Holding On to Hope in Huntington Disease

BY DANIEL O. CLAASSEN, MD, MS

Refining the Approach to Seizure Rescue Medications

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SPECIAL COVERAGE
Experts Weigh In on Aducanumab’s Approval
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The State of Coma Care: A Call for Action
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Discover an oral therapy for your patients with relapsing forms of multiple sclerosis (MS)...

**ZEPOSIA—FOCUSED ON WHAT COUNTS**

ZEPOSIA was studied in the largest number of patients with RMS in 2 pivotal head-to-head trials against an active comparator (N=2659)²,³b:

- **POWERFUL** Efficacy:
  - Proven superior in reducing relapses vs Avonex³
  - Proven superior in reducing GdE and T2 lesions vs Avonex

- **COMPARABLE** Safety Profile vs Avonex
  - Consistently low discontinuation rates vs Avonex³
  - Comparable rates of serious infections and malignancies vs Avonex

- **The FIRST AND ONLY** STIP With No First-Dose Observation Required³,⁴,d
  - Full Prescribing Information for ZEPOSIA has NO FIRST-DOSE OBSERVATION required
  - NO genetic testing required
  - NO ophthalmic testing required for most patients⁵,e

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**Indication**

ZEPOSIA 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 who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.

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¹Study designs: SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-µg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, respectively). **Secondary endpoints:** ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.¹,³

²Adverse reactions: Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infections, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. **Serious infections:** The rate of serious infections at 1 year for ZEPOSIA was 1.1% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. Malignancy rates: The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.¹,³
A relapse was defined as the occurrence of new or worsening neurological symptoms persisting for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.2,3

Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations.1 Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation.1 For patients with a history of uveitis or macular edema, an ophthalmic assessment is required.1 An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.1

Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA.1

ARR=annualized relapse rate; CBC=complete blood count; ECG=electrocardiogram; GdE=gadolinium enhancing; RMS=relapsing multiple sclerosis; SIP=sphingosine-1-phosphate; VZV=varicella-zoster virus.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA.

Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (SIP) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another SIP receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leuкоencephalopathy (PML) is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with SIP receptor modulators and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued.

In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Use of live attenuated vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

**Bradyarrhythmia and Atrioventricular Conduction Delays:** Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class 1a or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome, or sinoatrial heart block

**Liver Injury:** Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease.

**Fetal Risk:** There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA.

**Increased Blood Pressure:** Increase in systolic blood pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

**Respiratory Effects:** ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated.

**Macular edema:** SIP modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued.

**Posterior Reversible Encephalopathy Syndrome (PRES):** Rare cases of PRES have been reported in patients receiving a SIP receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. 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, treatment with ZEPOSIA should be discontinued.

**Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs:** 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. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended.

**Severe Increase in Disability After Stopping ZEPOSIA:** Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a SIP receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment so patients should be monitored upon discontinuation.

**Immune System Effects After Stopping ZEPOSIA:** After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA.

**Most common Adverse Reactions (≥ 4%):**

- Upper respiratory infection
- Hepatic transaminase elevation
- Osteoporosis
- Hypogonadism
- Urinary tract infection
- Herpes zoster

**Progressive Multifocal Leukoencephalopathy (PML):**

- PML has been reported in patients treated with ZEPOSIA, including patients treated with ZEPOSIA alone and in combination with other immunosuppressant medications. PML was observed in patients with a diverse range of underlying conditions, including MS, other SMDs, and immunocompromised conditions. ZEPOSIA treatment should be suspended until PML has been ruled out.

**Cryptococcal Infection:**

- Cryptococcal meningitis has been reported in patients with HIV who have been treated with ZEPOSIA.

**Herpes Viral Infection:**

- Pre-existing or new active herpes zoster infections were observed in patients receiving ZEPOSIA.

**Risk of Infections:**

- Infections including urinary tract infections, and herpes zoster were more common in patients receiving ZEPOSIA.

**References:**


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**ZEPOSIA**® (ozanimod) capsules, for oral use

**INDICATIONS AND USAGE**

ZEPOSIA 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.

**DOSE AND ADMINISTRATION**

2.1 Assessments Prior to First Dose of ZEPOSIA

**Before initiation of treatment with ZEPOSIA, assess the following:**

- **Complete Blood Count**
  - Obtain a recent (i.e., within the last 6 months or after discontinuation of prior MS therapy) complete blood count (CBC), including lymphocyte count [see Warnings and Precautions (5.1)].

- **Cardiac Evaluation**
  - Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought [see Warnings and Precautions (5.2)].

- **Liver Function Tests**
  - Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels [see Warnings and Precautions (5.3)].

- **Ophthalmic Assessment**
  - In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula [see Warnings and Precautions (5.7)].

- **Current or Prior Medications**
  - If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.2)].
  - Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction [see Warnings and Precautions (5.2) and Drug Interactions (7.3)].

**Vaccinations**

Test patients for antibodies to varicella zoster virus (VZV) before initiating ZEPOSIA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.3)]. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

2.2 Dosing Information

**Maintenance Dosage**

After initial titration (see Treatment Initiation), the recommended maintenance dosage of ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8. ZEPOSIA capsules should be swallowed whole and can be administered with or without food.

**Treatment Initiation**

Initiate ZEPOSIA with a 7-day titration, as shown in Table 1 [see Warnings and Precautions (5.2)].

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>0.23 mg once daily</td>
</tr>
<tr>
<td>5-7</td>
<td>0.46 mg once daily</td>
</tr>
<tr>
<td>8-28</td>
<td>0.92 mg once daily</td>
</tr>
</tbody>
</table>

2.3 Reinitiation of ZEPOSIA After Treatment Interruption

If a dose of ZEPOSIA is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen (see Dosage and Administration [2.2]).

If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

4 CONTRAINDICATIONS

ZEPOSIA is contraindicated in patients who:

- In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure [see Warnings and Precautions (5.2)].
- Have the presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker [see Warnings and Precautions (5.2)].
- Have severe untreated sleep apnea [see Warnings and Precautions (5.2)].
- Are taking a monoamine oxidase (MAO) Inhibitor [see Drug Interactions (7.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

**Risk of Infection**

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues [see Clinical Pharmacology (12.2)]. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA.

Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA.

Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved.

In Study 1 and Study 2, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA was similar to that in patients who received interferon (IFN) beta-1a (35% vs 34% and 1% vs 8%, respectively). ZEPOSIA increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes zoster [see Adverse Reactions (6.1)].

**Reduction in Heart Rate**

Initiation of ZEPOSIA may result in a transient decrease in heart rate. In Study 1 and Study 2, after the initial dose of ZEPOSIA 0.23 mg, the greatest mean decrease from baseline in heart rate of 1.2 bpm occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. With continued titration, the maximal heart rate effect of ozanimod occurred on Day 8. The utility of performing first-dose cardiac monitoring when initiating ZEPOSIA in patients with characteristics similar to those studied in the clinical trials of ZEPOSIA is unclear. Heart rates below 40 bpm were not observed. Initiation of ZEPOSIA without titration may result in greater decreases in heart rate [see Dosage and Administration (2.2)].
ZEPOSIA® (ozanimod) capsules, for oral use

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Infections [see Warnings and Precautions (5.1)]
- Bradycardia and Atrioventricular Conduction Delays [see Warnings and Precautions (5.2)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]
- Severe Increase in Disability After Stopping ZEPOSIA [see Warnings and Precautions (5.10)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.8)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Drugs [see Warnings and Precautions (5.9)]
- Severe Increase in Disability After Stopping ZEPOSIA [see Warnings and Precautions (5.10)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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.

The safety of ZEPOSIA™ was evaluated in two randomized, double-blind, active comparator-controlled clinical studies in which 882 patients received ZEPOSIA® 0.92 mg [see Clinical Studies (14)].

Table 2 lists adverse reactions that occurred in at least 2% of ZEPOSIA-treated patients and greater than the 0.3% of patients who received IFN beta-1a.

5.7 Macular Edema

S1P modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a.

An ophthalmic examination of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA.

Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA 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 a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. 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.

5.8 Posterior Reversible Encephalopathy Syndrome

Rapid cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In controlled clinical trials with ZEPOSIA, one case of PRES was reported. Should a ZEPOSIA-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 in 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, treatment with ZEPOSIA should be discontinued.

5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Drugs

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

5.10 Severe Increase in Disability After Stopping ZEPOSIA

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

5.11 Immune System Effects After Stopping ZEPOSIA

After discontinuing ZEPOSIA, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)]. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA [see Drug Interactions (7.1)].
7 USE IN SPECIFIC POPULATIONS

7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

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Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a (Pooled Study 1 and Study 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ZEPOSIA 0.92 mg (n=882)</th>
<th>IFN beta-1a 30 mcg Intramuscularly Once Weekly (n=885)</th>
<th>Studies 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infection*</td>
<td>26 23</td>
<td>0 0</td>
<td>10</td>
</tr>
<tr>
<td>Hepatic transaminase elevation**</td>
<td>10 10</td>
<td>5 5</td>
<td>4</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>4 3</td>
<td>2 2</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 3</td>
<td>2 2</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 3</td>
<td>2 2</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 2</td>
<td>2 2</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2 1</td>
<td>1 1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.
** Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, upper respiratory tract infection, rhinorrhea,trakhesi, and laryngitis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women. In animal studies, administration of ozanimod during pregnancy produced adverse effects on development, including embryolethality, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity. In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures (see Data). The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

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

Oral administration of ozanimod (0.2, 0.1, or 0.5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/delayed ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. At the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Oral administration of ozanimod (0.2, 0.6, or 2.0 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality at the highest dose tested and increased fetal malformations ( malformed blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, plasma ozanimod exposure (AUC) was approximately 2 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0.2, 0.7, or 2 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycle) and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day) for adverse effects on pre- and postnatal development, plasma ozanimod exposure (AUC) was 30 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

Following oral administration of ozanimod, ozanimod and/or metabolites were detected in the milk of lactating rat at levels higher than those in maternal plasma.
Risk of Infections
Advising the patient to read the FDA-approved patient labeling (Medication Guide).

8.3 Females and Males of Reproductive Potential

Contraception
Before initiation of ZEPOSIA treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for contraception during treatment with ZEPOSIA [see Use in Specific Populations (8.1)]. Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing age should also use effective contraception for 3 months after stopping ZEPOSIA.

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

8.5 Geriatric Use
Clinical studies of ZEPOSIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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 Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of the ozanimod major active metabolites is unknown [see Clinical Pharmacology (12.3)]. Use of ZEPOSIA in patients with hepatic impairment is not recommended.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Oral administration of ozanimod (0, 8, 25, or 80 mg/kg/day) to Tg.rasH2 mice for 26-weeks resulted in an increase in hemangioma and hemangiosarcoma (combined) in males and females at the mid and high doses tested.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to rats for 2 years resulted in no increase in tumors. At the highest dose tested (2 mg/kg/day), plasma exposure (AUC) for ozanimod was approximately 100 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Mutagenesis
Ozanimod was negative in a battery of in vitro (Ames, mouse lymphoma tk) and in vivo (rat microincus) assays. Metabolite CC112273 was negative in in vitro (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an Ames assay, and positive in an in vivo chromosomal aberration assay in human (TK6) cells but negative in an in vivo rat microincus/comet assay.

Impairment of Fertility
Oral administration of ozanimod (0, 0.2, 2, or 30 mg/kg/day) to male and female rats prior to and during mating and continuing through gestation day 7 resulted in no adverse effects on fertility. At the highest dose tested (30 mg/kg/day), plasma ozanimod exposure (AUC) was approximately 1600 times that in humans at the maximum recommended human dose (MRHD) (0.92 mg/day); plasma AUCs for metabolites, CC112273 and CC1084037, at 30 mg/kg/day were 13 and 3 times, respectively, those in humans at the MRHD.

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Infections
Inform patients that they may be more likely to get infections, some of which could be life-threatening, when taking ZEPOSIA and for 3 months after stopping it, and that they should contact their healthcare provider if they develop symptoms of infection [see Warnings and Precautions (5.1)]. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection. Advise patients that some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with ZEPOSIA. If immunizations are planned, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA. 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 ZEPOSIA.

Cardiac Effects
Advising patients that initiation of ZEPOSIA treatment may result in a transient decrease in heart rate. Advise patients to contact their healthcare provider if they develop worsening heart rate, a decrease in heart rate exceeding 20% of their baseline, or a heart rate less than 50 bpm.

Liver Injury
Inform patients that ZEPOSIA may increase liver enzymes. Advise patients that they should contact their healthcare provider if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urines [see Warnings and Precautions (5.3)].

Pregnancy and Fetal Risk
Inform patients that, based on animal studies, ZEPOSIA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with ZEPOSIA and for 3 months after stopping ZEPOSIA. Advise a female patient to immediately inform her healthcare provider if she is pregnant or planning to become pregnant [see Warnings and Precautions (5.4)].

Respiratory Effects
Advise patients that they should contact their healthcare provider if they experience new onset or worsening dyspnea [see Warnings and Precautions (5.6)].

Macular Edema
Advise patients that ZEPOSIA may cause macular edema, and that they should contact their healthcare provider if they experience any changes in their vision. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema may be increased [see Warnings and Precautions (5.7)].

Posterior Reversible Encephalopathy Syndrome
Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological consequences [see Warnings and Precautions (5.8)].

Severe Increase in Disability After Stopping ZEPOSIA
Inform patients that severe increase in disability has been reported after discontinuation of a S1P receptor modulator like ZEPOSIA. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of ZEPOSIA [see Warnings and Precautions (5.10)].

Immune System Effects After Stopping ZEPOSIA
Advise patients that ZEPOSIA controls to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3 months after the last dose [see Warnings and Precautions (5.11)].

Manufactured for: Celgene Corporation
Summit, NJ 07901
Patent: www.celgene.com/therapies
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ZEP_HCP_BSV.001.05 03/2020
Holding On to Hope in Huntington Disease

BY DANIEL O. CLAASSEN, MD, MS

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50  The State of Coma Care: A Call for Action

BY WENDY ZIAI, MD, MPH
Down, but Not Out: Forging Forward in Neurology

NEUROLOGISTS, PARTICULARLY THOSE WHO CARE for patients with rare and complex diseases, are all too familiar with therapeutic failures in both treatment and development. On one hand, patients with conditions such as migraine and epilepsy can be burdened with refractory disease that can prove challenging to treat. On the other, those treating disorders such as Alzheimer disease have witnessed numerous therapies fail to reach their potential as they moved through the pipeline.

The latter sentiment has been felt very recently by the Huntington disease community, which was met with the harsh news of 2 clinical development programs discontinuing in March of this year. Despite the disappointment of these therapies not making it through to a possible approval, there remains much hope to hold on to in the field, as Daniel Claassen, MD, MS, highlights in this issue’s cover story on page 30. He notes that even with these programs falling short, there is much to be learned and more to come for those with Huntington disease.

Although the Alzheimer disease community has experienced similar failures and challenges in efforts to develop a disease-modifying therapy, after many years, their patience has been rewarded. The recent approval of aducanumab has reinvigorated and reenforced hope for the future of treatment, though this has not come without debate. As such, on page 38, a number of experts in the care of those with Alzheimer disease shared their opinions on the approval and the potential impacts it may have on the field for years to come.

Another aforementioned disease, epilepsy, has experienced the approval of a number of landscape-shifting agents in recent years. Specifically, the introduction and adoption of novel delivery platforms have allowed for a revamping of the approach to seizure emergency situations for both patients and physicians. This is detailed with insight from epilepsy experts Jacqueline French, MD, and Orrin Devinsky, MD, in our feature story on page 43.

This issue of NeurologyLive® also features a call to action from Wendy Ziai, MD, MPH, about the state of coma care on the heels of the first World Coma Day. She shares her insight into the work being done by the Neurocritical Care Society and its Curing Coma Campaign, as well as current and future scientific efforts devoted to curing disorders of consciousness, on page 50.

As we strive to keep you abreast of the latest research and tools to improve your clinical practice, we always welcome your feedback. If you have any comments or thoughts about our coverage or would like to contribute to NeurologyLive®, please email managing editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences™
Do We Finally Have a Useful “Sed Rate” for Multiple Sclerosis?

By Mark Freedman, MD, MSc, HBSc, CSPQ, FANA, FAAN, FRCPC

FOR THE LONGEST TIME, the only somewhat predictable marker for monitoring multiple sclerosis (MS) and offering something in the way of prognosis has been MRI. However, MRI typically looks only at the head and perhaps the cervical spine (missing the optic nerves and the rest of the spinal cord), has its greatest predictability in the early stages of MS and loses its predictability with length of disease, and cannot be used with any degree of accuracy to monitor response to therapy with disease-modifying treatments (DMTs). MRI is also fraught with differences in image acquisition from one machine to another, slice thickness, and even orientation in the scanner, making it problematic to compare one set of images to another in time, causing the “noise” or heterogeneity contributing to inaccuracy. The utility of MRI was validated in clinical trials where strict adherence to all the previously mentioned factors led to a significant reduction in this noise—a far cry from real life. Could a simple blood test be found that is measured in a standardized fashion to inform on prognosis and response to therapy similar to the erythrocyte sedimentation rate used for years by rheumatologists?

The call has been answered with the measurement of neurofilament light chain (NfL), which is found within neurons and axons and, when measured in the blood or spinal fluid, results from neuro-axonal injury. In that sense, it is nonspecific and any cause for neuro-axonal injury could lead to an increase in this measured marker. However, in a situation such as MS, uncomplicated with other nervous system comorbidity, it can reflect the amount of damage that is arising from that disease. It is first released into cerebrospinal fluid (CSF) but eventually leaks out into the periphery, where it can be measured in blood or serum, albeit at ~1/500 the CSF concentration. Although, in the serum, NfL can remain increased for several months. This is important, since a spot measurement does not necessarily reflect real-time damage but accumulated damage that may have occurred within a few months of the measurement, drawing a similarity with the hemoglobin A1 measurement used by endocrinologists to look at glycemic control in diabetics.

