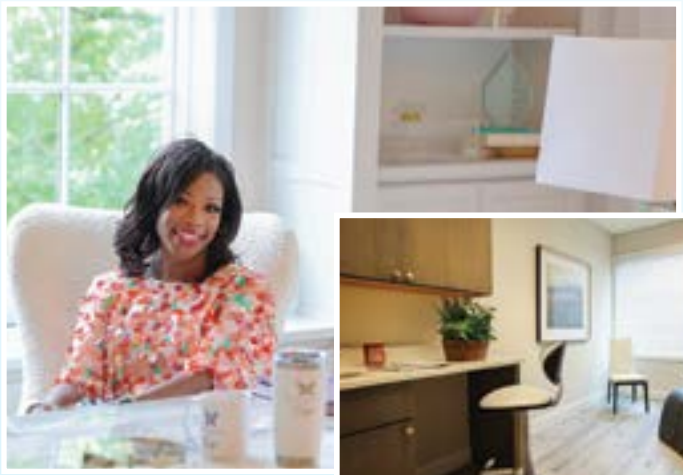
After a few years of planning and hard work, O'Brien's vision and dream for a "space and opportunity for the synergy of modern medicine and holistic remedies to produce wholeness and healing for a headache-free life" became reality at a June 15, 2021, grand opening of the new Headache Center of Hope in Cincinnati, OH. As the founder, CEO, and medical director, O'Brien has created a space where efficiency, empathy, personalization, inclusiveness, and comprehensive care come together in a warm, comfortable atmosphere. The center offers highly individualized consultation and therapeutic services, naturopathic and holistic therapies, injections and infusions, and medical device and prescription therapies.

Added O'Brien, "The center is now open for patients, and I am grateful to the American Academy Neurology's commitment and investment to developing leaders who will change outcomes for patients."

The Diversity Leadership Program is a crucial aspect of the AAN's leadership diversification strategy intended to identify, mentor, and engage AAN members from underrepresented groups. Learn more at *AAN.com/DLP*. ■

The AAN thanks these organizations supporting this program in part:

- Bristol Myers Squibb
- Eisai, Inc.
- Genentech, a member of the Roche group



Paper Examines Mentoring Women in Neurology

Inclusion is the reason the AAN was founded. To be an organization that is the home for all neurologists. It is what makes us stronger. In 2020, the AAN Board of Directors adopted a new goal to be a fully inclusive, deliberately diverse, and anti-racist organization. We also expanded our core values of Diversity and Equity to now include Inclusion, Diversity, Equity, Anti-racism, and Social Justice, otherwise known as IDEAS. We are working hard to achieve this new goal and demonstrate these expanded values through an actionable roadmap approved by the Board. Members should look for these monthly updates in AANnews to follow our progress.

The research paper "Current Status and Future Strategies for Mentoring Women in Neurology" was published in the June 4, 2021, online issue of *Neurology*®. Taking its cue from the AAN's 2017 Gender Disparity Report, which identified improving mentorship as a key intervention to fill the leadership and pay gaps for women in neurology, this paper summarizes the literature on mentoring women, provides an outline of ideal components of programs geared toward closing gender gaps, and presents a mentoring program for AAN members. The strategies discussed share similarities with those for closing gaps related to race, ethnicity, and religion. The authors report that developing effective mentorship and sponsorship programs is essential to ensure a sufficiently diverse pool of academic faculty and private practitioners, and to establish equal representation in leadership roles in this field. Read the full article at *Neurology.org*. ■

Congratulations New Fellows of the American Academy of Neurology!

The AAN congratulates the following members who were named prestigious Fellows of the American Academy of Neurology (FAAN) between March 2021 and May 2021.

