

HIGHLIGHTS FROM THE  
ECTRIMS MEETING

NOVEMBER 2015

## Ocrelizumab May Reduce Disability Progression in People With Primary Progressive MS

*Data support the hypothesis that B cells are central to the underlying biology of MS.*

**BARCELONA**—In people with primary progressive multiple sclerosis (MS), treatment with ocrelizumab may significantly reduce the progression of clinical disability sustained for at least 12 weeks, compared with placebo, according to results from a pivotal phase III study presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). In the study, which is called ORATORIO, clinical disability was measured by the Expanded Disability Status Scale (EDSS).

Ocrelizumab is an investigational, humanized monoclonal antibody designed to selectively target CD20-positive B cells. CD20-positive B cells are a type of immune cell thought to be a key contributor to myelin damage and axonal damage. Preclinical studies suggest that ocrelizumab binds to CD20 cell-surface proteins expressed on certain B cells, but not on stem cells or plasma cells, thus potentially preserving important functions of the immune system.

The ORATORIO trial was a randomized, double-blind, global multicenter study. Researchers administered placebo or 600 mg of ocrelizumab by IV infusion every six months to 732 people with primary progressive MS. The doses of ocrelizumab were given as two 300-mg infusions two weeks apart. The primary end point of the study was time to onset of confirmed disability progression, defined as an increase in EDSS that is sustained for at least 12 weeks.

Overall, the incidence of adverse events associated with ocrelizumab was similar to that of placebo. The most common adverse events were mild-to-moderate infusion-related reactions. The incidence of serious adverse events associated with ocrelizumab, including serious infections, was also similar to that of placebo.

“People with the primary progressive form of MS typically experience symptoms that continuously worsen after the onset of their disease, and there are no approved treatments for this debilitating condition,” said Sandra Horning, MD, Chief Medical Officer and Head of Global Product Development for Genentech, the developer of the therapy. “Ocrelizumab is the first investigational medicine to show a clinically meaningful and statistically significant effect on the progression of disease in primary progressive MS.”

In addition to ORATORIO, the phase III clinical development program for ocrelizumab includes OPERA I and OPERA II, which are randomized, double-blind, double-dummy, global multicenter studies in people with relapsing forms of MS. The results of the studies appear to validate the hypothesis that B cells are central to the underlying biology of MS. Genentech plans to pursue marketing authorization for ocrelizumab in relapsing MS and in primary progressive MS. The company will submit data from the OPERA I and II studies and from the ORATORIO study to the FDA in early 2016. ■



Whether it's your patients' first step or their next,

# POWERED FOR RESULTS

*Made for every day*

**TECFIDERA is one pill, twice a day.<sup>1</sup>**

## Indication

Tecfidera® (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

## Important Safety Information

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients experiencing signs and symptoms of anaphylaxis and angioedema (which have included difficulty breathing, urticaria, and swelling of the throat and tongue) should discontinue TECFIDERA and seek immediate medical care.

A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient who received TECFIDERA. 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. The 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. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation.

TECFIDERA may decrease lymphocyte counts; in clinical trials there was a mean decrease of ~30% in lymphocyte counts during the first year which then remained stable.

Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but not to baseline. Six percent of TECFIDERA patients and <1% of placebo patients had lymphocyte counts <0.5x10<sup>9</sup>/L. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