Many laboratories are now offering the specialized technology to measure NfL in the serum/blood using the SiMoA (single molecule assay) analytical method. These machines are now commercialized and standardized and able to measure NfL accurately in the serum well within the picogram range. Since the amount of NfL reflects neurological injury, it is not surprising that it has been studied in virtually all neurological conditions, such as the neurodegenerative diseases (eg, motor neuron disease, dementia, Parkinson disease), where levels can be confounded by the effects of age, which itself leads to serum increases, but typically not until age 60. That is why most of the research has been in MS, where patients are typically young and devoid of other conditions that might confound measurements.

We have shown that baseline measurement of serum NfL, when a patient presents with their disease for the first time, is a predictor of disease progression some decades later, and finding such levels might lead a neurologist to choose a higher-efficacy DMT to start. Studies now...
reveal that following NfL levels over time might predict patients who will relapse or show early progression, prompting, perhaps, a change in therapy.³ Serum NfL has even been more predictive of longer-term MRI changes, such as brain atrophy, than MRI itself.³ Serum NfL is now included as an outcome measure in all ongoing clinical trials for DMT in MS and, similar to MRI, all successful and approved therapies to date have demonstrated an ability to lower serum NfL levels. Some therapies’ efficacies are now being judged on the magnitude to which they lower NfL levels,⁷ the greatest being autologous hematopoietic stem cell transplantation.⁸ It may also be reflective of ongoing progression once patients are in the progressive phase of their illness.⁹

MRI is costly and time-consuming and, with all its inaccuracies, it has become difficult to use it as a guide to treatment response. Most accurate measurements are performed in the brain, but most progression tends to come from spinal cord lesions that are not accurately measured. Additionally, it is not clear what sort of change over time on the MRI would dictate a change in therapy. We have cautiously advised that if more than 3 new lesions develop over the course of a year on DMT, that alone might be cause for a change in therapy because such data come from group analyses that are difficult to apply to an individual.¹⁰ Serum NfL is also fraught with a similar problem in that we know that elevations indicate new levels of damage, but what sort of level change is important for an individual patient, since once again, all of the data have come from group analyses.

All agree that having a simple, standardized serum biomarker to measure disease activity would offer the greatest utility in treating a medical condition such as MS, which now has a variety of graded therapies available. I would argue that serum NfL is the closest we have to such a marker, and the sooner we all adopt it as our own “sed rate,” the more we will realize its utility.

REFERENCES
NeurologyLive’s® Future Leaders in Neurology seeks to connect the next generation of up-and-coming neurologists, advanced practice providers, and other healthcare professionals with individuals who have cultivated a range of clinical experiences.

Watch On-Demand Now: The Ever-Changing Face of MS
Featuring Ahmed Obeidat, MD, PhD; Hesham Abboud, MD, PhD; and Rana K. Zabad, MD

VISIT NEUROLOGYLIVE.COM/LEADERS-IN-NEUROLOGY TO LEARN MORE OR SCAN THE QR CODE BELOW
**Epilepsy Foundation and Eisai Partner to Develop Novel Patient Platform**

By Matt Hoffman

The Epilepsy Foundation announced this week that it has entered into a collaboration with Eisai to develop a novel platform for individuals with epilepsy, dubbed EDEN (Epilepsy Digital Experience Navigator).1

The aim, according to the foundation’s announcement, is to provide these patients, their caregivers, and their clinicians with an improved method of data utilization for a smoother journey with the disease. The Epilepsy Foundation said it plans to have EDEN up and running by the fall.

The EDEN platform is anticipated to enable those with epilepsy to easily connect to their care, as well as have access to resources and information individualized to their experience. The platform will collect and analyze patient medical records, and survey responses and data from connected devices to develop real-world insights for clinical research in an effort to support development of novel treatments and other care innovations for the epilepsy community.

“The Epilepsy Foundation is committed to shaping the future of epilepsy research and leveraging technology to create greater efficiency in epilepsy care and treatment,” Jacqueline French, MD, chief medical and innovation officer, Epilepsy Foundation, said in a statement. “Getting the right information to the right person at the right time is critical for successfully managing epilepsy. Our collaboration with Eisai empowers people with epilepsy to successfully manage their condition while contributing to research that we hope can help improve standards of care in the future for people living with epilepsy.”

EDEN is planned to be powered by the technology platform developed by Embleema, a regulatory-grade health data platform that utilizes blockchain. Embleema will capture clinical and real-world data, driven by patients and, according to the announcement, “continuously delivers insights to multiple care and research stakeholders,” which may help improve outcomes by streamlining the data interpretation process. Robert Chu, chief executive officer, Embleema, noted in a statement that the company was “delighted” to be part of the collaboration.

“For the first time, patients will be able to directly contribute to research by continuously sharing rich real-world insights with stakeholders in a fully remote and consented manner, while at the same time benefit from personalized digital services to better manage their condition,” Chu said.

According to Embleema, EDEN will provide those with epilepsy a way to stay on top of their disease both at home and on their mobile devices. The company noted that it prioritizes patient needs first, aiming for them to be “an equal voice in research” and able to receive multiple benefits from that research. EDEN, it notes on its website, was designed and developed fully based on patient feedback to build a system around those who will use it and derive the benefit from it.1

“At Eisai, everything we do is guided by our human healthcare mission, putting patients and their families first while we also listen and learn from them. We seek to enable people to live their fullest lives and continue to pursue the creation of solutions based on scientific evidence to help them achieve this,” Ivan Cheung, chairman, and global president, Neurology Business Group, Eisai, said in a statement. “Partnering with the Epilepsy Foundation on the launch of EDEN continues our commitment to patients and families in the epilepsy community, as we together pursue and advance new epilepsy solutions.”

**FDA Gives Trial Go-Ahead for Huntington Disease Gene Therapy**

By Marco Meglio

Voyager Therapeutics has received FDA clearance for its investigational new drug (IND) application for VY-HTT01, a gene therapy candidate for the treatment of Huntington disease (HD), and may proceed with its planned phase 1/2 clinical trial, according to a recent announcement.1

Voyager submitted the IND for the drug in September 2020 and was notified a month later that it had been placed on clinical hold pending the resolution of certain chemistry, manufacturing, and controls (CMC) matters.2 Upon full comprehensive review of those CMC matters, the FDA felt the company could proceed. The trial, named VYTAL, is a dose-escalation study to evaluate the safety and tolerability of VY-HTT01 in patients with early manifest HD and is set to be initiated this year.

“The decision by the FDA regarding our IND application for VY-HTT01 for Huntington disease represents an important milestone for Voyager and is the result of years of commitment to developing an impactful new therapy to address this devastating disease,” Andre Turenne, president and chief executive officer, Voyager, said in a statement.1

The gene therapy is made up of an adeno-associated virus capsid (AAV1) designed to reduce the expression of huntingtin (HTT), thereby altering disease progression. It is also made up of a proprietary transgene that harnesses the canonical RNA interference pathway to selectively knock down levels of HTT messenger RNA (mRNA).

At the 2018 Congress of the European Society of Gene and Cell Therapy (ESGCT), the company revealed that VY-HTT01 reduced HTT mRNA on average by 68% in the caudate, 67% in the putamen, 73% in the thalamus, and 32% in the cortical neurons among adult nonhuman primates.3

“Our investigational gene therapy has been designed to achieve broad knockdown of HTT mRNA throughout the brain via a onetime MRI-guided neurosurgical delivery,” Omar Khwaja, MD, PhD, chief medical officer and head of research and development, Voyager, said in a statement.1 “We are thrilled to be collaborating with leading experts in Huntington disease and neurosurgical delivery of gene therapies as we begin the planned evaluation of our promising candidate.”

HD is a fatal, inherited neurodegenerative disease that results in the progressive decline of motor, cognitive, and behavioral functions.
For more on aducanumab’s approval, go to page 38.

For a full list of references, see the article on NeurologyLive.com.

JOURNAL ROUNDPUP

Lecanemab Clears Amyloid in Alzheimer Disease Over 18 Months
By Marco Meglio

Data from Study 201 (NCT01767311), a phase 2b proof-of-concept clinical trial, showed that treatment with BAN2401, now known as lecanemab (Eisai and Biogen), demonstrated a reduction in brain amyloid accompanied by a consistent reduction of decline across several clinical and biomarker end points in patients with mild cognitive impairment (MCI) due to Alzheimer disease (AD) or Alzheimer dementia.1,2

Senior author Jeffrey L. Cummings, MD, ScD, director emeritus, Lou Ruvo Center for Brain Health, Cleveland Clinic; and vice chair, department of brain health, University of Nevada, Las Vegas, and colleagues conducted a Bayesian design clinical trial randomizing patients to lecanemab (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly) or placebo.

They identified 10 mg/kg biweekly as the effective dose 90% (ED90), defined as the simplest dose that achieves greater than or equal to 90% of the maximum treatment effect at the 12-month final Bayesian analysis. At 18 months, 10 mg/kg biweekly lecanemab had a 76% probability of achieving 25% less decline on the primary end point, the change on the Alzheimer’s Disease Composite Score (ADCOMS), than placebo.

Achievement of primary end point required 80% probability, though additional prespecified Bayesian analyses indicated a 97.6% and 97.7% probability of the 10-mg/kg lecanemab being superior to placebo by any magnitude at both 12 and 18 months, respectively. All dose-dependent reductions in amyloid positron emission tomography (PET) standardized uptake value ratio (SUVR) measures were observed using florbetapir as the imaging agent and whole cerebellum as the reference region. At 18 months, the least squares (LS) mean changes from baseline to whole cerebellum mask were −0.306 for 10-mg/kg biweekly lecanemab.

“Amyloid-beta aggregates are thought to be more toxic than monomers, and we hypothesized that reducing these could represent an effective treatment approach in early stages of Alzheimer disease,” Cummings said in a statement. “These results from lecanemab’s phase 2b clinical trial are encouraging and the scientific community is looking forward to learning more in the phase 3 studies, Clarity AD and AHEAD 3-45, currently under way.”

The aforementioned Clarity AD phase 3 clinical trial (NCT03887455) is a placebo-controlled, double-blind parallel-group, 18-month study with an open-label extension phase that will confirm the safety and efficacy of lecanemab in individuals with early AD. In March, the company completed enrollment for the study, with 1795 symptomatic patients included.

Eisai and Biogen, in conjunction with the Alzheimer’s Clinical Trials Consortium (ACTCT), launched their other study, AHEAD 3-45, in July 2020.3 It aims to enroll 1400 participants with preclinical AD who will be treated with lecanemab for 216 weeks. A common screening period will be conducted, after which patients will be randomized to 1 of 2 trials: A3 and A45.
In the conventional analyses of Study 201, 10 mg/kg biweekly treatment showed dose-dependent reduction in change from baseline in ADCOMS over 18 months, with 30% \((P = .034)\) less decline than placebo. Additionally, the same dose group had 26% less decline on Clinical Dementia Rating scale Sum of Boxes (CDR-SB; \(P = .125\)) and 47% less decline on Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14).

Numerical differences from placebo were noted as early as 6 months and were maintained over the 18 months of treatment. Investigators also noted a marginally greater hippocampal volume reduction (7.56% increased volume decline) was observed at 10-mg/kg biweekly compared with placebo without nominal significance. An increase in cerebrospinal fluid (CSF) amyloid-beta-42 (Aβ-42) and decrease in p-tau relative to placebo were observed in the 10-mg/kg dose arm, whereas inconsistent results were noted at 12 months and 18 months for total tau.

Amyloid-related imaging abnormalities-edema/effusion (ARIA-E) rates were below 10% at the highest doses for the overall population and at 14.3% for apolipoprotein E4-positive subjects. Other than ARIA-E, the most common treatment-emergent adverse events (TEAEs) were infusion reaction. Aside from ARIA-Es, the incidence rates of adverse events (AEs), serious AEs, and TEAEs were consistent with those expected for this population and similar across placebo and lecanemab groups.

“For these supportive findings from the lecanemab phase 2b study and the initiation of 2 phase 3 studies are exciting for the field and provide the opportunity to further explore the key role of the amyloid-beta pathway in the pathophysiology of Alzheimer disease,” Michael Irizarry, MD, vice president, deputy chief clinical officer, Neurology Business Group, Eisai, said in a statement.

VNS System Proves Effective for Post Stroke Upper Extremity Impairment
By Marco Meglio

In a recently published randomized, controlled clinical trial in Lancet Neurology, MicroTransponder’s Vivistim Paired Vagus Nerve Stimulation (VNS) System showed 2 to 3 times the improvement in upper extremity motor impairment and function in patients up to 10 years post stroke compared with controls who received intense rehabilitation alone.1,2

Among 108 patients randomly assigned to treatment (VNS group, \(n = 53\); control group, \(n = 55\)), the mean Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score increased by 5.0 points (standard deviation [SD], 4.4) in the VNS group on the first day after completion of in-clinic therapy compared with 2.4 (SD, 3.8) points in the control group (between group difference, 2.6 [95% CI, 1.0-4.2]; \(P = .0014\)).

“This is the first study to find clinically and statistically significant effects of a neuromodulation therapy for people with arm and hand weakness after chronic stroke,” Jesse Dawson, MD, BSc, professor of stroke medicine, University of Glasgow, said in a statement. “We saw improvement for the VNS group in both impairment and functional measures compared to controls. In particular, the clinically meaningful response rate doubled with paired VNS for both impairment and functional outcomes.”

The Vivistim Paired VNS System stimulates, as the name implies, the vagus nerve during task-specific rehabilitation. Stimulation of the vagus nerve has been shown to trigger the release of brain neuromodulators including acetylcholine and norepinephrine that strengthen motor circuits associated with movement, enabling the brain to effectively relearn the task.

Patients in the VNS group received 0.8-mA, 100-μs, 30-Hz stimulation pulses, lasting 0.5 seconds, whereas those in the control group received 0-mA pulses. Each patient received 6 weeks of in-clinic therapy, 3 times per week, totalizing 18 sessions, followed by a home exercise program. After 90 days of in-clinic therapy, a clinically meaningful response on the FMA-UE score was achieved in 23 (47%) of 53 patients in the VNS group compared with 13 (24%) of 55 patients in the control group (between group difference, 24% [95% CI, 6-41]; \(P = .0098\)).

The Wolf Motor Function Test (WMFT)-Functional score was significantly increased in the VNS group compared with the control group at 90 days after the end of in-clinic therapy (0.5 [SD, 0.4] vs 0.2 [SD, 0.3]; between group difference, 0.30 [95% CI, 0.16-0.43]; \(P < .0001\)). In a post hoc analysis, 30 of 53 (57%) of participants in the VNS group achieved a clinically meaningful response on the WMFT-Functional test, compared with 12 of 55 (22%) patients in the control group (\(P < .0001\)).

At least 1 adverse event (AE) occurred in 81% (43 of 51) and 76% (42 of 55) of patients in the VNS group and control group, respectively. There were 3 serious AEs in 2 (4%) participants in the VNS group (1 each of urinary tract infection, hyponatremia, and insomnia), and 2 severe AEs in 2 (4%) participants in the control group (1 headache and 1 syncope). No deaths were reported and none of the serious AEs was related to treatment device.

There were no unexpected AEs or serious AEs reported associated with the device. Investigators noted that there was 1 case of vocal cord palsy following device implantation in a control participant, which was resolved after 5 weeks.

“The results of this clinical study suggest that the addition of VNS enhances the effect of best practice stroke rehabilitation. It is also important to note that our physical and occupational therapists were able to easily incorporate the Vivistim System with intense rehabilitation, which was resolved after 5 weeks.”

Teresa Kimberley, PhD, PT, director, Brain Recovery Lab, MGH Institute of Health Professions, said in a statement.
TOP TWEETS

AASM Membership
@AASMmembership
AASM member Dr. William Noah discussed his practice’s recent study into patient adherence to PAP therapy with @neurology_live.
READ MORE: neurologylive.com/osa-testing

NIH Toolbox
@NIHToolbox
Richard Gershon, PhD, vice chair for research at @NUFeinbergMed sits down with @neurology_live to discuss the dissemination of the Mobile Toolbox and its aim for early detection of cognitive impairment.
READ MORE: neurologylive.com/cognitive-trajectory

Jill Dehlin, RN
@jdehlin
Spoke with @AmaalStarlingMD for @neurology_live about #migraine, use of empowering language, and #advocacy. Here’s a sneak peek: @NHF @CoalitionCHAMP.
VIEW VIDEO: neurologylive.com/migraine-advocate

UNMC Department of Neurological Sciences
@UNMC_neurology
DONS Professor Dr. Rana Zabad was recently part of a @neurology_live webcast titled: The Ever-Changing Face of MS: The Evolving Diagnostic Criteria for Multiple Sclerosis.
VIEW VIDEO: neurologylive.com/ms-face

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NEUROLOGYLIVE VIDEOS

EXPLORING NEW WAYS OF USING RESPONSIVE NEUROSTIMULATION IN EPILEPSY
Vineet Punia, MD, MS, neurologist, Cleveland Clinic, offered insight into the areas where he believes responsive neurostimulation could provide benefit to patients who need further examination.
+ VIEW VIDEO neurologylive.com/punia-stim

LEAVING A NEBULOUS STATE OF CARE FOR PATIENTS WITH NMOSD
Bruce Cree, MD, PhD, clinical research director at the UCSF Multiple Sclerosis Center, shared some of the takeaways from his research for the clinical community of specialists treating patients with neuromyelitis optica spectrum disorder.
+ VIEW VIDEO neurologylive.com/cree-nmosd

PROBLEM RECOGNITION: CEREBRAL PALSY DIAGNOSIS
Bhooma Aravamuthan, MD, DPhil, assistant professor of pediatric neurology, Department of Neurology, Washington University in St Louis, discussed a survey of child neurologists and neurodevelopmentalists regarding their inclusion in the diagnosis of cerebral palsy, and the current status of care.
+ LISTEN neurologylive.com/mm-ep-33

ZAVEGEPANT AND THE GEPANT CLASS FOR MIGRAINE CARE
Elyse Stock, MD, chief medical officer, Biohaven Pharmaceuticals, and Thomas Shiovitz, MD, director of California Neuroscience Research, discussed the recently initiated phase 2/3 clinical trial of zavegepant, an oral CGRP-targeting agent for the prevention of migraine developed by Biohaven.
+ LISTEN neurologylive.com/mm-ep-36
Rimegepant Is Safe for Those With Prior Triptan Failures

By Marco Meglio

DATA FROM A LONG-TERM, open-label safety study (NCT03266588) of adults with migraine and a history of triptan treatment failure revealed that long-term treatment with rimegepant 75 mg (Nurtec ODT; Biohaven) up to once daily is safe and well tolerated.¹

Kathleen B. Mullin, MD, medical director, clinical research, New England Institute for Clinical Research, presented the data at the 2021 American Academy of Neurology Annual Meeting, April 17 to 22. A total of 1800 individuals with 4 to 14 severe monthly migraine attacks were assigned to scheduled dosing of rimegepant 75 mg every other day for 12 weeks supplemented by as-needed dosing on nonscheduled dosing days. Of those, 546 (30.3%) had a history of treatment failure with 1 triptan and 246 (13.7%) had failed 2 or more triptans.