Heather S. Anderson, MD, FAAN
Martinson K. Arnan, MD, FAAN
Tracie Caller, MD, MPH, FAAN
Daniel Jose Correa, MD, FAAN
Gregory S. Day, MD, MSc, FAAN
Waleed Hamed El-Feky, MD, FAAN
John F. Foley, MD, FAAN
Edward I. Ginns, MD, PhD, FAAN
Jerome J. Graber, MD, MPH, FAAN
Ryan Hays, MD, FAAN
Keith A. Josephs, Jr., MD, FAAN
Monica A. Koehn, MD, FAAN
David G. Lichter, MBChB, FRACP, FAAN
Ami K. Mankodi, MD, FAAN
Sheryl Martin-Schild, MD, PhD, FAAN
Thomas Drake McDonald, MD, FAAN
Aaron McMurtray, MD, FAAN
Gayane Robert Melikyan, MD, FAAN
Edward Mistler, MD, FAAN
Yasir Osman Mohamed, MD, FAAN
Datta B. Nadgir, MD, FAAN
Sharon P. Nations, MD, FAAN
Olukemi A. Olugemo, MD, FAAN
Padraig Eoin O'Suilleabhain, MD, FAAN
Mary A. Picone, MD, FAAN
Hernan N. Posas, Jr., MD, FAAN
Edgar A. Samaniego, MD, FAAN
Kevin R. Scott, MD, FAAN
Amgad Shebl, MD, MBBS, FAAN
Shumaila Sultan, MD, FAAN
Annabel K. Wang, MD, FAAN
Lakshmi Warrior, MD, FAAN ■

Interested in Elevating Your Membership Status to FAAN?

Visit *AAN.com/FAAN* to see if you're eligible for the FAAN designation—or encourage a qualifying colleague to apply. Applying for FAAN status is free, acknowledges exemplary work and achievements in the neurosciences, the clinical practice of neurology, or academic/administrative neurology; helps set you apart both within the Academy and throughout your professional career; and offers eligibility to serve on the AAN Board of Directors. ■

Welcome New AAN Chief Health Policy Officer

The AAN is pleased to announce Sukhjeet Ahuja, MD, MPH, joined the Academy as our new Chief Health Policy Officer in June, working from the AAN Washington, DC, office. Ahuja leads the AAN's health policy division, he oversees advocacy efforts, guideline development, quality measurements, and tools and resources for practicing neurologists. Additionally, he will work with AAN member committees to demonstrate the value of neurology to policymakers, patients, and the public.

Ahuja joins us from the Society of Nuclear Medicine and Molecular Imaging where he served for over seven years, most recently as senior director of health policy and quality. He has held roles with the National Association for Public Health Statistics and Information Systems and the Louisiana Office of Public Health.

Ahuja earned a master's degree in public health, epidemiology, from Tulane University in New Orleans, LA, and a bachelor of medicine, bachelor of surgery (MBBS), which is equivalent to an MD, from Barkatullah University, Bhopal, in India. ■

Ahuja

AUGUST 2021

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SEPTEMBER 2021

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OCTOBER 2021

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AUGUST 5
Registration Opens
Fall Conference
AAN.com/Fall

AUGUST 26
Early Registration Deadline:
Fall Conference
AAN.com/Fall

AUGUST 31
AAN Trainee Trivia
AAN.com/TraineeTrivia

SEPTEMBER 2
Early Registration Deadline:
Advanced Practice Provider
Neurology Education Series
AAN.com/APP

SEPTEMBER 6–NOVEMBER 23
Advanced Practice Provider
Neurology Education Series
AAN.com/APP

SEPTEMBER 30
Advance Registration and Housing Deadline: Fall Conference
AAN.com/Fall

OCTOBER 1
Application Deadline:
2022 AAN Research Program
AAN.com/ResearchProgram

Groundbreaking Research Award Seeks Improved Diagnosis for Lewy Body Dementia

The American Brain Foundation has partnered with the Alzheimer's Association, The Michael J. Fox Foundation for Parkinson's Research, and the American Academy of Neurology to establish its 2022 Cure One, Cure Many Award: A Research Award for Early Diagnosis of Lewy Body Dementia. This $3 million, multi-year research award was created to improve the diagnosis of Lewy body dementia (LBD), which causes a progressive decline in cognitive function and is the second most common cause of neurodegenerative dementia, after Alzheimer's disease.

Carrillo

Sherer

Williams

The partnership highlights the interconnectedness of brain diseases and the American Brain Foundation's holistic approach that focuses on building bridges between different brain diseases—a belief that by investing in research across the whole spectrum of disorders, a cure for one brain disease will lead to cures for many.