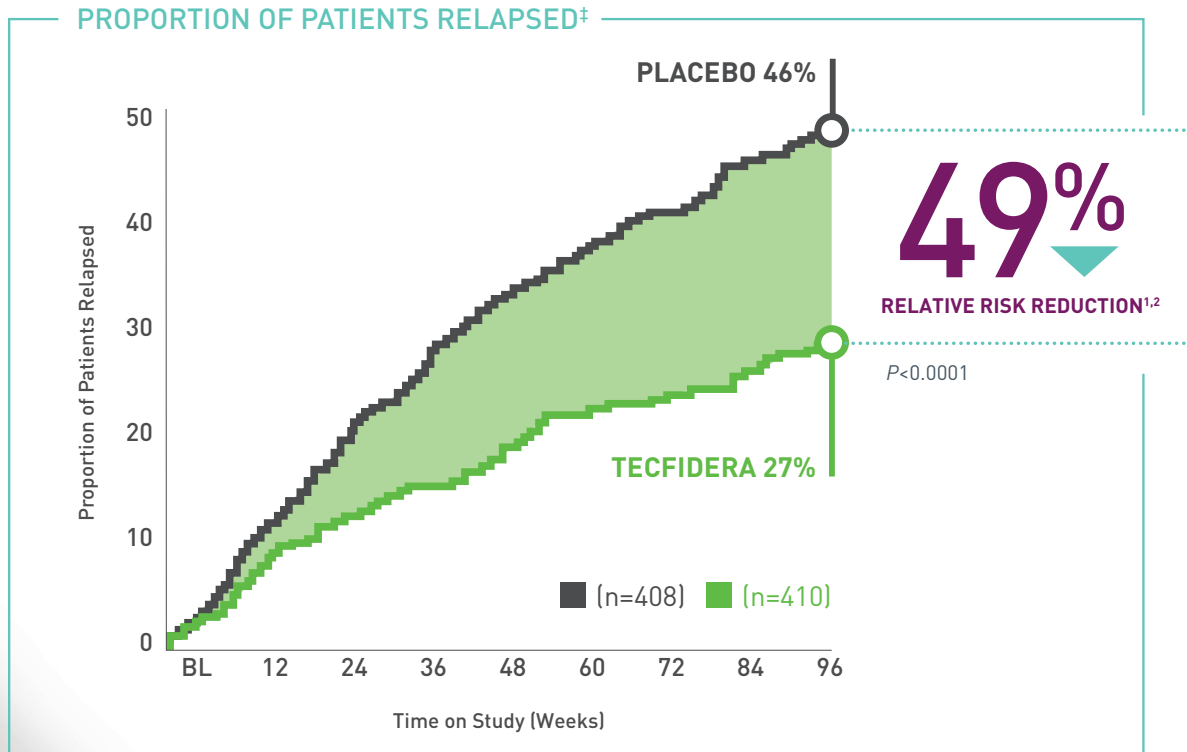
There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8x10<sup>9</sup>/L or 0.5x10<sup>9</sup>/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5x10<sup>9</sup>/L for 3.5 years). In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5x10<sup>9</sup>/L for at least six months. In these patients, the majority of lymphocyte counts remained <0.5x10<sup>9</sup>/L with continued therapy. A complete blood count including lymphocyte count should be obtained before initiating treatment, after 6 months, every 6 to 12 months thereafter and as clinically indicated. Consider treatment interruption if lymphocyte counts <0.5x10<sup>9</sup>/L persist for more than six months and follow lymphocyte counts until lymphopenia is resolved. Consider withholding treatment in patients with serious infections until resolved. Decisions about whether or not to restart TECFIDERA should be based on clinical circumstances.

TECFIDERA may cause flushing (e.g. warmth, redness, itching, and/or burning sensation). 40% of patients taking TECFIDERA reported flushing which was mostly mild to moderate in severity. Three percent of patients discontinued TECFIDERA for flushing and <1% had serious flushing events that led to hospitalization. Taking





With TECFIDERA, half as many patients relapsed in the 2-year DEFINE\* trial†



TECFIDERA with food may reduce flushing. Alternatively, administration of non-enteric coated aspirin prior to dosing may reduce the incidence or severity of flushing. TECFIDERA may cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Four percent of TECFIDERA patients and <1% placebo patients discontinued due to GI events. The incidence of serious GI events was 1%. The most common adverse reactions associated with TECFIDERA versus placebo are flushing (40% vs 6%) and GI events: abdominal pain (18% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%). Elevations in hepatic transaminases have been reported.

A transient increase in mean eosinophil counts was seen during the first two months. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage patients who become pregnant while taking TECFIDERA to enroll in the TECFIDERA pregnancy registry by calling 1-866-810-1462 or visiting [www.TECFIDERApregnancyregistry.com](http://www.TECFIDERApregnancyregistry.com).

**For additional important safety information, please see adjacent Brief Summary of full Prescribing Information.**

\*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS, a 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing-remitting multiple sclerosis (RRMS).<sup>1,2</sup>

†Included patients who had experienced at least 1 relapse over the year preceding the trial or had a brain magnetic resonance imaging (MRI) scan demonstrating at least 1 gadolinium-enhancing (Gd+) lesion within 6 weeks of randomization and had an Expanded Disability Status Scale (EDSS) score ranging from 0 to 5.<sup>1</sup>

‡Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.<sup>2</sup>

§Based on number of prescriptions from IMS NPA™ Weekly Data (September 27, 2013 to July 3, 2015).