Upper respiratory tract infection (1 triptan: 9.5%; ≥ 2 triptans: 8.9%), nasopharyngitis (1 triptan: 7.9%; ≥ 2 triptans: 8.1%) and sinusitis (1 triptan: 4.6%; ≥ 2 triptans: 8.1), were among the most common adverse events (AEs) observed.

A total of 1.6% and 2.0% of patients who had a history of treatment failure with 1 or 2 or more triptans discontinued rimegepant treatment because of AEs, respectively. Serious AEs occurred in 3.7% of subjects who had a history with 1 triptan failure, compared with 2.4% of those with at least 2 or more. None of these was considered to be related to treatment with rimegepant.

Mullin published data in January 2020 that explored the use of rimegepant in patients with refractory migraine. Among the 2 patients included in the cohort who experienced suboptimal response to medication, concomitant use of rimegepant and erenumab (Aimovig; Amgen) was shown to effectively treat this patient group.²

Rimegepant, an orally administered small molecule calcitonin gene–related peptide (CGRP) receptor antagonist, was used for 6 months prior to initiating 70-mg erenumab monthly in patient 1 and was used for 60 days before beginning 140-mg erenumab monthly in patient 2. This was the first clinical report documenting that 2 CGRP therapies can be used this way. Although the data were an exciting first step, Mullin and colleagues noted at the time that “the mechanism underlying the benefits of concomitant use of a small molecule CGRP receptor antagonist and an anti-CGRP receptor antibody is unknown and requires further study.”

In October 2020, Biohaven announced that its supplemental new drug application for rimegepant for the prevention of migraine had been accepted by the FDA, with a planned Prescription Drug User Fee Act action date set for the second quarter of 2021.³ The CGRP tablet was originally approved in a 75-mg dose for the acute treatment of migraine in February 2020, marking the first approval for Biohaven.⁴ If approved for this second indication, rimegepant would be the first and only CGRP targeting therapy with indications for both preventive and acute treatment of migraine.
COVID-19 Treatment Disparities and Neurologic Complications Are Clarified

By Victoria Johnson

THIS YEAR’S HOT TOPICS PLENARY SESSION at the 2021 American Academy of Neurology Annual Meeting, April 17 to 22, focused on neurological implications of COVID-19 and the data that have been collected to this point, more than a year into the pandemic.

The plenary was hosted by Natalia Rost, MD, MPH, FAAN, FAHA, chief, Stroke Division, Department of Neurology, and associate director, Massachusetts General Hospital Comprehensive Stroke Center; and professor, Harvard Medical School; along with Paul George, MD, PhD, MSE, assistant professor, neurology & neurological sciences, Stanford Medicine.

It opened with a question-and-answer session with Anthony Fauci, MD, director, National Institute of Allergy and Infectious Diseases, and chief medical adviser to the president, and Walter Koroshetz, MD, director, National Institute of Neurological Disorders and Stroke, before moving on to 4 presenters.

Fauci weighed in on the question of getting back to a prepandemic “normal,” noting that “as we get to the overwhelming majority of the population vaccinated, you are going to see a rather strong turning toward what you would consider much more normal than what [we] are living through right now.” He also speculated on the spectrum of disease severity that has been observed with COVID-19 and said that its wildly differing effects on the population, with some experiencing no symptoms while others are dying, are still not well understood.

Another issue the pandemic has highlighted, Fauci said, is the disparities in health care among demographics. He discussed some actions the federal government is taking to address these, including setting up community vaccine centers.

In response to a question on transmission risk, Fauci explained that studies are being conducted to clarify transmission of the virus in both asymptomatic and vaccinated people. He also stated his belief that antiviral therapies will be developed that will be able to efficaciously treat COVID-19.

Koroshetz endorsed the neurological safety of COVID-19 vaccines, stating that “the question of vaccines and different neurological conditions has been studied over the years. We don’t have any real concerns about the COVID vaccine being any different.” He also discussed the early neurological effects of COVID-19, including penetration of olfactory and endothelial cells, as well as the increasing visibility of chronic fatigue syndrome in people who have had COVID-19, an area that needs more research. He also praised the rise of technological innovation during the pandemic and shared his optimism on the development of vaccines for other conditions, such as the Epstein-Barr virus.

As Fauci and Koroshetz left, Sherry Chou, MD, MMSC, FNCS, associate professor, critical care medicine, neurology, and neurosurgery, University of Pittsburgh, began the first presentation by comparing the COVID-19 pandemic to the 1918 influenza pandemic. She discussed the debated origins of the 1918 encephalitis lethargica epidemic and how the phenomenon, following the 1918 flu, may be similar to neurological syndromes resulting from COVID-19. She outlined various causes of brain injury, including hypoxia, prolonged steroid, and paralytic use for mechanical ventilation, as well as sedatives.

Chou discussed several studies that have investigated neurological complications with COVID-19, such as acute cerebral vascular diseases, impaired consciousness, and the development of acute encephalopathies with COVID-19 infection. She also mentioned the Global Consortium Study of Neurological Dysfunction in COVID-19 (GCS) that was formed to address and research these complications.

She presented findings from an analysis of the GCS, which consisted of 475 patients. The study found that hospital mortality rate was around 14% in the general cohort, but up to 25% in the cohort with neurological conditions. Similarly, the prevalence of stroke increased from 3.1% to 20% between the general and neurological condition cohorts, and the prevalence of seizure increased 10-fold between cohorts. In addition to those factors, the study found that preexisting neurological disorders and White ethnicity increased one’s risk of developing new neurological signs and disorders by more than 2-fold.

Altogether, “having a clinically verified neurological sign syndrome increased mortality risk by as high as 6-fold in hospitalized COVID-19 patients. Specifically acute encephalopathy, which is the most common phenotype that we saw, increases the mortality risk by 5.5-fold. The risk factors for developing acute neurological signs and syndromes in this cohort include older age, male sex, White race, and specifically having a preexisting neurological disorder was the most important predictor of developing new neurological signs and syndromes,” Chou said during her presentation.

Following Chou’s presentation, Nicte Mejia, MD, MPH, FAAN, assistant professor, neurology, Harvard Medical School, shared her thoughts on disparities in care during the pandemic. “We continue to struggle with a complex web of health, economic, and other societal complications. Critical among them is the amplification of pervasive, longstanding health and health care disparities, including in neurology-marginalized communities around the world [that] continue to face an uneven burden of COVID-19,” she said.

Mejia outlined some disparities, including the fact that in the United States, indigenous Black and Latino communities are twice as likely to contract COVID-19.
as well as twice as likely to be hospitalized for it. Similar associations are seen in people living in poverty. She discussed previous studies that found poorer outcomes in Black patients with COVID-19 and stroke, and posited unequal access to thrombectomy and thrombolysis as a major culprit. Mejia also detailed some larger disparities that are issuing from the COVID-19 pandemic, such as disability, quality of life, medical bankruptcy, and job and housing security. She rallied physicians to combat racism and marginalization and pushed for advances in health care equality. In order to accomplish this, she listed 3 priorities that she believes must be addressed: the creation of a single-payer national health program, medical licensure reform, and rebuilding a stronger and more equal public health infrastructure.4,6

Next, Serena Spudich, MD, MA, professor, neurology and division chief, Neurological Infections and Global Neurology, Yale School of Medicine, discussed neurological syndromes following acute COVID-19. These effects range from muscular complaints to cognitive complaints and mood and psychiatric complaints. “Fortunately, many people survived COVID-19, but it leaves us with the question of what may be happening long term in people who survived the acute illness, and are now living with the consequences,” Spudich said.

Her presentation covered a survey conducted with 4000 respondents from 56 countries that reported mainly cognitive issues, such as speech and language issues, sensation changes like changes of smell and taste, and a variety of psychiatric syndromes. Another abstract, presented at AAN 2021 by Lindsay McAlpine, MD, Yale School of Medicine, reported that stroke in younger patients was associated with inflammation and endothelial activation or endothelial apathy.7

Other studies led Spudich to posit that patients with underlying neurological syndromes may have altered immune responses to SARS-CoV-2 infection. She discussed a few case studies, as well as a study being conducted at Yale that is looking at effects of COVID-19 infection in patients with HIV infection.

“One of the key takeaway messages here is there’s not a single entity of a post-COVID neurological syndrome. After COVID, there’s actually a panoply of different syndromes that may have similar etiologies or may have actually distinct etiologies,” Spudich said.

The last presentation of the session was given by Igor Koralnik, MD, FAAN, neuroinfectious disease, Northwestern Medicine, who discussed different COVID-19 and antibody tests. Early COVID-19 tests, he said, were not well calibrated to mild disease cases, and while sensitivity has been much improved since then, tests are not perfect. Commercial antibody tests also have varying sensitivities to different levels of COVID-19 infection severity and may not accurately reflect SARS-CoV-2 immunity.

“The take-home message is that there’s really no gold-standard test for SARS-CoV-2 infection in individuals with mild disease,” Koralnik said. He discussed several studies, including the Post-Acute Sequelae of COVID-19 (PASC) study, which has so far found that patients with long-term effects of COVID-19 have T cells that respond to SARS-CoV-2 spike proteins, while asymptomatic and patients with previous infection without long-term effects do not.

Koralnik also discussed different responses to COVID vaccines. He discussed positive results seen in the trials of the Pfizer, Moderna, and Johnson & Johnson vaccines in preventing hospitalization and death, as well as incidence of adverse events. He briefly touched on the cases of cerebral venous thrombosis seen in response to the Johnson & Johnson vaccine to say that they are being studied and nothing conclusive has been found, before closing by discussing the trends in vaccine hesitancy and the possible future of vaccine cards and passports.

REFERENCES
Fremanezumab Demonstrates Efficacy and Safety in High-Frequency Migraine

By Marco Meglio

DATA FROM A PAIR OF STUDIES REVEALED that treatment with fremanezumab (Ajovy; Teva Pharmaceuticals) is similarly effective in patients with higher-frequency episodic migraine (HFEM) and moderate-frequency episodic migraine (MFEM), as well as safe for patients with a previous history of cardiovascular (CV) risk.1,2

Both studies were presented at the 2021 American Academy of Neurology Annual Meeting, April 17 to 22, by Stephanie J. Nahas, MD, associate professor, director, Headache Medicine Fellowship Program, Thomas Jefferson University. The data included in both abstracts were from 2 double-blind phase 3 trials (HALO EM, NCT02629861; FOCUS, NCT03308968), which randomized patients 1:1:1 to quarterly fremanezumab, monthly fremanezumab, or placebo for 12 weeks. The first included 1174 patients with episodic migraine (EM), 659 of whom had MFEM and 515 with HFEM at baseline.3

From baseline, least-square mean reductions in monthly migraine days (MMDs) were significantly greater with fremanezumab vs placebo in the MFEM group (quarterly, –3.5 [standard evaluation (SE), 0.35]; monthly, –3.4 [SE, 0.22]; placebo, –1.5 [SE, 0.21]) and HFEM group (quarterly, –4.2 [SE, 0.35]; monthly, –4.7 [SE, 0.35]; placebo, –2.8 [SE, 0.35]; all P < .0009), indicating similar therapeutic gains.

Reductions in monthly headache days were also similar between the MFEM (quarterly, –3.0 [SE, 0.19]; monthly, –2.8 [SE, 0.19]; placebo, –0.8 [SE, 0.18]) and HFEM (quarterly, –3.5 [SE, 0.31]; monthly, –3.7 [SE, 0.31]; placebo, –1.8 [SE, 0.30]) groups. Proportions of patients with greater than 50% reduction in MMDs were also significantly higher with fremanezumab vs placebo in both groups (MFEM: quarterly, 51%; monthly, 50%; placebo, 25%; HFEM: quarterly, 38%; monthly, 42%; placebo, 21%; all P < .0005).

In the second presentation, Nahas and colleagues assessed the CV safety of fremanezumab in patients with EM and chronic migraine (CM) based on CV medical history and CV risk factors (CVRFs).2 Among patients with CV medical history (fremanezumab, n = 325; placebo, n = 153), CV adverse events (CVAEs) occurred in similar low proportions across treatment groups (3%-6%), the most common being hypertension (0%-2%). In comparison with patients without CV medical history (fremanezumab, n = 1572; placebo, n = 792), CVAEs occurred in similar, low proportions of patients across treatment groups (1%-2%).

“This is important because we have theoretical concerns about antagonizing a system that is in part responsible for visual reactivity and cardiovascular and cerebrovascular autoregulation,” Nahas told NeurologyLive®. “If you interfere with that, could you, in theory, be putting somebody at risk for a vascular acute event? Yes, you could.”

Patients with 2 or more CVRFs accounted for 499 of the 2842 pooled population. Of these, 66% had CV medical history. Among patients with ≥2 or ≥3 CVRFs, CVAEs were infrequent (0%-2%). Additionally, no CVAEs were reported in patients with at least 4 or more CVRFs.

“It’s interesting that there were some participants with 4 or more cardiovascular risks and there were no cardiovascular adverse events in that group. That was perhaps a little bit surprising,” Nahas added.

Fremanezumab, an anti–calcitonin gene-related peptide (CGRP), was approved by the FDA in September 2018 for the prevention of migraine in adults. The drug was originally made available for administration via a prefilled syringe indicated for 1-time use. In January 2020, the FDA approved an autoinjector for the delivery of fremanezumab, joining Amgen’s erenumab (Aimovig), and Eli Lilly’s galcanezumab (Emgality) as the anti-CGRP agents on the market available for administration via autoinjector.3

REFERENCES
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.
FOR PATIENTS WITH FIRST SIGNS OF PROGRESSION IN RMS AND ACTIVE SPMS

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.

THE DUAL MOA OF MAYZENT targets S1P1,5—2 key receptors thought to play a role in RMS inflammation and neurodegeneration.

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.

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

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

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

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 syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
IMPORTANT SAFETY INFORMATION (CONT)

Bradycardia and Atioventricular Conduction Delays (cont):
- history or observed at screening, unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class la 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-phototherapy 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.

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


MAYZENT® (siponimod) tablets
0.25 mg - 2 mg

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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 CYP2D6*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 myoclonus infarction, unstable angina, stroke, TIA, uncompensated 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 (SIP) 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 SIP 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 opthalmic 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 Bradycardia 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 uncompensated heart failure requiring hospitalization

• New York Heart Association Class II-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 discontinue treatment of MAYZENT.

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 II] 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 ibudralat 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 reintroduced 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 (7.3)].

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 (FEV1) 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 FEV1 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 FEV1, at 2 years was 2.8% (95% CI: -4.5, -1.0) There is insufficient information to determine the reversibility of the decrease in FEV1 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 FEV1 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-phototherapy 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 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 Ativoventricular 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 (7.7)]
  • 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 of at Least 1% Higher Than in Patients Receiving Placebo)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MAYZENT 2 mg (N = 1099)</th>
<th>Placebo (N = 546)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Transaminase increased</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Falls</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Terms were combined as follows:
- headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.
- hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.
- 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.
- edema peripheral, joint swelling, fluid retention, swelling face.
- bradycardia, sinus bradycardia, heart rate decreased.

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), asthma, 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 (FEV1) 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)].

**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 1a (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, diltiazen), or other drugs that may decrease heart rate (e.g., aprocin, digoxin) [see Warnings and Precautions (5.2) 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., ralimipine) 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 strong 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 CYP3A4 inducers.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Data

Animal Data

When siponimod (0.1, 0.5, 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, only the 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 of 0.5 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 was approximately 18 times that in humans at the recommended human dose of 0.5 mg/day.

When siponimod (0.0, 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 RLD, on a mg/m² basis.

8.2 Lactation

Data

Animal Data

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

Data

Safety and effectiveness in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Oral administration of siponimod (0.5, 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. Neuro-behavioral 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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No Negative Impacts on Cognition Are Observed With Pimavanserin for Dementia-Related Psychosis

By Victoria Johnson

DATA FROM A RECENT REVIEW suggest that patients with neurodegenerative diseases (NDDs) treated with pimavanserin (Nuplazid; Acadia Pharmaceuticals) did not experience negative impacts on cognitive function with up to 9 months of treatment compared with placebo.1

These findings were presented at the 2021 American Academy of Neurology Annual Meeting, April 17 to 22, by Clive Ballard, MD, professor, age-related diseases, and pro-vice-chancellor and executive dean, University of Exeter Medical School. Ballard and colleagues sought to evaluate pimavanserin’s impact on cognition in patients with neuropsychiatric manifestations of NDD across multiple studies.