Currently, LBD can only be definitively diagnosed with a brain autopsy after death. As a result of a delay in diagnosis and misdiagnosis, people with LBD and their caregivers endure daily challenges and uncertainty. LBD and other neurodegenerative diseases like Alzheimer's disease and Parkinson's disease share many similarities, and patients often experience overlapping symptoms—as well as the abnormal synuclein protein clusters called Lewy bodies. As a result, they are often mistaken for one another, which hinders diagnosis, treatment, and research.

"Better biological measures of brain disease are urgently needed to speed therapeutic development and improve care," said Todd Sherer, PhD, executive vice president, research strategy of The Michael J. Fox Foundation. "More resources, research, and collaboration are critical toward those goals. Shared pathology across Parkinson's disease and Lewy body dementia means that better understanding the biology of one can help advance research into the other, growing the impact of this program across diagnostic lines."

The goal of the Cure One, Cure Many Award is to attract the best minds in brain disease research to find a biomarker for LBD in the hope that this will lead to an accurate method of diagnosing the disease and give patients and their loved ones clarity about the prognosis. This will also allow researchers to better study LBD and develop effective therapies.

"I am so hopeful about the inaugural Cure One, Cure Many Award and the changes it could bring," said American Brain Foundation Board Vice Chair Susan Schneider Williams, who spearheaded this initiative in honor of her late husband, actor and comedian Robin Williams, who was diagnosed with Lewy body dementia after his death. "Diagnosis is vital—not only for the LBD patients and caregivers but also for the doctors and researchers. So much time, effort, resources, and life itself can be saved by having an accurate diagnosis."

"The Alzheimer's Association is pleased to collaborate with these other passionate and dedicated organizations to inject much-needed energy and resources into Lewy body dementia research," said Maria C. Carrillo, PhD, chief science officer. "As an added benefit, it may also increase the understanding of degenerative brain diseases, including Alzheimer's and all other dementia, leading to better diagnosis, improved treatments and effective prevention strategies that may benefit millions of people around the world."

Visit *AmericanBrainFoundation.org/com* to learn more about the award and to see how you can help support this initiative. ■

The American Brain Foundation gives me hope that there is an organization whose sole focus is to fund research across the full spectrum of brain diseases. It gives me hope that a discovery in one area will have a profound ripple effect on our understanding and treatment of other diseases. And that is the benefit of studying brain diseases across the spectrum.

— David Dodick, MD, FAAN
Board Chair

How is the American Brain Foundation working to create a world without brain disease?

- Investing in research across all brain diseases and disorders knowing they are all connected
- Bringing donors and researchers together to find better treatments, prevention, and the cures of tomorrow
- Advocating for all those impacted by brain disease

A cure for one brain disease will lead to cures for many.
Learn more about our mission and research initiatives at
AmericanBrainFoundation.org/About

AMERICAN BRAIN FOUNDATION

Neuromuscular Physician - Scripps Clinic Medical Group, Inc—La Jolla, California

https://careers.aan.com/job/52899652/neuromuscular-physician/

Scripps Clinic is seeking a Neurologist with expertise in EMG and Neuromuscular disease (board certified with American Board of Psychiatry and Neurology and American Board of Electrodiagnostic Medicine) to join a large collegial multi-specialty group, which in the Neurology division, consists of 14 Neurologists with varying subspecialties. We are looking for candidates who can deliver excellent, compassionate clinical care to our patients. Opportunities are available to participate in graduate medical teaching and collaborative research. The candidate will see primarily Neuromuscular and general Neurology patients in our offices in San Diego, California. Workload would consist of mainly outpatient Neurology care with outpatient clinic call, as we have full-time Neuro-hospitalists and Vascular/stroke Neurologists covering the inpatient Neurology service. Having single fiber emg skill and strong interest in seeing autonomic neuropathy patients are favorable candidates. We have an established autonomic lab as well as varying other medicine subspecialties with autonomic interests. A competitive salary package is offered, and benefits include medical/dental/vision insurance, medical malpractice coverage, contributions to retirement savings, and a stipend for continued education. Scripps hospitals are consistently ranked among America's Best Hospitals according to US News. San Diego, California is in a large urban setting with diverse cultural backgrounds and access to many family-friendly forms of entertainment, including sports, music, theater, museums, and diverse restaurants. San Diego has one of the best climates anywhere on the planet and is home to sunny and beautiful beaches. Please contact *Hwynn.Nelson@scrippshealth.org* with your C.V. and a letter of interest.