**References:** 1. TECFIDERA Prescribing Information, Biogen, Cambridge, MA. 2. Gold R, Kappos L, Arnold DL, et al. *N Engl J Med.* 2012;367:1098-1107. Erratum in: *N Engl J Med.* 2012;367:2362. 3. Biogen, Data on file.

**For more information, visit [TECFIDERAHCP.COM](http://TECFIDERAHCP.COM)**



**170K**  
**PATIENTS**  
TREATED GLOBALLY<sup>3</sup>

TECFIDERA has been prescribed in the US more than any other oral therapy for RMS<sup>3</sup>



**5+ YEARS**  
OF CLINICAL AND  
REAL-WORLD EXPERIENCE<sup>1,3</sup>

TECFIDERA is contraindicated in patients with known allergy to dimethyl fumarate<sup>1</sup>



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**Tecfidera**  
(dimethyl fumarate) delayed-release capsules 240 mg

## **Tecfidera® (dimethyl fumarate) delayed-release capsules, for oral use**

### **Brief Summary of Full Prescribing Information**

#### **1 INDICATIONS AND USAGE**

TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

#### **2 DOSAGE AND ADMINISTRATION**

##### **2.1 Dosing Information**

The starting dose for TECFIDERA is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally. TECFIDERA should be swallowed whole and intact. TECFIDERA should not be crushed or chewed and the capsule contents should not be sprinkled on food. TECFIDERA can be taken with or without food.

Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed. Discontinuation of TECFIDERA should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of TECFIDERA with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing [see *Clinical Pharmacology* (12.3)].

##### **2.2 Blood Test Prior to Initiation of Therapy**

Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy [see *Warnings and Precautions* (5.3)].

#### **3 DOSAGE FORMS AND STRENGTHS**

TECFIDERA is available as hard gelatin delayed-release capsules containing 120 mg or 240 mg of dimethyl fumarate. The 120 mg capsules have a green cap and white body, printed with "BG-12 120 mg" in black ink on the body. The 240 mg capsules have a green cap and a green body, printed with "BG-12 240 mg" in black ink on the body.

#### **4 CONTRAINDICATIONS**

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or to any of the excipients of TECFIDERA. Reactions have included anaphylaxis and angioedema [see *Warnings and Precautions* (5.1)].

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 Anaphylaxis and Angioedema**

TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms have included difficulty breathing, urticaria, and swelling of the throat and tongue. Patients should be instructed to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

##### **5.2 Progressive Multifocal Leukoencephalopathy**

A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient with MS who received TECFIDERA for 4 years while enrolled in a clinical trial. 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. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly  $<0.5 \times 10^9/L$  for 3.5 years) while taking TECFIDERA [see *Warnings and Precautions* (5.3)]. The role of lymphopenia in this case is unknown. The patient had no other identified systemic medical conditions resulting in compromised immune system function and had not previously been treated with natalizumab, which has a known association with PML. The patient was also not taking any immunosuppressive or immunomodulatory medications concomitantly.

At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. 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.

##### **5.3 Lymphopenia**

TECFIDERA may decrease lymphocyte counts. In the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA and then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of TECFIDERA patients and  $<1\%$  of

placebo patients experienced lymphocyte counts  $<0.5 \times 10^9/L$  (lower limit of normal  $0.91 \times 10^9/L$ ). The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts  $<0.8 \times 10^9/L$  or  $0.5 \times 10^9/L$  in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly  $<0.5 \times 10^9/L$  for 3.5 years) [see *Warnings and Precautions* (5.2)]. In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts  $<0.5 \times 10^9/L$  for at least six months. In these patients, the majority of lymphocyte counts remained  $<0.5 \times 10^9/L$  with continued therapy. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

Before initiating treatment with TECFIDERA, a CBC including lymphocyte count should be obtained. A CBC including lymphocyte count should also be obtained after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of TECFIDERA in patients with lymphocyte counts  $<0.5 \times 10^9/L$  persisting for more than six months. Given the potential for delay in lymphocyte recovery after discontinuation of TECFIDERA, consider following lymphocyte counts until lymphopenia is resolved. Withholding treatment should be considered in patients with serious infections until the infection(s) is resolved. Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances.