“Neuropsychiatric symptoms, including psychosis, are common among patients with dementia and are associated with poorer clinical outcomes. No therapies are approved in the United States for treating dementia-related psychosis (DRP). Off-label antipsychotic use is associated with significant adverse outcomes, including accelerated cognitive decline,” Ballard and colleagues wrote in the abstract.

The investigators analyzed cognitive function via the Mini-Mental State Examination (MMSE) that was an outcome in 3 parallel-arm, double-blind studies (019, 032, 046) that compared 34 mg of pimavanserin with placebo as well as the phase 3 randomized withdrawal HARMONY study (NCT03325556). This study consisted of a 12-week open-label phase followed by a randomized double-blind period. There were 697 patients receiving pimavanserin across all studies, and 622 had DRP. Cognition-related treatment-emergent adverse events (TEAEs) were also analyzed.

Ballard and colleagues found that the MMSE score least squares mean (LSM) change from baseline to week 12 was −0.25 (standard error [SE], 0.42) in study 019 and 0.0 (SE, 0.57) in study 032, and similar to placebo in both. LSM change from baseline to week 8 was 1.2 (SE, 0.21; n = 132) for pimavanserin and 0.5 (SE, 0.21; n = 128) for placebo in the interim analysis of study 046.

In the HARMONY study, the mean change from baseline to week 12 was 1.0 (SE, 0.22; n = 145). During the double-blind period, mean MMSE score with pimavanserin treatment did not decline and was similar to placebo. Patients treated with pimavanserin for the whole 9 months of the study (n = 46) had a mean change from baseline of 1.2 (SE, 0.51).

The investigators also found that confusion and memory impairment were the only cognition-related TEAEs reported. These TEAEs were infrequent and occurred at rates similar to placebo.

“Across studies, mean MMSE score changes in pimavanserin-treated patients with NDD were small and were similar to placebo. Cognition-related TEAEs were reported infrequently. Overall, pimavanserin did not have a negative impact on cognitive function with up to 9 months of treatment,” Ballard and colleagues concluded.

Pimavanserin, a selective serotonin inverse agonist and antagonist preferentially targeting 5HT₂₄ receptors, was approved for the treatment of hallucinations and delusions associated with Parkinson disease psychosis in April 2016.2

In April 2021, the FDA issued a complete response letter to Acadia Pharmaceuticals due to deficiencies in its supplemental new drug application (sNDA) filing for pimavanserin for the treatment of DRP. The FDA stated that the treatment cannot be accepted with the sNDA in its current form, citing a lack of statistical significance in some of the subgroups of dementia, and insufficient numbers of patients with certain less common dementia subtypes as lack of substantial evidence of effectiveness to support approval. ■

REFERENCES

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DATA-DRIVEN CATEGORIZATION OF PATIENTS WITH MULTIPLE SCLEROSIS
Daniel Ontaneda, MD, PhD, associate professor of Neurology, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, discussed the findings of his presentation at the AAN Annual Meeting.

View video or scan the QR code: neurologylive.com/ontaneda-categorization
Switch to Siponimod Is Safe and Tolerable With No Washout, Study Finds

By Alicia Bigica

PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS (RMS) looking to switch their disease-modifying therapy (DMT) to siponimod (Mayzent; Novartis) can do so safely and tolerably with no washout period, according to interim results from the ongoing EXCHANGE clinical trial.1

The findings, presented by Amit Bar-Or, MD, FRCPC, at the 2021 American Academy of Neurology Annual Meeting, April 17 to 22, demonstrate that switching to siponimod from other oral or injectable DMTs, including fingolimod and teriflunomide, is associated with a low rate of treatment-related adverse events (AEs).

Approved in March 20192 for the treatment of RMS, including clinically isolated syndrome, relapsing-remitting MS (RRMS), and active secondary-progressive MS (SPMS), siponimod has demonstrated significant clinical benefit through slowed disability progression and improvements in cognitive processing speed.

The phase 3b EXCHANGE clinical trial (NCT03623243) was launched to better understand the requirements for converting to siponimod. The prospective, open-label, single-arm trial has a target enrollment of 400 patients, 100 of whom will be enrolled in a virtual study cohort that includes at-home monitoring via telemedicine. The primary end point is treatment-related AEs over 6 months, with secondary end points of any AE or hospitalization and change in heart rate from baseline to 6 hours post first dose.

This interim analysis included data from 112 patients age 18 to 65 (median, 45.5 years) with advancing RMS, including RRMS (n = 83), SPMS (n = 24), and primary progressive MS (n = 4), with a median Expanded Disability Status Scale score of 3.5. Notably, 42% of participants had 1 or more relapses in the prior 12-month period. Fingolimod was the most common DMT used, followed by glatiramer acetate, dimethyl fumarate, any interferon, and teriflunomide.

Study participants were being treated for at least 3 continuous months with another oral or injectable DMT prior to study enrollment, at which point they underwent conversion to siponimod within 24 hours. Of note, those who were receiving treatment with teriflunomide were required to undergo an 11- to 14-day washout period with cholestyramine or activated charcoal prior to siponimod conversion.

Following conversion to siponimod, 34.8% of patients reported 1 or more treatment-related AEs (95% CI, 26.2-44.5) 4.5% reported 1 or more serious AEs; and 5.4% had 1 or more AE that led to treatment discontinuation. Among those who either completed or discontinued the study (n = 74), 40.5% had at least 1 treatment-related AE (95% CI, 29.5-52.6). SAEs reported include asthenia, MS relapse, noncardiac chest pain, aspiration pneumonia, seizure, and tubulointerstitial nephritis. AEs leading to treatment discontinuation included abnormal behavior, cognitive disorder, peripheral edema, fatigue, insomnia, nausea, pain in extremities, tremor, and vomiting. Treatment-related AEs occurring in greater than 5% of patients included gastrointestinal disorders (8.9%); infections (6.3%); and nervous system disorders, including headache and dizziness (15.2%).

Notably, no meaningful reductions in heart rate were observed from baseline to 6-hours post first dose across the study cohort.

The findings thus far suggest that conversion to siponimod from other oral or injectable DMTs is safe and tolerable. These data will further help characterize important management guidelines for health care providers seeking to switch their patients to siponimod from other DMTs. ■

REFERENCES

More on NEUROLOGYLIVE.COM

ASSESSING WHEN TO TAKE A NONORAL APPROACH TO MIGRAINE

Jessica Ailani, MD, director, MedStar Georgetown Headache Center, spoke to the considerations she makes in determining when patients with migraine may need a nonoral therapy to address their disease.
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Holding On to Hope in Huntington Disease

Despite a few surprising program failures early this year, there is plenty of potential worth holding on to in the Huntington disease pipeline.

By Daniel O. Claassen, MD, MS
Director, Level 1 HDSA Center of Excellence, Vanderbilt University Medical Center

THE DISAPPOINTING NEWS of 2 halted programs reverberated around the Huntington disease (HD) community in late March. Tominersen (Roche), WVE-120101, and WVE-120102 (both Wave Life Sciences) were proposed as antisense oligomer (ASO) treatments for HD patients. These treatments do not currently appear to be viable options for therapy, but for different reasons. It’s difficult to express the profound hype and the hope that accompanied these trials. ASO treatments appear promising for neurologic disease: Nusinersen (Spinraza; Biogen) was approved for the treatment of spinal muscular atrophy, and the videos of children who can now walk are miraculous to see. I was at a European HD program and when watching these videos, I remember a comment from the audience microphone: “Can we imagine a world where HD patients will have a treatment like this?”

Fast forward to 2021, and the mood is—flat. GENERATION-HD (NCT03761849) was a massive undertaking. More than 800 HD patients were intrathecally dosed with tominersen in the phase 3 trial. The global scope of this trial, the speed at which it enrolled, and the effort to methodically follow the protocol were simply astonishing. Participants were dosed initially every 4 or 8 weeks, and later the schedule was amended to every 8 or 16 weeks. There was a lot of enthusiasm about this program, despite the sacrifice involved. The criteria ensured a motor manifest population, rather independent in activities of daily living (ADLs) and without substantial comorbidities.

Reflecting on this undertaking, many of my colleagues (including me) were somewhat nervous about committing to perform this many lumbar punctures (LPs), over such a long period of time. It was amazing how quickly we adapted to this reality. Some of us learned how to use ultrasound-guided LP techniques. We mobilized a diverse set of expertise (neurologists, anesthesiologists, and sometimes even radiologists) to ensure that the LPs and intrathecal delivery would go smoothly. Then there was the massive pressure on the sites when getting started. We received fraudulent phone calls from “interested” physicians who turned out to be nefarious schemers looking for insider trading information on what was in the informed consent, or when the trial was going to start, or what safety concerns could be uncovered. And of course, the phone calls from the families were almost nonstop. We were offered, “I will sell my house, move to Nashville, donate the proceeds of the house to the clinic, if you can get me into the ASO study.” VIPs of the hospital called demanding entry because they knew the provost or someone who was apparently important. This work fell on the coordinators. A clinical research team is only as strong as the sum of the coordinators. The massive effort to arrange complicated screening, MRI, blood work, LPs, drug delivery, dosing, postdosing assessments, overnight stays in the hospital—all of it rested on the shoulders of our coordinators. I have a renewed and sincere respect for our coordinators!

But back to the trial. Phase 1 data from tominersen showed clear reductions in mutant Huntington protein in a dose-dependent level. This nonselective allele approach would also theoretically reduce wild-type huntingtin (Htt) expression (remember, there are 2 alleles: a mutant expanded CAG-repeat and a wild-type allele). A total of 46 patients with early HD were enrolled into the phase 1/2 trial. Treatment with tominersen showed dose-dependent reductions of mHTT protein in the cerebrospinal fluid (CSF), with the greatest reductions recorded in the 2 highest-dose groups (90 mg: 42% reduction; 120 mg: 38% reduction).1 Several
early concerns regarding elevation of neurofilament light chain and increased ventricular size were noted, but the treatment seemed to hit the target.

Perhaps we should have paid more attention to this issue? I remember a question from a young woman at the HDSA convention. She had read the New England Journal of Medicine phase 1 report. She asked, “Should I be worried about the safety of this medication?” The answer from the speaker was an emphatic no.

The Wave program was much earlier in phase, phase 1/2, and took a different approach, using a single nucleotide polymorphism (SNP)–targeted approach to reduce only the mutant Htt protein, leaving the wild-type protein alone. Side by side, the pros and cons of selective or nonselective approach appear to have encouraged a vigorous debate regarding the role of wild-type Htt in neurodevelopment, response to stress, and safety. Several recent reports have emphasized the potential deleterious effects of wild-type Htt reductions, but overall these programs have forced the field to consider what role, if any, wild-type Htt has in humans. This has been a welcome discussion in the field, and one that will continue long after these trials. It appears that Wave has developed a promising method to assess wild-type Htt, and we hope that Roche and others will test this method on their stored samples.

For the Wave program, PRECISION-HD2 (NCT03225846) and PRECISION-HD1 (NCT03225833), intrathecal dosing was every 4 weeks, with similar clinical criteria for inclusion, but these were a dose finding and safety study, respectively (FIGURE). Although the treatments were well tolerated, the results from all participants (n = 88) in the PRECISION-HD2 core trial showed no evidence of a dose response across the dose levels tested. As well, there was no statistically significant change in mutant Htt protein compared with placebo after single or multiple doses of WVE-120102, up to and including 32 mg monthly. The 16-mg dose of WVE-120101 being evaluated in PRECISION-HD1 (n = 51) yielded similar results, and thus Wave elected to halt clinical development.²

The end points of Roche’s GENERATION-HD deserve consideration. It is clear that regulatory agencies around the globe cannot agree what end point is considered useful for HD. The FDA allowed only the Total Functional Capacity (TFC) scale, a crude marker of ADLs in persons with HD. In Europe, a composite end point that includes objective motor (Unified Huntington Disease Rating scale), cognitive, and TFC measurements was accepted as a primary end point. It is fair to say that coming to a global agreement on end points is crucial for rare diseases. However, it’s easier to agree on an end point like COVID-19 infection, but harder for one like disease progression in a neurodegenerative disorder. It does not help patients to have bickering among countries on which end point to pursue. Hopefully, we will see regulatory bodies work in tandem, and not in opposition, for drug development. It’s a tall order, but it would make for better science and an assessment of treatments.

On the topic of end points, there is a movement in neurodegeneration to find better, reliable end points that are quantifiable and not subject to noise. The promotion of quantitative digital biomarkers appears to be a way forward. GENERATION-HD employed a secondary outcome measure assessing digital outcomes. As a global community, we would anticipate data from this study to be publicly available for use in developing better biomarkers of disease progression in HD. There is always tension with private companies collecting data, but allowing for algorithm development, hypothesis testing, and analytic approaches to this vast data set will only help the field.

Of course, one of the substantial questions in neurodegeneration is, when should we intervene? The field of HD needs measures that can identify the earliest symptoms of HD. Longitudinal studies in at-risk HD populations emphasize that the onset of motor symptoms in HD is preceded by decades of cognitive and behavioral symptoms. We typically measure working memory, processing speed, and impulsive behaviors, and see psychiatric symptoms in this premotor stage. However, these symptoms are highly variable and may be influenced by life stress and other environmental factors. Perhaps the use of “cold” cognitive functions, such as attention, working memory, and processing speed, fail to consider cognitive changes that are a response to reward, or emotional responses. What about neurodevelopment? Does HD impact this? If it does, we need new ideas on when to intervene and how to assess progression.

Where Do We Go From Here?
Given the potential issues with outcomes, treatment adverse effects, and patient inclusion, it is not fair to say we should abandon mutant Htt protein reductions. There is no reason, at present, to believe that the pathophysiologic progression of HD is not driven by mutant Htt protein expression. Undoubtedly, a deep dive into the data from GENERATION-HD will allow us to look at patient subtypes, clinical safety, variation in treatment responses, longitudinal clinical progression, and subanalysis on imaging, digital, and other secondary biomarkers. These will be important and help us move forward. For Wave, it appears that there are continued advances in the SNP–targeted therapy, with promise of an improved allele-specific ASO in development. This approach is touted to provide improved drug distribution and efficacy. □
It is worth reminding the community of current and future studies in HD. UniQure is testing the hypothesis that AAV-mediated gene therapy can reduce mutant Htt and is currently in the midst of a phase 1 sham-controlled study. Several other companies, including Voyager and Spark, are pursuing similar approaches. These are invasive treatments, requiring surgical delivery of the AAV virus to the striatum. There are a number of potential impediments to scalability of this method, but the potential benefit of direct-to-striatum delivery appears promising.

Aside from these studies, there are others of interest. One of the more compelling ideas is the concept of somatic instability in HD (increasing CAG repeat number over time). This is now an important treatment target, and companies like Triplet Therapeutics are pursuing therapies that may stabilize this instability. Oral medications offer an important convenience for patients. Here, novel approaches including RNA splicing (PTC Therapeutics) and repurposing of branaplam (Novartis) are in early stages of development. These offer additional opportunities to assess how reductions in mutant Htt will potentially alter the disease course in HD. There are so many diverse approaches to HD, it is honestly hard to keep track. There will undoubtedly be more negative studies, more setbacks, more frustration, but overall, it seems that the clinical research opportunities are vast.

Offering Hope for Our Patients

Soon after we heard the news about GENERATION-HD, we called all our patients in the trial. It was hard to tell them that the trial was stopped. We later learned during the CHDI convention that patients dosed seemed to have worsening cognitive status and greater ventricular size. The sum of these setbacks was much grief, frustration, and disappointment. The dread of a failed trial has left many of us searching for what gives us hope and how we communicate this with our patients. Our team was reminded by a very savvy pediatric neurologist we work with, in a quote from an opinion piece, also published in the New England Journal of Medicine. In this commentary, the author reflects on where patients find hope and how to give difficult news. “This breadth of hopes, ranging from the miraculous to the mundane, reveals the internal architecture of hope—a framework, complete with ceiling, floor, and diverse supporting pillars.”

We have changed the way we talk about clinical trials. Yes, they are important. Yes, getting into trials can be extremely encouraging for patients and families. But trials are not the only source of our hope or the only source of vitality. Our HD families have reminded us that our hope is not necessarily in the immediate promise of disease-modifying treatments, but in things like family, faith, and the support of the HD community. I always find that my HD patients remind me of what is important, and they exemplify resilience in the face of adversity.

About a year before these trials started, my team spent a wonderful night watching a documentary, Why She Smiles, about a young woman who was adopted, and her journey to a diagnosis of HD. There are many films about HD, but this movie hit home as I observed the physical symptoms, grief, emotional turmoil, and altered family dynamics that come with a diagnosis of HD. The directors were students of a local university, and I wrote them a brief note a couple days later. These words seem to ring true now.

The story you tell is the contemporary answer to Thornton Wilder’s, Our Town, where towards the end of that play, it is said, ‘That’s what it was to be alive....To spend and waste time as though you had a million years. To be always at the mercy of one self-centered passion, or another.’

Why She Smiles “offers another perspective. Life doesn’t need to be this way. We can embrace the bone-jarring, tear-filled moments, smiling with a loving kindness—not of this world.”

I think many of us in the HD community feel this way. We will continue to serve this population with steadfast resolve.

REFERENCES

Myostatin Inhibition in Amyotrophic Lateral Sclerosis

By Jennifer S. Sun, PhD

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a fatal neurodegenerative disorder characterized by progressive death of motor neurons, which causes muscle atrophy that results in disability. Although no cure exists for ALS, available therapeutics have focused on managing symptoms to prolong survival and improve quality of life, while experimental treatments for ALS seek to stop or reverse motor neuron damage and muscle atrophy to slow or stop disease progression.