Neurologist - Assistant/Associate Professor—Central Vermont Medical Center—Vermont, Four Seasons of Outdoor Activities at Your Doorstep!

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The Robert Larner, M.D. College of Medicine at the University of Vermont (UVM) and the University of Vermont Medical Center (UVMMC) seek to recruit a physician to join our established program in General/Comprehensive Neurology. The successful applicant will be involved in a primarily clinical care role at University of Vermont Health Network—Central Vermont Medical Center (CMVC) in Berlin, Vermont. This position offers the unique opportunity to work in a community setting while still being involved with an academic center. Located in the heart of the Green Mountain state, CVMC has a reputation for clinical excellence with a staff deeply rooted in our community. The general neurology practice sees a wide variety of neurologic conditions, including epilepsy/seizure disorders, stroke, chronic headaches/migraines, multiple sclerosis, Parkinson's and Alzheimer disease, as well as movement and neuromuscular disorders. The ideal candidate will be skilled in reading EEGs and/or conducting/interpreting EMGs. This is a full-time, 12 month, salaried position with attending staff privileges at CVMC. All applicants must be American Board of Psychiatry and Neurology board eligible/certified. Fellowship training in a clinical neurology discipline is desired, however not a requirement. Our goal is to continue the high level of clinical care and education currently provided as we develop our clinically integrated network. The Central Vermont Medical Center site is evolving as a graduate medical education site and opportunities for teaching will be supported. UVM is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal. UVM and UVM Medical Center are Equal Opportunity/Affirmative Action Employers. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution. The application receipt and review process will begin immediately and continue until the position is filled. Interested individuals should apply online for position #45098 at *www.uvmjobs.com.* For more information, contact Sarah Child at *Sarah.Child@CVMC.org* or phone (802) 225-1739. For more information regarding the Department of Neurological Sciences, please see our website at *http://www.uvm.edu/medicine/neuro/*

Excellent Neurology Opportunity in Picturesque Coastal California—United Neuroscience Institute—California

https://careers.aan.com/job/52899524/excellent-neurology-opportunity-in-picturesque-coastal-california/

Young multi-subspecialty 12-member group seeking their next colleague! Recruiting Neurologists—with and without fellowship training. Opportunity to practice in an area of tremendous growth. Multiple locations in California to choose from. Excellent compensation package! Clearly defined partnership track. Generous paid time off. CME, relocation, malpractice and professional expense stipends. Opportunity for academic involvement/position; Flexible work/call schedule; Tremendous opportunity for professional and personal growth. The Neuroscience Institute is a partnership between the leading hospitals and independent group of physicians—soon to be 13 and growing, providing comprehensive neurological care encompassing all aspects of neurological sub-specialties including epilepsy, neurophysiology, neuro-critical care, vascular neurology and neuro-endovascular surgery. The group also has contractual affiliations with other regional healthcare organizations. New graduates welcome to apply; Enjoy unmatched fellowship and camaraderie from experienced colleagues in a robust program that handles the entire spectrum of neurological disorders. Group has established exceptionally robust and successful programs in Interventional Neuroradiology, Epilepsy, and Neurological Critical Care. Visa-H-1B sponsorship available. Can consider J-1 waiver. Multiple locations to choose from. The diverse community offers an excellent and affordable environment to live and raise the family. The area includes several upscale residential communities with great school systems. The city is centrally located to many urban as well as natural attractions. Recreational opportunities such as golf, sailing, beaches and excellent dining are abundant in the region. For more information, please contact (617) 849-0321 or *kthomas@unitedneuroscience.org* ■

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Ad copy for the October 2021 print edition of *AANnews* must be submitted by September 1, 2021. The same deadline applies to changes/cancellations.

The American Academy of Neurology reserves the right to decline, withdraw, or edit advertisements at its discretion. Every care is taken to avoid mistakes, but the responsibility for clerical or printer errors does not exceed the cost of the ad. ■