##### **5.4 Flushing**

TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials, 40% of TECFIDERA treated patients experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued TECFIDERA for flushing and  $<1\%$  had serious flushing symptoms that were not life-threatening but led to hospitalization. Administration of TECFIDERA with food may reduce the incidence of flushing. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing [see *Dosing and Administration* (2.1) and *Clinical Pharmacology* (12.3)].

#### **6 ADVERSE REACTIONS**

The following important adverse reactions are described elsewhere in labeling: Anaphylaxis and Angioedema (5.1), Progressive multifocal leukoencephalopathy (5.2), Lymphopenia (5.3), Flushing (5.4) [see *Warnings and Precautions*].

##### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 most common adverse reactions (incidence  $\geq 10\%$  and  $\geq 2\%$  more than placebo) for TECFIDERA were flushing, abdominal pain, diarrhea, and nausea.

##### Adverse Reactions in Placebo-Controlled Trials

In the two well-controlled studies demonstrating effectiveness, 1529 patients received TECFIDERA with an overall exposure of 2244 person-years [see *Clinical Studies* (14)].

The adverse reactions presented in the table below are based on safety information from 769 patients treated with TECFIDERA 240 mg twice a day and 771 placebo-treated patients.

**Table 1: Adverse Reactions in Study 1 and 2 reported for TECFIDERA 240 mg BID at  $\geq 2\%$  higher incidence than placebo**

	TECFIDERA N=769 %	Placebo N=771 %
Flushing	40	6
Abdominal pain	18	10
Diarrhea	14	11
Nausea	12	9
Vomiting	9	5
Pruritus	8	4
Rash	8	3
Albumin urine present	6	4
Erythema	5	1
Dyspepsia	5	3
Aspartate aminotransferase increased	4	2
Lymphopenia	2	$<1$



### **Gastrointestinal**

TECFIDERA caused GI events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The incidence of GI events was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with TECFIDERA compared with placebo. Four percent (4%) of patients treated with TECFIDERA and less than 1% of placebo patients discontinued due to gastrointestinal events. The incidence of serious GI events was 1% in patients treated with TECFIDERA.

### **Hepatic Transaminases**

An increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA was seen primarily during the first six months of treatment, and most patients with elevations had levels <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase to  $\geq 3$  times the ULN occurred in a small number of patients treated with both TECFIDERA and placebo and were balanced between groups. There were no elevations in transaminases  $\geq 3$  times the ULN with concomitant elevations in total bilirubin >2 times the ULN. Discontinuations due to elevated hepatic transaminases were <1% and were similar in patients treated with TECFIDERA or placebo.

### **Eosinophilia**

A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

### **Adverse Reactions in Placebo-Controlled and Uncontrolled Studies**

In placebo-controlled and uncontrolled clinical studies, a total of 2513 patients have received TECFIDERA and been followed for periods up to 4 years with an overall exposure of 4603 person-years. Approximately 1162 patients have received more than 2 years of treatment with TECFIDERA. The adverse reaction profile of TECFIDERA in the uncontrolled clinical studies was consistent with the experience in the placebo-controlled clinical trials.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animals, adverse effects on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate (DMF) was administered during pregnancy and lactation at clinically relevant doses. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rats administered DMF orally (25, 100, 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the recommended human dose (RHD) of 480 mg/day. In rabbits administered DMF orally (25, 75, and 150 mg/kg/day) throughout organogenesis, embryoletality and decreased maternal body weight were observed at the highest dose tested. The plasma AUC for MMF at the no-effect dose is approximately 5 times that in humans at the RHD.

Oral administration of DMF (25, 100, and 250 mg/kg/day) to rats throughout organogenesis and lactation resulted in increased lethality, persistent reductions in body weight, delayed sexual maturation (male and female pups), and reduced testicular weight at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD.

### **Pregnancy Registry**

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TECFIDERA during pregnancy. Encourage patients to enroll by calling 1-866-810-1462 or visiting [www.TECFIDERApregnancyregistry.com](http://www.TECFIDERApregnancyregistry.com).