The etiology of ALS is largely unknown; symptoms vary by individual and are dependent on the associated genes and presence of comorbidities. Moreover, these symptoms can initially be subtle and mimic those of other neurodegenerative disorders, making early diagnosis challenging. Approximately 90% of ALS cases are of sporadic origin, whereas 10% are familial. This multifactorial disease has only recently been associated with causative or disease-modifying mutations in 20 genes that encode proteins with diverse functions, including RNA metabolism, vesicle trafficking, proteasomal function, and oxidative stress. Promising ALS therapeutic targets therefore include proteins in pathways that regulate protein homeostasis.

Myokines are one such family of cytokines that can function as autocrine, paracrine, or endocrine stimuli. Muscle contraction induces the biosynthesis and release of myokines, whereas reduced physical activity impairs the myokine response. Understanding the biological implications of myokines can help inform development of therapeutics to halt or reverse the physiological effects of progressive brain disorders.

Myostatin, a myokine in the TGF-β superfamily of ligands (also known as growth/differentiation factor 8; GDF8), disrupts protein synthesis and negatively regulates skeletal muscle mass. Characteristic of the structure of TGF-β family members, immature myostatin exhibits an N-terminal prodomain with a C-terminal signaling domain. A proteolytic cleavage removes the prodomain, but it remains noncovalently associated with the signaling domain, maintaining it in an inhibited latent state. The mature signaling domain becomes activated when the prodomain is fully removed via a second cleavage, which can be caused by fluctuations in pH. Activated myostatin can then bind its cell surface receptor complex consisting of a type I receptor (ALK4/5) and a type II receptor (ACTRIIA/B), thereby acting as a potent negative regulator of muscle mass.

Genetic or chemical disruption of myostatin has been shown to substantially promote skeletal muscle growth. A high abundance of myostatin, compared with levels of its natural inhibitor follistatin, is positively correlated with muscle wasting and fat loss in mouse models. Conversely, myostatin inhibition consistently increases muscle mass in animal models of a variety of muscle disorders. Myostatin downregulation is also achievable naturally through sustained regular exercise of moderate intensity.

Myostatin inhibition is under investigation as a means to reverse progressive muscle wasting (FIGURE). Most investigational antmyostatin drug candidates are antibodies designed to block receptor binding. However, receptor recognition surfaces of TGF-β family members share a high degree of similarity. Toxicity could result from antibody promiscuity. Moreover, these protein targets are known to bind to a number of ligands, so therapies may not specifically block myostatin action.

To overcome this high ligand homology, prodomain-targeting therapeutics (neutralizing antibodies, short interfering RNA, small molecules, etc) are currently under development. Myostatin-specific drugs promise increased specificity and tolerability. These novel therapeutic approaches aim to block myostatin maturation from the latent state. For example, exogenous follistatin (FS-344) delivered by a single adeno-associated virus (AAV1) injection has long-lasting benefits in dystrophic muscles: reduced inflammation accompanied by a high abundance of myostatin, compared with levels of its natural inhibitor follistatin, is positively correlated with muscle wasting and fat loss in mouse models. Conversely, myostatin inhibition consistently increases muscle mass in animal models of a variety of muscle disorders. Myostatin downregulation is also achievable naturally through sustained regular exercise of moderate intensity.

Activated myostatin binds to its cell surface receptor complex to negatively regulate muscle growth. Inhibition of myostatin occurs naturally via its prodomain, follistatin, and GASP1. Both natural and therapeutic myostatin inhibitors may work by preventing maturation of latent myostatin or blocking receptor binding.

Ab, antibody; ActRIIB-Fc, activin receptor type IIB crystallizable fragment; AKT, protein kinase B; ALK 4/5, activin receptor-like kinase 4/5; FOXO, forkhead box O protein; GASP1, G protein–coupled receptor–associated sorting protein 1; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; Smad, mothers against decapentaplegic homolog.

FIGURE. Myostatin Signaling Pathway Containing Numerous Potential Targets for Therapeutic Intervention

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by increased muscle size and strength.\textsuperscript{3,4} GASP1, which shares binding domain sequence similarity with follistatin, is capable of complexing with latent and active myostatin.\textsuperscript{5,6} Investigators have recently identified the amino acid residues in the prodomain that maintain myostatin in the latent state.\textsuperscript{7} This knowledge may help inform design of effective prodomain-targeting molecules. Gene therapy may provide lasting results and overcome potential immune responses toward recombinant protein injection.\textsuperscript{11}

Antisense oligonucleotide (AON) therapy has been validated in mouse models, where a resulting decrease in activated myostatin expression corresponded with a significant increase in muscle mass.\textsuperscript{10,11} Combinatorial therapy with AON and AAV-based therapies has been associated with adverse effects (AEs), including thrombocytopenia.\textsuperscript{11} However, AON therapy has some advantages over traditional AAV-based gene therapies: (1) the possibility of local or systemic administration, (2) easily tailored dosing regimen and downregulation intensity, (3) low toxicity and immunogenicity, and (4) no risk of uncontrolled insertion into the genome.\textsuperscript{11,12}

Myostatin inhibition appears to be a useful therapeutic approach for attenuating and reversing the muscle atrophy characteristic of patients with ALS.\textsuperscript{10} However, studies have shown that oxidoreductases such as superoxide dismutase (SOD1) accelerate disease progression despite increased muscle mass or strength.\textsuperscript{13} Edaravone (Radicava; Mitsubishi Tanabe Pharma America) is an FDA-approved ALS therapy that counteracts excessive oxidative stress, although it is not specific and has been linked to serious AEs in nontarget organs.\textsuperscript{3} Other investigational therapeutics for ALS include low-dose administration of an iron chelator such as Deferiprone to offset oxidative stress in motor pathways.\textsuperscript{14}

There is still much to learn about the etiology of ALS, both familial and sporadic. Until then, symptomatic treatment remains focused on helping preserve quality of life and prolong survival.\textsuperscript{8}

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Managing the Intricacies and Age-Specific Challenges of Pediatric Multiple Sclerosis

Two experts in pediatric MS care, Lauren B. Krupp, MD, and Tanuja Chitnis, MD, offer tips and insight on the diagnosis of the disease and the specific challenges faced by patients stemming from their own clinical experience.

By Matt Hoffman

MULTIPLE SCLEROSIS (MS) IS ESTIMATED to impact more than 2 million adults in the United States, with approximately 3% to 5% of all instances of disease onset occurring in individuals younger than 16 years of age. This exclusively relapsing-remitting form of the disease is referred to as pediatric-onset MS, and those affected often experience 2 to 3 times more frequent clinical relapses than adults.

The disease has a number of additional differences for pediatric patients compared with adult patients, including the challenges associated with managing disease during youth. To discuss these differences and the overall approach to the care of this patient population, NeurologyLive® presented this Insights series, “Diagnosis and Management of Multiple Sclerosis in Pediatric Patients,” featuring Lauren B. Krupp, MD, Nancy Glickenhaus Pier Professor of Pediatric Neuropsychiatry, Department of Neurology, NYU Grossman School of Medicine, and Tanuja Chitnis, MD, associate neurologist, Brigham and Women’s Hospital, professor of neurology, Harvard Medical School.

The pair elucidated some of the contrasts between adult MS and the pediatric population, as well as the clinical presentation of the disease, the challenges faced by young patients, and their treatment.

Differential Diagnosis of Pediatric MS

The McDonald criteria, the most recent iteration of which were published in 2017, have been largely adopted for the pediatric patient population in addition to the adult population. The differential diagnosis of pediatric disease, according to Chitnis, is fairly broad, with a variety of other autoimmune diseases needing to be ruled out. As well, autoimmune syndromes such as lupus and anti-phospholipid antibody syndrome, among others, can mimic pediatric MS, making them critical to consider.

“This includes, but is not limited to, the emerging disease myelin oligodendrocyte glycoprotein-associated disease [MOGAD], which can be tested for by MOG antibodies; as well as neuromyelitis optica, which can also be tested for using aquaporin-4 antibodies,” Chitnis explained. “The other areas that one should consider are infectious diseases; rarely, some infectious diseases can mimic pediatric MS. I would examine the cerebrospinal fluid.”
fluid [CSF] very carefully for any evidence of viruses and/or bacteria or fungus infections.”

She also noted that occasionally, large tumefactive lesions can be present, making it important to rule out any sort of malignancies and tumors. As well, nutritional disorders including B12 deficiency and other ischemic disorders caused by autoimmune conditions can also be mimics of MS.

Krupp added that the biggest difference between the pediatric and adult age groups is the aforementioned rarity of a progressive disease course in younger patients. When pediatric patients present with a history of progressive decline—in school performance, walking, or dexterity—and there is no halt or improvement, she said, despite its similarities to primary progressive MS in adults, that subtype in the pediatric group is extraordinarily rare. “You want to rule out diagnoses like leukodystrophy or a genetic disorder that could present in that kind of fashion,” Krupp explained.

Clinical Presentation of Pediatric MS

In addition to differences in the frequency of clinical relapses, pediatric individuals with MS often also have more inflammatory lesions and tend to accumulate lesions more frequently. Krupp explained that prior to patients becoming clinically treated, it is not unlikely for them to have experienced more than 1 clinical event. Additionally, even when treated with a disease-modifying therapy (DMT), depending on the agent, pediatric patients may still experience several relapses.

“One of the interesting challenges among those with pediatric MS are the youngest patients,” Krupp said. “The majority of children are in the adolescent age range, but there are a number who are also quite young. The youngest patient I ever saw was 27 months old when I made the diagnosis. Children in that age group and in the preteen years are more likely to have an acute disseminated encephalomyelitis [ADEM]–like presentation. They can present with encephalopathy or change in mental status or behavioral changes and have lesions on the brain MRI that are large and fluffy.”

Those individuals are then reclassified as having MS upon the occurrence of a second event with characteristics of the disease. Additionally, Krupp noted that younger children tend to have more brain stem and cerebellar involvement. Previous research has suggested that younger individuals are less likely to have positive oligoclonal bands, but many patients with pediatric MS are now recognized to have MOG syndromes, leading to questions about the need to reassess the CSF profile differences.

Symptoms among the pediatric population are similar to those in adults, but as Krupp noted, they can sometimes be overlooked by nature of children’s behavior. “For example, a child may have optic neuritis but not say anything to their parents. It’s only when the second event of optic neuritis occurs in the other eye that the patient presents for clinical evaluation,” she explained. These individuals also often experience issues with balance, dexterity, gait, and strength. In certain cases, Krupp explained that they can also experience episodes of double vision and vertigo—symptoms referable to the brain stem or cerebellum.

“One of the differences between pediatric patients with MS and adults is that fortunately, kids tend to recover very well from their clinical attacks,” Krupp said. “It’s not uncommon in a day where I’m seeing only pediatric patients with MS for most of those children to have normal or nearly normal neurologic exams. In contrast, in the adult MS group, you might have patients using a cane or with much more obvious neurologic impairment.”

Many wonder if the cognitive function of these younger patients is affected by the disease, and Krupp explained that having MS naturally presents itself as a challenge for kids. As they seek connection in social environments while they grow up, feelings of being different or outside the norm can present a major emotional challenge for them. This, in turn, can lead to mood disturbance issues.

“One of the interesting challenges among those with pediatric MS are the youngest patients. The majority of children are in the adolescent age range, but there are a number who are also quite young. The youngest patient I ever saw was 27 months old when I made the diagnosis.”

—LAUREN B. KRUPP, MD

To this point, it has been estimated that up to 30% of pediatric patients with MS may have either cognitive slowing on speed tasks or other cognitive changes relative to the norms established in the literature. However, more studies are still needed with healthy controls to see if those prior reports are holding true. Krupp noted that MS specialists are hopeful that there may be less cognitive impairment than was previously thought in this modern era. More recently, early diagnosis and prompt initiation of DMT have been thought to aid those cognitive deficits.

“We and others have been concerned about the cognitive well-being of kids with MS. After all, pediatric patients with MS are in a living laboratory. They’re in school; they’re in the process of learning the tools that they need to become independent adults,” Krupp said. “Kids can have cognitive challenges, academic issues, or emotional stress. Early identification of cognitive involvement is really important. There fortunately are a variety of screening methods in which that can be done, even in the neurologist’s office.”

Emotional, Social, and Cognitive Challenges

For pediatric patients, approaching an MS diagnosis and management plan from a multidisciplinary standpoint is essential when...
possible. Although this is certainly not available to every individual, Krupp advises ensuring that at least nursing is involved in the patient’s care plan. Doing so gives parents reassurance about their child’s care.

“There is kindness and time and ability to answer all the questions that the neurologist will do their best to provide. But sometimes the needs are beyond what the time allotment is for the doctor,” Krupp explained. “The nursing staff, with experience on the disease-modifying therapies and the details of going for tests, can provide tremendous support.”

Patients with pediatric MS also experience challenges in the psychosocial sphere, particularly in the teenage years—a time that can be naturally challenging for all individuals. In this time, Krupp explained, young adults are often trying to differentiate from their parents and toward independence, which can make having to go in for office visits or testing an incredibly stressful experience. “They want to be with their friends; they don’t want to be different. Social workers or psychologists who can reach out to the families and try to help them cope constructively with the stresses that dealing with a chronic illness can bring can be very useful,” she said.

Additionally, existing learning impairment can occur in this patient population and can present as a challenging combination for the patient and their families. This can make access to neuropsychology critically important as a part of care, when available. Among other challenges are those of dexterity and cognition, which can lead to issues in schoolwork such as handwriting and exams. Some children can require occupational and physical therapy because of relapses causing limitations in walking, strength, dexterity, or hand use. Access to that expertise is also critically important from a care perspective. All of this can require the use of a 504 plan, or in more pronounced instances, an individualized educational program (IEP).

“A neuropsychologist can help in the identification of where the weaknesses and strengths are, so that cognitive rehabilitation, if needed, can be initiated early,” Krupp said. Chitnis noted that studies have shown that roughly one-third of pediatric MS patients might have 2 major areas of cognitive deficits, while the other two-thirds might have 1 area of deficit. She said neuropsychological testing can help in the implementation of an IEP.

“This can impact not only their everyday life, but also school, eventual job goals, or maybe college. It’s very important to address these cognitive issues as early as possible,” Chitnis said. “In terms of depression, it does vary; it ranges anywhere from 10% to 40% in different studies of patients with pediatric MS. It’s an important factor to consider, and we should always screen for depression, ask the question, and make sure that depression is managed and treated as well as possible.”

Another major problem for both pediatric and adult patients with MS is fatigue. With children, however, this symptom can be slightly more complicated. Pediatric patients may not be attuned to their fatigue levels, and when coupled with other common issues such as emotional distress, it can go beyond just a lack of awareness around it.

Krupp suggested that nonpharmacologic management is the best option to manage fatigue. Fatigue, she said, is best managed nonpharmacologically. Exercise, in this instance, cannot be emphasized too much and can be an excellent approach to help fatigue. Additionally, reviewing good sleep hygiene and sleep practices—simple techniques to improve sleep—can alleviate fatigue, which is otherwise at times quite challenging for physicians to manage.

“I think children today with MS, and even those without MS, have to be encouraged to exercise, to be physically active, to participate in team sports when team sports become available again, and not just be passive and sitting on the couch playing video games,” Krupp explained.

Support groups are available nationwide for pediatric MS, and Tanuja recommended utilizing the resources provided by the National Multiple Sclerosis Society. Additionally, she mentioned camps and similar events for patients with pediatric MS. As well, there are support groups for parents. “That’s a very important factor to remember and consider. Parents need support to help get their young person through this disease and treatment,” Chitnis explained.
Aducanumab for Alzheimer Disease: Landmark Moment or False Hope for Patients?

Experts in the treatment and management of patients with Alzheimer disease and dementia weigh in on the FDA’s controversial approval of Biogen’s antiamyloid drug, aducanumab.

By Matt Hoffman

FOLLOWING A LONG AND WINDING JOURNEY to the FDA, Biogen’s antiamyloid agent, aducanumab (Aduhelm), crossed the finish line victorious, winning approval for the treatment of Alzheimer disease as the first therapy with the potential to slow disease progression. The decision came down after nearly 2 years of debate among members of the health care, research, and patient communities who grappled with the treatment’s promising—but questionable—clinical trial data.

Undoubtedly a monumental decision with major implications for clinical research and drug development as a whole, aducanumab’s approval is driving a very apparent wedge between opposing parties who support or question its clinical impact. Similar sentiment was expressed by the clinical community following the FDA’s Advisory Committee meeting in November 2020, in which the committee voted not to recommend regulatory approval of the intravenous infusion drug. Adding further fuel to the fire, the Institute of Clinical and Economic Review (ICER) released a statement following the approval, calling the FDA’s decision a failure in the regulator’s “responsibility to protect patients and families from unproven treatments with known harms.”

In a statement, the FDA said that the data from EMERGE (NCT02484547) and ENGAGE (NCT02477800) suggested aducanumab “consistently and very convincingly” reduced amyloid plaques in both a dose- and time-dependent fashion and that it anticipates that this reduction will result in a corresponding reduction in clinical decline. As such, the agency’s approval is “contingent upon verification” of this potential clinical benefit in a phase 4 confirmatory trial.

Keen to take the pulse of the clinical community following the approval, NeurologyLive spoke to several physicians who treat these patients and have varying opinions on this news: These include Marwan Sabbagh, MD, director, Cleveland Clinic Lou Ruvo Center for Brain Health, and investigator in the aducanumab trials; Lon Schneider, MD, MS, professor of psychiatry and the behavioral sciences, and Della Martin Chair in Psychiatry and Neuroscience, University of Southern California Keck School of Medicine; Anton P. Porsteinsson, MD, director, Alzheimer’s Disease Care, Research and Education Program, University of Rochester School of Medicine and Dentistry, and investigator in the aducanumab trials; and Robert Howard, MD, MRCPsych, professor of old age psychiatry, Faculty of Brain Sciences, University College London.

Q: What is your immediate reaction to the FDA’s decision to approve aducanumab?