### **8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **8.5 Geriatric Use**

Clinical studies of TECFIDERA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information)

### **Dosage**

Inform patients that they will be provided two strengths of TECFIDERA when starting treatment: 120 mg capsules for the 7 day starter dose and 240 mg capsules for the maintenance dose, both to be taken twice daily. Inform patients to swallow TECFIDERA capsules whole and intact. Inform patients to not crush, chew, or sprinkle capsule contents on food. Inform patients that TECFIDERA can be taken with or without food [see *Dosage and Administration* (2.1)].

### **Anaphylaxis and Angioedema**

Advise patients to discontinue TECFIDERA and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema [see *Warnings and Precautions* (5.1)].

### **Progressive Multifocal Leukoencephalopathy**

Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in a patient who received TECFIDERA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that 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. [see *Warnings and Precautions* (5.2)].

### **Lymphocyte Counts**

Inform patients that TECFIDERA may decrease lymphocyte counts. A blood test should be obtained before they start therapy. Blood tests are also recommended after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated [see *Warnings and Precautions* (5.3), *Adverse Reactions* (6.1)].

### **Flushing and Gastrointestinal (GI) Reactions**

Flushing and GI reactions (abdominal pain, diarrhea, and nausea) are the most common reactions, especially at the initiation of therapy, and may decrease over time. Advise patients to contact their healthcare provider if they experience persistent and/or severe flushing or GI reactions. Advise patients experiencing flushing that taking TECFIDERA with food or taking a non-enteric coated aspirin prior to taking TECFIDERA may help. [see *Adverse Reactions* (6.1)].

### **Pregnancy and Pregnancy Registry**

Instruct patients that if they are pregnant or plan to become pregnant while taking TECFIDERA they should inform their physician.

Encourage patients to enroll in the TECFIDERA Pregnancy Registry if they become pregnant while taking TECFIDERA. Advise patients to call 1-866-810-1462 or visit [www.TECFIDERApregnancyregistry.com](http://www.TECFIDERApregnancyregistry.com) for more information [see *Use in Specific Populations* (8.1)].

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Biogen  
Cambridge, MA 02142

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## Treatment Effects of Alemtuzumab Are Maintained Over Five Years

*The drug was associated with a decreased annualized relapse rate and slowing of brain atrophy.*

**BARCELONA**—Alemtuzumab's benefits for patients with relapsing-remitting multiple sclerosis (MS) may persist for five years, according to data from an extension study presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

Participants who received alemtuzumab in the phase III pivotal studies CARE-MS I and CARE-MS II had positive outcomes throughout the course of the two-year trials. These benefits were maintained through three additional years in the extension study. In the pivotal studies, courses of treatment were administered at month zero and at month 12. After the initial two courses of treatment, 68% of treated patients from CARE-MS I and 60% of treated patients from CARE-MS II did not receive additional alemtuzumab during the following four years (ie, through month 60).

The low annualized relapse rates observed in patients who received alemtuzumab in CARE-MS I (0.18) and CARE-MS II (0.27) were maintained from year three (0.19 and 0.22, respectively) to year five (0.15 and 0.18, respectively). Through year five, 80% and 76% of patients who received alemtuzumab in CARE-MS I and CARE-MS II, respectively, did not have worsening of disability progression confirmed over six months, as measured by the Expanded Disability Status Scale (EDSS). Through year five, 33% and 43% of patients who had disability before receiving alemtuzumab in CARE-MS I and CARE-MS II, respectively, had improvement in EDSS score confirmed over at least six months, as compared with pretreatment baseline.

Furthermore, through year five, patients who received alemtuzumab in CARE-MS I and II had a slowing of brain atrophy, as measured by brain parenchymal fraction on MRI. In years three, four, and five, the median yearly brain volume loss was 0.20% or less, which was lower than the rate observed during the two-year pivotal studies. In each of years three, four, and five, most patients had no evidence of MRI disease activity (70–72% in CARE-MS I and 68–70% in CARE-MS II).

Through year five, the incidence of most adverse events during the extension study was comparable to or lower than that of the pivotal studies. The frequency of thyroid adverse events was highest in year three and declined in the subsequent years.

The phase III trials of alemtuzumab were randomized, rater-blinded, two-year pivotal studies comparing alemtuzumab with high-dose subcutaneous interferon beta-1a in patients with relapsing-remitting MS who had active disease and were either new to treatment (ie, in CARE-MS I) or who had had an inadequate response to another therapy (ie, in CARE-MS II).