MARWAN SABBAGH, MD: This is a seminal moment in the field. I was surprised at how polarizing it was—we really had strong opinions for and against—but if you take the pro-patient aspect and look at this in the context of the fact that many drugs are starting to show similar signals, I think this is a great step forward. People have to understand that contextually, medically speaking, we need the first drug in the class to get the class going forward. Otherwise, there’s going to be no progress. I would remind you, of course, that we always have a first before we get to the third, fourth, fifth—we don’t know if aducanumab will be the final drug, but we need the first drug. And we know that it has a consistent signal, we know it can remove amyloid very robustly. I’m overjoyed. I cannot tell you how excited I am to actually have a treatment option for my patients. I’ve been waiting 2 decades to get a new treatment option.

ANTON P. PORSTEINSSON, MD: It was a relief and excitement for those of my patients where aducanumab is indicated. The relief is that I do believe that having aducanumab approved, basically, is going to slowly usher in a new era in Alzheimer disease. It’s not so much because aducanumab is available, but because we have a treatment that targets the underpinning of the disease. Because of that, there will need to be a change in clinical practice. We will have greater access to and greater utility for biomarker validation, be it through cerebral spinal fluid (CSF) analysis, or amyloid PET scans, or, hopefully soon, plasma biomarkers. Now we have something to offer if a patient has elevated amyloid burden. We have a drug that is approved for amyloid reduction, and in the right patient population, this can be a reasonable treatment.

LON SCHNEIDER, MD, MS: The FDA did what they started out to do and what they were going to do, even before the Advisory Committee in November 2020. Perhaps they were surprised by the Advisory Committee’s negativism, but it’s now easy to understand why they weren’t deterred by it. Remember, the Advisory Committee voted unanimously with 1 abstention, to say, there is no evidence for efficacy or effectiveness. And specifically, that the so-called positive study could not be primary evidence of effectiveness and could not be primary evidence of effectiveness with support from the negative study or the phase 1 study, or with support of any pharmacodynamic effect. The FDA asked several times about pharmacodynamic effects, which is kind of unusual, as the applicant presented strong evidence for a pharmacodynamic effect on Alzheimer disease physiology. There, the committee said, yes—though they voted 5 yes and 6 uncertain and they had a lot of discussions—it has a pharmacodynamic effect, the drug hits the target that you wanted it to hit and does what it wants.

This is an antibody; these are antibodies that are designed to break down and lower amyloid plaque. So now what was the basis
for this approval? The basis for this approval was not efficacy, as the FDA statement itself says. It was an effect on a biomarker. The basis of the approval was that this thing broke down plaque, which is what we all know and totally agree on. This is an effective antibody for breaking down plaque—and that's all it is. The FDA has, from the beginning, been relying on their own draft guidance for early-stage Alzheimer disease or dementia, which was from 2018, that said that biomarkers, if valid, could support efficacy, and we're open to considering biomarkers at the time that a new drug or biological licensing application is submitted. They said that.

Then, the next part of this is that the FDA advanced this on the basis of accelerated approval. Accelerated approval is a full-approved pathway—there isn't such a thing as conditional approval—but provisional approval. But very specifically, and as Patricia Cavazzoni, MD, said in her letter, the approval of aducanumab is based on a surrogate clinical end point—in this case, the reduction of amyloid plaques in the brain. A surrogate end point is a biomarker that is thought to predict clinical benefit but is not itself a measure of clinical benefit. They're saying essentially, "Never mind the lack of effectiveness—aducanumab lowers plaques, and we think plaque lowering is reasonably likely to predict clinical benefits." This is the whole basis for approval: It lowers plaques, it's reasonably likely to predict clinical benefit, and now we want you to do a study post marketing—not necessarily a clinical trial; we don't know what the study is—to validate that. Efficacy is optional, effectiveness is optional. This is essentially what is being laid out here, and that, in some ways, is a stunner.

**ROBERT HOWARD, MD, MRCPSYCH:** They've used this accelerated approval category, which, to my understanding, is generally used when there isn't really enough data to know whether something works or not. But there's evidence of engaging with biomarkers and good reasons to think that, given more data, we'll know if it works or not. I suppose my point would be that we've already had 3000 patients go through the aducanumab clinical trials, and there is a large amount, really, of efficacy data available from those trials that indicate that there isn't efficacy—or not significant efficacy. If you set the bar for approving dementia drugs to the point where all you have to do is show that you've engaged with a biomarker by reducing amyloid rather than actually having a significant effect on cognition and function decline, that's going to be terribly damaging for the field—and is essentially what they've done. This decision will now open the floodgate for those who've got drugs that have failed to show efficacy but have engaged with the amyloid marker. Almost all the antiamyloid antibodies have shown a reduction in amyloid in the brain, even though, of course, they failed on the clinical outcome measures.

We need more blinded, placebo-controlled data. We don't need phase 4 data. Phase 4 data are not blinded—they are useless—and it's going to take 10 years. Basically, what we could have discovered in 3 years, if we'd done more trials, is actually going to take us 10 years now, before we realize, actually, that this is useless, isn't it? In our clinics, we're going to see this, and it's such a shame.

**Q:** What impact will this have on the future development of Alzheimer disease treatments?

**MARWAN SABBAGH, MD:** It opens the door. In the future, the option is going to be like chemotherapy, right? Just like cancer, it's going to be not 1 drug, but an applied drug cocktail. When you look at aducanumab, people forget the fact that, contextually, we're talking about this is in addition to background therapies. If you actually put it from that paradigm, that aducanumab plus amantadine, plus donepezil or a cholinesterase inhibitor, and then you'll see something else added. Our future is going to be a 4- or 5- or 6-drug cocktail, and the consequence, of course, is that we'll slow the rate of decline.

**ANTON P. PORSTEINSSON, MD:** First of all, aducanumab can be used with currently available treatments; those medications were not restricted in any way, shape, or form, at entry into the clinical trial. As well, as we know that Alzheimer disease is kind of a multidomain disease. There are amyloid plaques, there are tau tangles, there is neuroinflammation, there is oxidative stress. To do combination treatments where you have an amyloid-modulating agent and you add something on top of that, the amyloid-modulating agent needs to be able to stand on its own. I do think that this opens up the possibility for combination treatments, be that amyloid-lowering and tau-lowering treatment, amyloid and neuroinflammation, amyloid and oxidative stress, etc. And we do know that Alzheimer disease has all of these components.

Do we begin to stage patients with Alzheimer disease? If you look at, for example, the TRAILBLAZER study with donanemab and the whole TRAILBLAZER development program, in that study they looked not only at amyloid burden but also tau burden. That was kind of a first, and I think we're going to see a continuation of that, where maybe it's going to be the so-called ATN network—amyloid, tau, neurodegeneration; or amyloid, tau, neurodegeneration, and neuroinflammation. I think that ultimately, and not everyone is happy with this, that the treatment of Alzheimer disease is going to look quite a bit like oncology. In that, your Alzheimer disease will be staged or typified, and you will have validated the amyloid burden, tau burden, oxidative stress, neuroinflammation, etc. Then we'll develop a medication cocktail that treats what has gone awry for you. We are a certain ways away from that in clinical practice, but it wouldn't surprise me if, in the next couple of years, we'll see this emerge in clinical trials.
**CLINICAL VIEWPOINT | ALZHEIMER DISEASE**

**ROBERT HOWARD, MD, MRCPSYCH:** [Combination therapy] is based on the way that the treatments for AIDS and [tuberculosis] have worked, which is that 1 drug doesn’t do much, but you put together a combination of 3 of them and you get an amazing effect. That’s what I think this has come from. What we need, first of all, is drugs that work. I can buy that we might have drugs that do a little bit, and if you combine them and you hit different parts of the pathway, you get a bigger effect. But we haven’t really established that aducanumab works clinically. I just think this has become a sort of mantra that people can use that, of course, we need to do combination drugs. It’s very easy to say that, isn’t it? No one’s got any evidence that it is going to work, so it’s a way of sort of comforting ourselves when none of the drugs that we have, at the moment and in development, appear to be working. We think, “Well, maybe if we were to put them all together, it would somehow be better and work.” But until we do the trials, and we actually demonstrate a significant sort of effectiveness or efficacy, we just don’t know.

I’ve been in this field for 30 years. We’ve always been so optimistic. We’ve always overpromised that within 5 or 10 years, we’re going to have treatments that are going to revolutionize and be life-changing. It hasn’t come. I think we should just have a little bit of modesty and just accept that it may take a long time to find treatments that work. Obviously, that’s frustrating and difficult for people who’ve got dementia now. But, you know, what’s far worse, I think, is to go down an avenue of false hope. Or basically licensing a treatment that essentially doesn’t work. I said this on Twitter, and I don’t know if it’s an accident or not, but I really feel that Biogen has pulled off a heist with this approval. It’s the great dementia heist. Hats off to them. It’s an accident or not, but I really feel that Biogen has pulled off a heist with this approval. It’s extraordinary.

**Q:** What does this mean for the patients, many of whom have been clamoring for this approval?

**MARWAN SABBAGH, MD:** I have patients literally waiting—literally, I have a list of patients ready to go—for as soon as they get the approval, so I can get them infused in a matter of weeks. Patients are desperate. Imagine having mild cognitive impairment, knowing you have amyloid in your brain, and knowing that one direction you’re going to head for is terminal dementia and that there was nothing that we could do until now to prevent that from occurring. How great it is, as a doctor, where this has been my whole career, to say, “Maybe that’s not your inevitable future.” That’s what’s so exciting about this moment.

**ANTON P. PORSTEINSSON, MD:** What I’m worried about, after having read the label, is that the label is fake. It’s a provisional approval of a drug for amyloid lowering. There are not a lot of specifications about the severity of the patients. There are some general discussions about how to manage adverse effects. Basically, they say it’s indicated for 10 mg/kg and extended use, so there’s no stop date, per se. I think that the biggest challenge right now, is how we operationalize treatment with aducanumab. This is not for everyone. It’s not a cure. There is a meaningful potential for adverse effects. Those adverse effects are, thankfully, pretty narrow, but not uncommon. We have about the 35% to 40% that will have ARIA-E and ARIA-H. Whereas for most patients, it’s mild to moderate and asymptomatic, there is about 25% of patients that get ARIA-E that will have symptoms, and a small percentage—maybe only 1% or something like that—that will have substantial symptoms that have to be dealt with.

I believe that ARIA-E and ARIA-H are manageable adverse effects, but it definitely doesn’t mean that we can be nonchalant about it. There needs to be careful clinical monitoring, there needs to be clinical MRI monitoring, there needs to be monitoring that the titration is done correctly, that you basically screen for any clinical symptoms that would suggest the emergence of vasogenic edema, and that if there is enough suspicion that an unscheduled MRI might be done. We have the recommended MRI monitoring, basically month 6 and month 12, roughly.

This is not a simple process—not for the clinicians, and not for the patients. In my opinion, it has to be done well. We have to select the right patients that are most likely to benefit from treatment, we have to treat them in the right manner (which is a dose escalation, where the dose is steadily pushed and toward 10 mg/kg), and that everything is done as long as it’s safe for ongoing treatment, 10 mg monthly for an extended period. Those are the patients that did best.

Clearly, having a treatment that differs from all other available treatments—because it targets the underpinning of disease, may work to normalize plaque burden, and appears to be associated with a modest but meaningful delay in progression—is exciting, and we should make it available. But I really think that there is a high need to have a careful process and careful conversation with the potential patients and family about what aducanumab does and what it doesn’t do, and the possible tolerability issues, the cumberboseness of the infusion, and the monitoring, so that nobody is surprised.

**LON SCHNEIDER, MD, MS:** There’s a complete lack of evidence that this is beneficial for a patient. That the drug is directly beneficial. Can it be beneficial in some way? Well, it can be beneficial in a lot of indirect ways. You can get people excited; you could increase hope; you can lay out the hypothesis to a greater extent—the hypothesis is yes, of course, that lowering amyloid plaques will lead to a better clinical course. But there’s no evidence of that. So, you can get excited, of course, and people could feel excited. But in order for my colleagues to honestly be excited, they have to be agreeable to this. They have to believe that the reduction of amyloid plaques does predict cognitive improvement, or they have to believe that the clinical trial showed cognitive improvement. Notice that the FDA doesn’t even [focus] on the clinical trials showing improvement.
First and foremost, it’s good for patients. I mean, first of all, it doesn’t work, and secondly, it is not a drug I’d really want them to take. We don’t know what the long-term effects of those MRI hyperintensities and those hemorrhages in the brain are, but they can’t be good. If you’d asked me 5 or 10 years ago, “How do you think you’d be feeling on the day that the first Alzheimer drug got approved?” I would have been walking on air. I’d thought I’d be punching the air; I’d be so happy. I actually just feel a little bit sick on this news, I’m afraid.

Q: Do you have any closing thoughts on this, the next step for aducanumab, or research in Alzheimer disease?

ROBERT HOWARD, MD, MRCPSYCH: I don’t think it’s good for patients. I mean, first of all, it doesn’t work, and secondly, it is not a drug I’d really want them to take. We don’t know what the long-term effects of those MRI hyperintensities and those hemorrhages in the brain are, but they can’t be good. If you’d asked me 5 or 10 years ago, “How do you think you’d be feeling on the day that the first Alzheimer drug got approved?” I would have been walking on air. I’d thought I’d be punching the air; I’d be so happy. I actually just feel a little bit sick on this news, I’m afraid.

On the one hand, it’s good for patients. I mean, first of all, it doesn’t work, and secondly, it is not a drug I’d really want them to take. We don’t know what the long-term effects of those MRI hyperintensities and those hemorrhages in the brain are, but they can’t be good. If you’d asked me 5 or 10 years ago, “How do you think you’d be feeling on the day that the first Alzheimer drug got approved?” I would have been walking on air. I’d thought I’d be punching the air; I’d be so happy. I actually just feel a little bit sick on this news, I’m afraid.

ANTON P. PORSTEINSSON, MD: First and foremost, I want to see the other amyloid-lowering agents that appear to have a similar profile of efficacy potential move forward. Some people have said, “Well, if they are also well established as amyloid-lowering agents, could they be approved on a provisional basis?”

I don’t know where we’re at with that. But I would love for those drugs to have undisputable data sets. By that, I don’t mean that we can’t have a discussion about the response and the effect size and all of that, but that there is no premature stopping. That the studies ran their course and that they were executed without flaw, that we can then have confidence that the data sets that are submitted don’t have some sort of execution flaw, and then the efficacy data will have to stand on their own. Hopefully, we’ll have 2 data sets that support each other where both show a somewhat similar degree of benefits.

Beyond that, I hope that we continue to expand the treatment targets beyond amyloid. Amyloid is clearly a potential therapeutic avenue. Now that we know that and we have an approval, maybe we can start to expand on quote, what is available. But I hope that we will see better, simpler, safer treatment options for targeting amyloid plaques and amyloid oligomers. I hope that we will come up with products that make sense in terms of reducing tau tangles. We are starting to develop drugs that target neuroinflammation, and there are multiple other pathways that are being explored. I hope that we continue to see us branch beyond amyloid and that the approval of aducanumab will not lead somehow to a concentration of efforts on amyloid—I hope that the broadening of potential targets will continue and even proliferate.

LON SCHNEIDER, MD, MS: On the one hand, it’s a stunner that [the FDA] would do this. But on another, looking back on it, this had been their evaluation all along. That is, this is the basis for what they’re going to approve on because that’s also how they asked the questions. There was substantial political pressure, and this is what it is. Now, the devil is in the details. How exactly is this going to be launched? And how exactly is it going to be provided and paid for? And then to whom will this be given?

This stage 3 and stage 4 conceptualization is the FDA’s conceptualization in their 2018 guidance for early-stage Alzheimer disease. So again, they’re using their own language to help define this. The study itself didn’t say we’re enrolling stage 3 and stage 4 people. The clinical trial said we’re taking people with mild cognitive impairment due to Alzheimer disease, or mild dementia due to Alzheimer disease. In one sense, it’s totally remarkable. In another way, it was in retrospect, of course, totally predictable.
Biohaven’s Zavegepant Aims to Expand CGRP Migraine Treatment Options

After showing early success, zavegepant eyes a pivotal phase 2/3 trial with potential regulatory submission around the corner.

By Marco Meglio

AS THE MIGRAINE TREATMENT TOOLBOX has expanded in recent years, the most notable option has been the introduction of the calcitonin gene-related peptide (CGRP) inhibitors. Biohaven’s third-generation, highly soluble small molecule zavegepant may be next to join that list of therapies.

In early April, the company announced that the first patient in a phase 2/3 clinical trial (NCT04804033) had been dosed with oral zavegepant. The pivotal double-blind, placebo-controlled study will enroll approximately 2900 participants to evaluate the safety and efficacy of 100-mg and 200-mg zavegepant over a 12-week study period. “It is designed to be able to provide the FDA with what it will require for approval if we are ultimately successful,” Elyse Stock, MD, chief medical officer, Biohaven, told NeurologyLive.

The primary end point of the study is mean reduction from baseline in the number of monthly migraine days, during weeks 9 to 12. Secondary end points included are the proportion of subjects achieving greater than or equal to 50% reduction from baseline in moderate to severe headache days, as well as safety and tolerability of zavegepant (FIGURE).

Stock noted that the company hopes to complete the study in the second half of 2022 and did not anticipate any interim data readouts. Rimegepant (Nurtec ODT), which was approved in February 2020 for the acute treatment of migraine in adult patients, was Biohaven’s first approved migraine medication and was crucial in better constructing the zavegepant clinical trial process. “The whole clinical trial process with rimegepant made this easier. There clearly is some guidance that we, and others, have gotten from the regulatory agencies across the globe on how to run these programs so that, if we’re successful and have a positive study, we get an approval,” Stock said.

Rimegepant, another CGRP-targeted treatment, was granted approval based on the results from 2 clinical trials: the phase 3 Study 303 (NCT03461757) and the long-term, open-label safety trial, Study 201 (NCT03266588). In its clinical development, more than 3100 patients were treated with more than 113,000 doses of the therapy.