More than 90% of the patients who received alemtuzumab in the CARE-MS phase III trials enrolled in the extension study. These patients were eligible to receive additional treatment with alemtuzumab in the extension study if they had at least one relapse or at least two new or enlarging brain or spinal cord lesions.

“These data illustrate that most alemtuzumab patients experienced sustained effects of treatment, despite the absence of additional treatment courses,” said Eva Havrdová, MD, PhD, Professor of Neurology at Charles University in Prague. “It is encouraging to see consistent effects maintained across multiple meaningful outcomes through five years.”

Serious side effects associated with alemtuzumab included infusion-associated reactions, autoimmune disorders (eg, thyroid disease, autoimmune cytopenias, and nephropathies), infections, and pneumonitis. The most common side effects of alemtuzumab are rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in an extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. ■

## Anti-LINGO-1 Monoclonal Antibody BIIB033 Improves Optic Nerve Latency in Acute Optic Neuritis

*Benefits appear to be greater in older people and individuals who receive treatment early.*

**BARCELONA**—Anti-LINGO-1 improved full-field visual evoked potential (FF-VEP) latency of the eye affected by acute optic neuritis relative to placebo, consistent with improved remyelination, according to a study reported at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). This latency recovery was greater in older subjects, subjects given the first dose earlier, and subjects with more severe pretreatment visual impairment.

In a primary efficacy analysis of the RENEW study, Orhan Aktas, MD, of Heinrich-Heine-Universität in Düsseldorf, Germany, and colleagues demonstrated an improvement versus placebo in optic nerve latency (-7.55 ms at week

**Investigators demonstrated an improvement versus placebo in optic nerve latency (-7.55 ms at week 24; -9.13 ms at week 32) consistent with remyelination in subjects with acute optic neuritis.**

24; -9.13 ms at week 32) consistent with remyelination in subjects with acute optic neuritis.

Research subjects ages 18 to 50 with a first unilateral acute optic neuritis episode were treated with high-dose steroids, then randomized to 100 mg/kg anti-LINGO-1 IV or placebo once every four weeks (ie, six doses) and followed to week 32. Optic nerve latency was measured using FF-VEP in the

affected eye versus the baseline value for the unaffected eye. Between-treatment comparisons were evaluated by ANCOVA in the per-protocol population, defined as subjects who completed the study and did not miss more than one study dose or receive disease-modifying therapy for multiple sclerosis. Further analyses of latency recovery at week 24 (affected eye FF-VEP latency  $\leq 10\%$  worse than baseline of fellow eye) and efficacy stratified by prespecified baseline characteristics using the median as the cutoff were performed.

FF-VEP latency recovery in the affected eye versus baseline of the fellow eye was compared between 33 subjects who received anti-LINGO-1 and 36 treated with placebo. At week 24, 24 subjects had normal or mildly prolonged FF-VEP latency, 15 from the anti-LINGO-1 and nine from the placebo group. Assessment of subjects stratified by prespecified baseline characteristics showed that improvement in FF-VEP latency in the affected eye at week 24 with anti-LINGO-1 was greater in the following patient subgroups: age 33 or older (difference vs placebo, -14.17 ms compared with -0.89 ms in subjects younger than 33); those who received treatment less than 25 days from the onset of acute optic neuritis (-9.01 ms vs -6.68 ms for those receiving treatment more than 25 days after acute optic neuritis onset); and those who had a high-contrast visual acuity score less than 49 (-10.92 ms vs -4.14 ms for a score of 49 or more). None of the subgroup-by-treatment interactions reached statistical significance due to the small sample size. ■

## Sodium Channel Blockade With Phenytoin Has a Neuroprotective Effect After Acute Optic Neuritis

***The treatment appears to thicken the macular retinal nerve fiber layer and the macular ganglion cell complex.***

**BARCELONA**—In addition to its neuroprotective effect on the peripapillary retinal nerve fiber layer, sodium channel blockade with phenytoin also appears to prevent degeneration of the macular ganglion cell complex after acute optic neuritis, according to data presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

**In one comparison, mean adjusted affected eye macular retinal nerve fiber layer thickness at six months was 4.67  $\mu\text{m}$  greater in the active group (a 42% treatment effect).**

Rhian E. Raftopoulos, MbChb, of University College London, and colleagues previously reported in a phase II trial that sodium channel blockade with phenytoin is neuroprotective in acute optic neuritis. The primary outcome measurements were the thickness of the peripapillary retinal nerve fiber layer and macular volume, measured using optical coherence tomography (OCT).