As for zavegepant, Biohaven announced topline results from another phase 2/3 clinical trial (BHV3500-201; NCT03872453) evaluating the efficacy and tolerability of its intranasal form in 5-mg, 10-mg, and 20-mg doses vs placebo in 1673 patients for the acute treatment of migraine. At 2 hours, treatment with a single dose of zavegepant 10 mg or 20 mg showed statistically superior results to placebo on the coprimary end points of pain freedom and freedom from the most bothersome symptom (MBS; photophobia, phonophobia, or nausea).

The drug also demonstrated a duration and sustained effect profile through 48 hours (nominal P<.05). This included sustained pain freedom 2 to 24 hours (5 mg, 10 mg, and 20 mg), sustained pain freedom 2 to 48 hours (5 mg, 10 mg, and 20 mg), sustained pain relief 2 to 24 hours (5 mg, 10 mg, and 20 mg), and sustained pain relief 2 to 48 hours (5 and 10 mg). Across a number of secondary end points, the treatment continued to show its early activity (nominal P<.05). The treatment also had rapid onset with pain relief at 15 minutes (10 and 20 mg), with patients returning to normal function as early as 30 minutes in the 20-mg dose group. Therapeutic benefits on both pain relief and return to normal function at 2 hours were observed in both the 10-mg and 20-mg dose groups.

Zavegepant, which was known at the time as vazegepant, eventually had its named revised by the World Health Organization and was accepted by the United States Adopted Names (USAN) Council for use in the US. Stock noted that there are a number of benefits that both oral and intranasal zavegepant can bring to patients. Discussing intranasal zavegepant, she told NeurologyLive, “It may be more appropriate for someone who is getting a migraine all of a sudden and will need something that they will rapidly respond to and where they don’t want to take anything by mouth at all.”

She said there are a number of other disorders outside the migraine space that could benefit from CGRP. She explained that the company is looking into respiratory, dermatologic, and infectious disease spaces. Biohaven currently has ongoing studies involving patients with COVID-19 as well as psoriasis and is planning to start another that will include patients with asthma.

FIGURE. Phase 2/3 Trial of Zavegepant in Migraine

Eligibility criteria
• 1 year history of migraine
• Age of onset of migraines prior to 50 years of age
• Migraine attacks, on average, lasting 4-72 hours if untreated

Randomization
• 1:1:1 to zavegepant 100 mg or 200 mg or placebo

Primary end points
• Mean reduction from baseline in number of migraine days per month in the last 4 weeks of the double-blind treatment phase

For a full list of references, see the article on NeurologyLive.com.
WHEN THE FDA APPROVED THE FIRST intranasal benzodiazepine, midazolam (Nayzilam; UCB), in 2019 for the acute treatment of seizure clusters, it marked the first approval for that indication in the United States in over 20 years. Approval of intranasal diazepam (Valtoco; Neurelis) followed about 6 months later, providing an alternative with different pharmacokinetics and indicated age group but similar efficacy and ease of use.

Importantly, both provided an alternative to rectally administered diazepam as the only option for prehospital outpatient treatment of seizure cluster by non–health professional caregivers. The advantage of this new dosage form relative to the rectal gel was a game changer, according to Jacqueline French, MD, professor of neurology, Comprehensive Epilepsy Center, NYU Langone Health in New York, New York; president, The Epilepsy Study Consortium; and chief medical and innovation officer, the Epilepsy Foundation. She was involved with the clinical trials of both intranasal products.

“They will practically do anything to not use that formulation, and there are very significant cultural issues in regard to whoever the person would be who would administer it.

“The only time that I would have luck in getting people to accept that it would be administered is if they were [at risk of] having a major tonic-clonic convulsion and would be completely unconscious. They would sometimes say, ‘OK, under those circumstances, it would be OK for my spouse to administer a rectal form.’”

At that time, there was an effort at some hospitals and compounding pharmacies to extemporaneously formulate an intranasal dosage form of midazolam from the injectable product.

“So that led to 2 problems,” French recounted. “One is that it was a relatively dilute solution, which would require trying to administer, for the most commonly used formulation, 3 squirts in each nostril—that’s a lot to do. The second thing is that, because it was a large amount of volume in the nose, a lot of it would just go right down the back of the throat and get swallowed. That’s going to take longer to work and produce a potential risk of aspiration.”

Developing and Distinguishing Formulations

The challenges in developing the intranasal benzodiazepine formulations were recently reviewed by James Cloyd, PharmD,
While the rectal formulation is perfectly fine for young children or people with developmental delay, it is absolutely not fine for people who are essentially adults. They will practically do anything to not use that formulation, and there are very significant cultural issues in regard to whoever the person would be who would administer it.”

— JACQUELINE FRENCH, MD

Experimental and clinical pharmacology, University of Minnesota College of Pharmacy in Minneapolis, and colleagues. The reviewers described the features of the ideal rescue therapy:

“The route and formulation should offer rapid absorption, consistent and high bioavailability, good potency at small dose volumes, reliable and early onset of action, a wide therapeutic index, sufficient duration of action—ie, hours—a good safety profile, low interpatient variability, dosing guidelines for adults and children, and a long shelf life.”

The reviewers point out that the intranasal route posed the theoretical advantages of easy access, noninvasive administration, rapid onset of effect, and avoidance of first-pass hepatic metabolism, as well as being a socially acceptable mode of administration that does not require patient cooperation.

The challenges presented by this route, according to Cloyd and colleagues, include the small surface area of the nasal cavity, which limits drug delivery to 200 μl and optimally 100 μl to avoid leakage or swallowing. There is also a challenge with benzodiazepines as a class, they point out, in that they are hydrophobic molecules with poor solubility in water.

To improve the pharmacokinetics of intranasal midazolam, Cloyd and colleagues indicate, the formulation utilized several organic solvents, while maintaining the pH in the range of 5 to 9. A different approach was taken for diazepam, they explain, with dodecylmaltoside (DDM) (Intravail A-3) used to reversibly loosen tight junctions between cells to enhance nasal absorption. Vitamin E is also used as a nonaqueous solvent for delivering the diazepam and to protect against phospholipid-mediated inflammation and damage to the sinonasal mucosa.

“Both are effective, and both are part of my practice,” Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry, NYU Grossman School of Medicine in New York, New York; and director of the NYU Langone Comprehensive Epilepsy Center in New York, New York, and the Institute of Neurology and Neurosurgery at Saint Barnabas in Livingston, New Jersey, told NeurologyLive®. “The major differences are in the pharmacokinetics. Nayzilam peaks in the blood in approximately 15 minutes and effects last up to 6 hours on average. Valtoco reaches a peak blood level after approximately 1.5 hours and can last for 1.5 to 2 days (TABLE).

“This leads me to favor Nayzilam for more rapid onset, when that is needed. However, for patients whose seizure clusters last more than 6 hours, or there is often a second cluster more spread out, Valtoco may be preferred,” Devinsky explained.

Approval of intranasal diazepam followed demonstration of at least comparable bioavailability relative to the rectal gel. Approval of intranasal midazolam was based on a randomized, placebo-controlled trial that demonstrated significantly more patients on active drug had seizure termination within 10 minutes without recurrence within 6 hours. An open-label extension of median 16.8 months found treatment success with a single dose in 55.5% of episodes, and in 80.2% with a second dose.

An inhalation form of alprazolam (Staccato Alprazolam; UCB) may also become available, having recently completed phase 2 clinical testing. French and Devinsky anticipate successful completion of phase 3 and its addition to the rescue armamentarium for seizure clusters.

“With the nasal forms, you’re talking about acting in maybe 10 minutes,” French said, “although it could be slightly shorter in

### TABLE. Nasal Rescue Medications: Use and Dose

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<thead>
<tr>
<th>AGENT</th>
<th>DOSAGES</th>
<th>USE</th>
<th>SECOND DOSE</th>
<th>TIME TO PEAK LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (Nayzilam, UCB)</td>
<td>5 mg</td>
<td>5 mg: 1 spray into a single nostril. Used for 1 seizure cluster every 3 days.</td>
<td>Second dose can be given 10 minutes or longer after the first dose if prescribed. Should not be given amid concerns about breathing or sleepiness.</td>
<td>15 minutes, can last up to 6 hours.</td>
</tr>
<tr>
<td>Diazepam (Valtoco, Neurelis)</td>
<td>5 mg, 10 mg, 15 mg, 20 mg (determined by patient weight)</td>
<td>5-mg or 10-mg dose: 1 spray into a single nostril.</td>
<td>Second dose can be given at least 4 hours after the first dose if prescribed.</td>
<td>15 hours, can last up to 2 days.</td>
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<tr>
<td></td>
<td>15-mg dose: Two 7.5-mg nasal sprays are used, one spray in each nostril.</td>
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<tr>
<td></td>
<td>20-mg dose: Two 10-mg nasal sprays are used, 1 in each nostril. Used for 1 seizure cluster episode every 5 days.</td>
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some cases, but we don’t have the data to support that. The inhaled form works in at least 2 minutes, and probably even faster than that. It’s really what we call a rescue inhaler for epilepsy.”

The double-blind, placebo-controlled, inpatient, dose-ranging efficacy study of the inhaled alprazolam was conducted with 156 participants with epilepsy and a predictable seizure pattern. The primary outcome was the percentage in each treatment group achieving seizure activity cessation within 2 minutes and no recurrent seizure within 2 hours.

Devinsky noted the favorable results with the inhaled alprazolam in the phase 2 study and its portent. “New forms of delivery can allow more rapid onset of the medication and allow more tailored use of benzodiazepines for individual patients based on pharmacokinetics and other features,” he said.

Utilization of Rescue Medication

James Wheless, MD, director, Le Bonheur Comprehensive Epilepsy Program & Neuroscience Institute, Le Bonheur Children’s Hospital, University of Tennessee Health Science Center in Memphis, Tennessee, and lead author of the intranasal midazolam extension study and a coauthor of the randomized control trial has written on the significance of the dosage form enabling caregivers to provide rescue treatment without the delay of accessing emergency personnel.

“[It] allows for outpatient treatment by caregivers and other non–health care professionals and may particularly be meaningful to patients who have limited treatment options,” Wheless wrote. “For example, hypersalivation, jerking movements of the jaw, or general restlessness may rule out buccal administration of clonazepam and midazolam, and rectal diazepam may not be suitable because of the physical and social constraints to rectal administration.”

In addition to the relative ease of administration, Wheless pointed out the pharmacokinetic advantages of intranasal midazolam to the buccal and intramuscular forms. He noted that peak absorption of 5 mg intranasal midazolam is reached “slightly” faster than with either buccal or a 10-mg intramuscular dose. Although bioavailability of the intranasal form is lower, the half-life ($T_{1/2}$) of the different formulations is comparable.

Wheless expressed concern, however, that utilization of the dosage form might lag from lack of or inconsistent treatment guidelines, as well as from insufficient training on its administration.

“There are currently no guidelines on the treatment of seizure clusters in the US,” Wheless indicated. “The American Academy of Neurology and American Epilepsy Society have published joint guidelines on epilepsy treatment in general, but these do not include specific guidance on seizure clusters.”

In addition, one study Wheless described “showed that among the patients with a prescribed rescue medicine, only 61% of the families received training on how to administer the drug. Therefore, insufficient training may also contribute to the underutilization of rescue medications.”

Instructions to the caregiver on the use of the dosage form, according to the Epilepsy Foundation, should include: direction to not open individual blister packs or test the device before use, specifying the dose and corresponding spray(s), defining when a second dose should be administered and holding a second dose of Nayzilam if there is concern about patient’s breathing or sedation, and specifying the maximum number of doses within designated time periods.

Avoiding Seizure Clusters

The ideal rescue is one that isn’t needed, and Devinsky and French employ means to lessen the occurrence of seizure clusters and the requirement for rescue.

“How I treat clusters varies with the patient,” Devinsky said. “For some, an extra dose of their usual medication, such as levetiracetam, valproic acid, or others can be used to avoid the need for benzodiazepines, thereby reducing the potential for tolerance and desensitization of the GABA-A receptors and the potential for withdrawal seizures if they are used regularly.”

French looks forward to developments and programs that could help to predict and avert the occurrence of seizure clusters. She anticipates that the My Seizure Gauge, in development with grants from the Epilepsy Foundation, will yield data from monitoring patients physiology, implanted electroencephalograms, and seizure diaries that translate to opportunities for timely self-intervention with wearable devices.

“A lot of these devices are minimally invasive. In other words, you don’t have to stick something in the head; you just put it subscalp. It can be done as an office procedure,” French said. “Certainly, for people who have very severe seizures with a high likelihood of cluster, having an implanted device that forecasts may be well worth it.”

“If we could give a benzo even before the first seizure happened, wouldn’t we be much better off doing that?” French asked. “I have a very strong hope that 5 years from now, that may be a solved problem.”

For a full list of references, see the article on NeurologyLive.com.

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Love and a Lab Coat: One Couple’s Quest to Treat Alzheimer Disease

Luca Giliberto, MD, PhD, and Cristina d’Abramo, PhD, share more than a marriage: After years of research, their combined efforts to develop a passive immunotherapy for Alzheimer disease have earned them a $2 million grant from the National Institutes of Health.

By Matt Hoffman

THE SUCCESSFUL TREATMENT of Alzheimer disease (AD) has eluded scientists and physicians for decades, with efforts to develop disease-modifying therapies for the complex neurodegenerative disease culminating mostly in failures. Despite this, much of the field remains highly motivated on the overall quest to provide patients with options that can quell the devastation of AD’s progression. Although those labors have so far fallen short of providing effective therapies, they have led to a better understanding of the pathogenesis of AD as well as advances in imaging and detection.

Among this group of physician scientists aiming to change the course of AD treatment are a unique pair operating out of Northwell Health’s Feinstein Institutes for Medical Research in Manhasset, New York: Cristina d’Abramo, PhD, an assistant professor in the Institute of Molecular Medicine, and Luca Giliberto, MD, PhD, an assistant professor in the Institute of Molecular Medicine and at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, and attending neurologist at the Cushing Neuroscience Institute. They were recently awarded a $2 million grant from the National Institutes of Health for their work exploring the potential use of small vectorized single-chain variable fragment (scFv) antibodies in targeting tau pathology observed in AD.

Specifically, they aim to employ an epitope-based dual therapy combining scFv-melanocortin 1 (MC1) with scFv directed against other tau epitopes, and are assessing a dual delivery strategy—intracranial and intramuscular—in order to fulfill both a proof-of-concept and a translational approach to their idea.

D’Abramo and Giliberto are an exceptional pairing both inside and outside the lab. As research partners and a married couple, their clinical conversations about AD often follow them home—all for the betterment of their research. They can often be found running together, sharing the ideas that spring up from the papers they read that day, or discussing translational science at the dinner table.

“It’s a 24-7, 365 proposition. We constantly have ideas and thoughts,” Giliberto told NeurologyLive®. “The good thing is that we can bounce them immediately off of each other. We don’t waste any
time waiting or facing the ‘I’ll talk to them next week,’ scenario. We do it right away, and we sit back on the computer, check the literature, and then go on.”

D’Abramo spends her days in the lab working on basic and translational science research into the role of the immune system in the development of AD, particularly focusing on the interaction between tau and microglia activation, as well as on the generation of tau antibodies and on the development of assays to detect tau in biological fluids. Giliberto, meanwhile, operates both in the clinic and in the lab—roughly 40%, he says, is spent in the clinic and the remaining time in the laboratory. Part of his clinical time is spent with patients taking part in clinical trials for potential AD therapies, offering him additional perspectives for his research.

The varying perspectives they have amassed while at the Feinstein Institutes for Medical Research have allowed for a very complementary professional relationship. D’Abramo explained that while her time is spent in the lab, Giliberto’s clinical work fills in some of the gaps that she does not experience in her own time. Ultimately, their success as scientific partners stems from the respect that they carry for one another and their labors.

“A lot of people say, ‘How can you work together? I could never make that work,’” d’Abramo told NeurologyLive®. “But it is really this deep, professional respect that we have that allows us sometimes to erase arguments that we have at home. We come back to work, and everything goes smoothly, and I would say that’s really because of this respect.”

That respect also allows them to bounce ideas and theories off one another that might be too outlandish to suggest to other colleagues. Giliberto explained that often he’ll see patients in different scenarios who are going through different experiences, and as a result come to d’Abramo with “weird ideas” that she will help to elucidate. These quick chats in the elevator between patient visits have produced a multitude of their research projects. The conversations then carry over from the elevator to the dinner table. As Giliberto put it, “The trick has been to choose to never stop thinking about it.”

“Even in the clinic days [I don’t stop],” he said. “If a patient doesn’t show up, I open the browser and I look for papers and I look at the news. I look for things. That’s the trick. If you stop thinking about it, then you sit back, and you’re done. You’re sucked into the routine, and it doesn’t happen. I never stop thinking about it.”

Originally from Italy, Giliberto and d’Abramo met during residency at the Laboratory of Experimental Medicine at the University of Genova, and their professional relationship blossomed. Giliberto’s interest in AD was piqued during his time in medical school in the late 1990s as he explored the genetic aspects of the disease and apolipoprotein E ε4’s role in its pathology. Originally, Giliberto’s captivation with the brain was rooted in the processes leading to the formation of thoughts and emotions, and specifically, the relationship between the brain and music. In addition to his fascination with the brain, his love of the arts was another trait he would share with d’Abramo.

“When we first met, actually, ballet was the big thing for us, besides looking at the microscope and brains, and we kept going”
to shows together,” d’Abramo said. “We also kept dancing here in New York when we first came in 2004. Unfortunately, now with COVID, we can’t really go to the city and enjoy any art. But art for sure has been a big, big thing in our life, and it is, still.”

In their years at the University of Genova, d’Abramo’s research was mostly in aging cell biology in collaboration with Massimo Tabaton, MD, exploring the relationships between oxidative stress, activation of kinases, and the metabolism of amyloid precursor protein. Her work in AD stemmed from her interest in neurochemistry and neurobiology, which led to her choosing the lab in Genova. Giliberto, meanwhile, was working on the properties of amyloid beta peptides as signaling molecules, as well as exploring the pathways involved in the biology of AD and regulation by oxidative stress. This led them to collaborate on a project, with Giliberto instructing d’Abramo on compiling brain immunohistochemistry.

After working together for some time, Giliberto was offered a postdoctoral opportunity at Albert Einstein College of Medicine in New York, and left to work with Luciano D’Adamio, MD, a renowned expert in AD. A few years later, d’Abramo followed with an opportunity to work with acclaimed AD investigator Peter Davies, PhD, who would offer the pair an opportunity to come to the Feinstein Institutes together to work with him. Davies, whose work on antibodies in AD helped lay the foundation for the grant that d’Abramo and Giliberto were awarded, died in 2020 just before the award was announced. According to the couple, he was, ultimately, a cornerstone of their work in the field and played the role of mentor for both of them as they ventured further into research and therapeutic development in AD.

Once in the US, Giliberto needed to redo his residency at North Shore University Hospital, and although d’Abramo had originally planned to stay for only 10 months as part of her PhD program to improve her curriculum vitae, she stayed on. “That’s often the story. You go out of the country for an experience, and then you get sucked in and you stay. That’s it,” Giliberto said.

Their efforts since arriving in the US have, along with several years of applications to and conversations with the NIH, led to this grant. The funding will last for 5 years and will offer them the opportunity to further pursue their hypothesis that takes an approach to AD often used in cancer: passive immunotherapy. “What we are trying to do is to really develop a novel immunotherapeutic approach, where instead of using the conventional antibodies—the big 150 kilodalton proteins—we are engineering the antibodies and making them smaller,” d’Abramo explained. “We don’t inject the single chains directly in the animals, but we insert the complementary DNA in an adeno-associated virus [AAV]. We’re using these nonpathogenic, nonreplicating viruses, and we insert the sequence for the scFv in this vector. With 1 injection, you’re going to get your animal—or later, patient—expressing these recombinant antibodies that are, possibly, able to cross the blood-brain barrier and find tau, bind it, and clear it.”

To this point, she said, they have developed a muscle injection with a specific AD serotype that acts as a tropism for muscle cells. Their idea is to generate a muscle niche to continuously release the recombinant antibodies into the circulation. If successful, it would require only a single injection, as opposed to the monthly or quarterly infusions that traditional immunotherapy requires.

“Now, not everyone is going to get the therapy, and not everyone is diagnosed. Many of them are hidden at home—that’s another problem,” Giliberto said. “But you’re talking about, reasonably, 30,000 to 40,000 people [on Long Island, New York, alone] that may be treatable with these options. How do you get them into the clinic every month to infuse them? It’s a long conversation. There are a lot of logistics to it. Certainly, the costs and the logistics of that approach are some of the elements that led us to this process.”

D’Abramo and Giliberto are working with multiple antibodies for this grant project, with the hope of applying different scFv antibodies in various paradigms. One of the goals is to explore if the treatment can clear the existing pathology as well as prevent the development of new pathology. The third aspect is to study the mechanism of the immunotherapy, specifically by investigating the microglia.

Giliberto noted that much of the conversation among his colleagues in 2021 has been centered around Biogen’s controversial AD agent, aducanumab. When such a therapy is granted FDA approval, he explained, it can be disruptive to individual health systems because of patient demand for the treatment. “Are we ready for it? Are we able to infuse patients every month, and then check their MRI and spinal fluid? Having these types of alternative approaches where you get intramuscular injection that lasts for months and maybe you’ll get a boost—that’s probably much better.”

“There is one concern that has been voiced about AAV-mediated therapies, which is how do you turn it off if you don’t need it or if you have a problem? There are ways to do it,” he explained. “There are tetracycline-controlled transcriptional activation systems; there are hormonal responsive promoters. There are a bunch of...
ways to do it. That should not scare us from pursuing these types of approaches.”

At this point, the pair have published 2 studies from this work. The first was a proof-of-concept study of an intracranial injection of the therapy, published in 2018, which assessed the scFv immunotherapy in adult JNPL3 mice. After performing extensive biochemical analysis of soluble, oligomeric, and insoluble tau species in the hippocampus, cortex, and hindbrain, they observed a consistent pattern of tau reduction upon treatment with the recombinant antibody. The results showed a decrease in soluble pThr231 common to the 3 brain areas analyzed upon astrocytic expression of the scFv-MC1 (hippocampus: −35%; cortex: −25%; hindbrain: −33%), without major effects on other soluble tau/phosphorylation residues. Supporting those data, they also observed that pThr231 immunoreactivity in the hippocampus and entorhinal cortex was significantly reduced in the injected mice (hippocampus: −60% circa; entorhinal cortex: −70% circa), consistent with the reduced tau-MC1 immunostaining (hippocampus: −60% circa; EC: −70% circa).

A lot of people say, ‘How can you work together? I could never make that work.’ But it is really this deep, professional respect that we have that allows us sometimes to erase arguments that we have at home. We come back to work, and everything goes smoothly.”

—CRISTINA D’ABRAMO, PHD

Then, in August 2020, they published another study, this time assessing an intramuscular injection with the antibodies in JNPL3 (n = 26) and P301S (n = 12) mice. That work showed a dramatic decrease of cortical insoluble tau in the P301S cohort upon treatment with scFv-MC1, as well as in total tau (−70%; P < .01), pThr231 (−70%; P < .01), pSer202 (−60%; P < .05) and pSer396/404 (−65%; P < .01). Additionally, a similar significant reduction was confirmed in the JNPL3 cohort following a sustained peripheral release of scFv-MC1, both as total tau (−50%; P < .001) and phosphorylation at Thr231 (−65%; P < .001), Ser202 (−50%; P < .001) and Ser396/404 (−60%; P < .0001).

“In the new study, we have shown that MC1 single chain is absolutely working with significant effect,” d’Abramo said. “You do your intramuscular injection in mice, and you get the antibodies in brain reducing pathology in the cortex, hippocampus, and hindbrain at different levels. We looked at different species of tau—soluble tau and insoluble tau—so it’s more complicated than just, ‘OK, it’s working.’

“There are a lot of regional differences, which is another thing that is really striking because it might bring us back to the idea that microglia are really working in different regions different ways,” she added.

Now that they’ve acquired the grant, they explained, the real work begins. They noted that this is the product of multiple rejections for funding over the years. But for this uncommon pair of research partners, the failure is all part of the process. In fact, for Giliberto, it’s almost symbolic of the field in which they have chosen to work. Research and development in AD have been subjected to uncountable failures, and getting over the proverbial hill requires resilience, innovation, and a willingness to accept that a complex, multipathological disease will likely require a multifaceted, complicated approach.

“By no means have we arrived,” he said. “We have so much work to do. One grant doesn’t mean anything. You have to continue going, but it’s a good testament to the fact of continuing to push and working with an ethical statement in your head to do things right. That’s a common thread here. And we need to keep an open mind. Enough of just focusing on one aspect of the disease. This is a very complex disease. We cannot solve it by looking at one aspect. We need to move forward. We need to have a little bit more inventiveness.”

REFERENCES

More on NEUROLOGYLIVE.COM

STUDYING THE TRAJECTORY OF COGNITIVE DECLINE
Richard Gershon, PhD, vice chair for research, Northwestern University Feinberg School of Medicine, discussed how the cognitive mobile toolbox can be used to assess cognition in all populations.

View video or scan the QR code: neurologylive.com/cognitive-trajectory
The State of Coma Care: A Call for Action

By Wendy Ziai, MD, MPH

ON MARCH 22, 2021, the Neurocritical Care Society (NCS) and the Curing Coma Campaign launched the first World Coma Day, an international 24-hour symposium with a mission of awareness of coma as a treatable and recoverable clinical entity aimed at encouraging medical providers, scientists, industry, patients, and patient advocates to get involved in the Curing Coma Campaign; and motivating partnerships to participate in specific current and future scientific efforts devoted to curing disorders of consciousness.

More than 1200 participants attended this year, and we are looking forward to this annual event to raise awareness of disorders of consciousness and coma for many years to come. But before March 22, 2022, there is much work to be done. There is hope for patients with prolonged disorders of consciousness as a result of brain injury or other conditions and our goal is to improve patient outcomes related to coma.

Recovery From Coma Is Possible

While we have learned a great deal about coma, there is still limited knowledge with the overall care of the patient who is comatose. From a clinical perspective, we are familiar with what happens in the intensive care unit (ICU) and the hospital during the early stages of coma, but we don’t often observe or fully understand the trajectory of recovery in rehab and the home care environment. That is the key to unlocking the path toward curing coma.

The Challenge: How Do We Assess Coma?

A major challenge in neurocritical care is a patient with altered consciousness. Attempts to improve patients with altered consciousness have focused principally on separate treatment of specific types of brain injury or dysfunction rather than primarily on common pathways that could lead to treatment. There is a lack of large data sources tracking long-term recovery metrics and we need to develop better statistical and machine learning approaches for analyzing this data to effectively develop and implement treatments to impact recovery.

Given the unifying importance of alteration in consciousness and cognition and the major gaps in current management, one goal for the Curing Coma mission is developing an international registry for the collection of data to begin to determine common elements across assessments. There are a number of committees that are actively working on common data elements and registry creation. As it stands, the way we currently assess coma is generally imprecise. Up to 40% of assessments are inaccurate because of lack of useful measures for serial assessment, fluctuations in the clinical exam, and medication-induced impairment.

As a community, we first need to determine what data elements are required as a baseline for clinical assessment and determination of response to treatment. We all need to collect the same type of data to even begin working toward a common understanding. Agreement is needed on definitions of disorders of consciousness so that we can develop treatment options in a consistent way.
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Once we agree on how to collect and assess data at meaningful time points, we can then design proof-of-concept intervention studies to better manage and ultimately treat disorders of consciousness with a universal approach.

Avoiding Pessimism
Another challenge we need to tackle is the ability to better describe recovery trajectories of coma patients over the intermediate and longer term. Over 70% of deaths resulting from a traumatic brain injury occur in the early stages as a result of the early withdrawal of life support, which could be premature in some cases. As clinicians in the care of acute neurocritical patients, we tend to have an overly pessimistic outlook on coma recovery, and this may negatively impact the long-term outcomes of patients. Because of this uncertainty and limited knowledge regarding trajectory of recovery, we may be making premature and potentially inaccurate predictions for patients.

How to Prognosticate
Prognostication is one of the biggest challenges we face, especially in the short term. Without a crystal ball, we cannot predict how patients are going to look in 3 months, 6 months, or even 1 year from the onset of coma. Ultimately, we need to be flexible in how we prognosticate and develop an individualized approach in how each patient is managed. No 2 patients are ever alike, and in flexibly managing the way we react to a patient based on personal biology and biomarkers, we can hopefully make better-informed decisions for long-term care. Evaluating the brain’s response and capacity for recovery will likely include electroencephalography, functional imaging, genetic and blood-based biomarkers, and other tools. By studying the underlying causes and mechanisms affecting patient consciousness and responsiveness and more fully understanding the biological mechanisms of coma, we can begin to develop appropriate treatments and therapies to promote recovery from coma.

Over the long term, we don’t have enough information to determine functional outcomes. We need to track patients over multiple years to have useful predictive potential. This will enable those involved in the acute care of patients in a coma the ability to give a prediction along with a confidence interval around that prediction. For example, in the ICU, there may be pressure for early decisions to be made for patients who are comatose. From financial and hospital space issues to considerations for organ donation and even unconscious bias, the pressures in an acute care setting to make decisions quickly can sometimes usurp the time needed to monitor a patient to determine a long-term care strategy. Armed with multiyear data and the ability to make much stronger outcome predictions, the approach to how we care in the early stages for patients who are comatose is likely to change.

As such, we must keep in mind that not every patient has the potential for long-term recovery, so developing protocols for treating patients on both ends of the spectrum is something we are hoping to achieve.

A Call to Action
In 2019, the NCS launched the Curing Coma Campaign as its signature clinical, scientific, and public health effort. The Curing Coma Campaign is the first global public health initiative to tackle the unifying concept of coma as a treatable medical entity.

By understanding the biology of coma and involving everyone engaged in the care of coma patients—doctors, scientists, long-term caregivers, industry, regulatory agencies, patients’ families, and even recovered patients—we can develop support and collaboration with a unified approach to disorders of consciousness, resulting in improved patient outcomes.

This is our moon shot: We are all working together for the grand challenge of awakening hope.

Wendy Ziai, MD, MPH, is a professor of neurology at Johns Hopkins University and a member of the NCS Curing Coma Campaign Scientific Steering Committee. For more information on NCS and its Curing Coma Campaign, visit https://www.curingcoma.org/home.

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DIAGNOSIS THROUGH TELENEUROLOGY
Jason Poon, MD, neurologist, University of Utah, spoke to the current state of and potential for teleneurology in the diagnosis of neurological conditions.

View video or scan the QR code: neurologylive.com/poon-teleneurology
Keisha Greaves Is Named MDA's 2021 National Ambassador

The Muscular Dystrophy Association named Keisha Greaves, a 35-year-old woman who has been active in the MDA community since receiving a diagnosis of limb-girdle muscular dystrophy in 2010, as the company’s 2021 National Ambassador. She will represent families living with muscular dystrophy and other related neuromuscular diseases alongside current National Ambassador Ethan LyBrand, an 11-year-old from Decatur, Alabama. Keisha and Ethan will share their mission with the public as well as their partners, sponsors, and supporters through national and social media. They will also attend live events, in effort to reach larger audiences and ultimately educate and champion improved services for individuals and their families living with disabilities and neuromuscular disease through donations or volunteer action.

Andrew B. Singleton, PhD, Is Named Director of NIH Alzheimer Disease Research Laboratory

The National Institute on Aging (NIA) announced that Andrew B. Singleton, PhD, is the director of the new NIH intramural laboratory, the Center for Alzheimer’s and Related Dementias (CARD). Singleton, who had been serving as the CARD acting director since its construction plan launched in January 2020, brings decades of experience with neurodegenerative disease research. He will lead the lab’s scientific and administrative oversight to basic, translational, and clinical research for Alzheimer disease and related dementias, and collaborate with researchers throughout the world. In 2001, Singleton joined the NIH’s Intramural Research Program and became a principal investigator leading its Molecular Genetics Unit the following year. He became an NIA tenured senior investigator in 2007 and was named chief of the NIA Laboratory of Neurogenetics 1 year later.

Rudolph Tanzi, PhD, Is Named ProMIS Neurosciences Advisory Board Chair

ProMIS Neurosciences announced that Rudolph Tanzi, PhD, was appointed as the new chair for the company’s scientific advisory board after serving on the board for several years. Tanzi also serves as the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard University, as well as co-chair of the Genetics and Aging Research Unit, and co-director of the Henry and Allison McCanse Center for Brain Health at Massachusetts General Hospital. He has spent his career as a neuroscientist and geneticist with scientific expertise in Alzheimer disease (AD) and brain health. He served on the team that was the first to identify a disease gene for Huntington disease, using human genetic markers, helping to launch the field of neurogenetics, and he went on to identify all 3 early-onset familial AD genes, and the Wilson disease gene and several other neurological disease-related genes.

NIH Funds Facilitate Neurodegenerative Disorder Study Using New AI Tool

Under a new $5 million grant from the National Institutes of Health (NIH), researchers at the University of Florida will broadly test a new artificial intelligence (AI) tool aimed at distinguishing the precise diagnosis for patients with early Parkinson disease (PD) or 2 related neurodegenerative syndromes. The other 2 disorders, multiple system atrophy, Parkinsonian variant; and progressive supranuclear palsy, can be difficult to differentiate from PD because they share overlapping motor and nonmotor features. Principal investigators David Vaillancourt, PhD; Angelos Barmoutsis, PhD; and Michael Okun, MD, will create a new web-based software tool that will include MRI images from 315 patients across 21 sites in North America. The novel, noninvasive biomarker technique using diffusion-weighted MRI was previously developed in Vaillancourt’s lab and demonstrated its efficacy in an international, 1002-patient study published in The Lancet Digital Health in 2019.

Johns Hopkins Medicine Adds Neuropathy Center Following Gift

A recently announced gift from the Mervin and Rose Mary Merkin Foundation helped establish the Merkin Peripheral Neuropathy and Nerve Regeneration Center at Johns Hopkins Medicine, in Baltimore, Maryland. Richard Merkin, MD, founder of the Merkin Family Foundation, is also the founder and chief executive officer of Heritage Provider Network. Research activities at the center will include interdisciplinary teams working to significantly expedite nerve regeneration research, underlying causes, and progression, as well as identify developing new regenerative therapies. Ahmet Hoke, MD, PhD, director of the neuromuscular division and professor of neurology in the department, will be the inaugural director of the Merkin Center. “The Merkin Center will create a platform for speeding up the research in this area,” Hoke said in a statement. “We are looking forward to investing in pilot projects to stimulate research and attract new investigators to the field.”
AMYOTROPIC LATERAL SCLEROSIS (ALS) DISEASE PATHWAYS: EMERGING INSIGHTS

Advances in understanding neuronal survival and degeneration underscore the central role that the endoplasmic reticulum (ER) and mitochondria play in ALS.¹-⁴

1. In ALS, ER stress and dysfunction, in combination with abnormal DNA transcription, lead to misfolded proteins and accumulating protein aggregates, worsening ER stress, and neuronal death.²,³,⁵,⁶

2. In ALS, mitochondrial dysfunction and release of cytochrome C, along with an imbalance of pro- and antiapoptotic factor production, trigger the mitochondrial apoptotic pathway, leading directly to neuronal death.²