In the present study, the researchers sought to determine whether this neuroprotective effect is selective for particular anatomical layers of the retina. They enrolled patients with acute optic neuritis and randomized them within two weeks of symptom onset to receive phenytoin or placebo for three months. Spectral domain fast macu-

lar and papillomacular bundle (PMB) OCT scans were performed at baseline and after six months. Masked automated retinal layer segmentation was performed to obtain average thickness measures of retinal nerve fiber layer, ganglion cell and inner plexiform layer (GC/IPL), and the composite ganglion cell complex. The ganglion cell complex (GCC) encompassed the retinal nerve fiber layer plus GC/IPL. Active versus placebo differences in mean six-month affected eye retinal nerve fiber layer, GC/IPL, and GCC were calculated from macular ( $n=60$ ) and PMB ( $n=48$ ) scans, adjusted for the corresponding baseline measurements in the unaffected eye.

At baseline, the mean thicknesses of the retinal nerve fiber layer, GC/IPL, and GCC were similar in the active and placebo groups in the macula and papillomacular bundle. In the intention to treat comparison, mean adjusted affected eye macular retinal nerve fiber layer thickness at six months was 4.67  $\mu\text{m}$  greater in the active group (a 42% treatment effect). Mean adjusted macular GCC thickness was 5.63  $\mu\text{m}$  greater in the active group (a 28% treatment effect). Treatment had no significant effect on macular GC/IPL when measured alone.

In the PMB, mean adjusted retinal nerve fiber layer thickness was 2.49  $\mu\text{m}$  greater in the active group at six months, mean GC/IPL thickness 2.79  $\mu\text{m}$  greater, and mean GCC thickness 5.41  $\mu\text{m}$  greater. ■



## Teriflunomide Slows Brain Atrophy in People With Relapsing MS

***The difference between drug and placebo in reduction in brain volume was maintained for 24 months.***

**BARCELONA**—Teriflunomide significantly slows brain-volume loss, compared with placebo, over two years in people with relapsing-remitting multiple sclerosis (MS), according to new data presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). In this analysis, researchers examined MRI data from the TEMSO study using structural image evaluation, using normalization, of atrophy (SIENA).

**By month 12, median reduction from baseline in brain volume was 0.39%, 0.40%, and 0.61% for patients receiving 14 mg of teriflunomide, 7 mg of teriflunomide, and placebo, respectively.**

In the phase III TEMSO study, 1,088 participants with relapsing-remitting MS between ages 18 and 55 were randomly assigned to daily oral doses of placebo, 7 mg of teriflunomide, or 14 mg of teriflunomide for 108 weeks. The treatment arms were approximately equal in size, and randomization was stratified according to the baseline Expanded Disability Status Scale score and according to trial site, with a block size of six. Researchers regularly assessed the patients' change in brain volume from baseline. The study's primary end point was the annualized relapse rate, and the key secondary end point was confirmed progression of disability for at least 12 weeks. A total of 796 patients completed the study, with similar proportions of patients in the three study groups.

By month 12, median reduction from baseline in brain volume was 0.39%, 0.40%, and 0.61% for patients receiving 14 mg of teriflunomide, 7 mg of teriflunomide, and placebo, respectively. This change was lower for both teriflunomide groups, compared with placebo. For patients receiving 14 mg of teriflunomide, the change in volume was 36.9% lower than that for placebo. For patients receiving 7 mg of teriflunomide, the change in volume was 34.4% lower than that for placebo.

The significant difference in reduction of brain atrophy for teriflunomide versus placebo was maintained at month 24. Median reduction in brain volume from baseline was 0.90%, 0.94%, and 1.29% for 14 mg of teriflunomide, 7 mg of teriflunomide, and placebo, respectively. This change was lower for both teriflunomide groups versus placebo. For patients receiving 14 mg of teriflunomide, the change was 30.6% lower than that for placebo. For patients receiving 7 mg of teriflunomide, the change was 27.6% lower than that for placebo. In the MS clinical studies of teriflunomide, including TEMSO, the incidence of serious adverse events was similar between patients who received teriflunomide and those treated with placebo.

"Control or prevention of brain atrophy is an important target for MS treatment," said Ludwig Kappos, MD, Chair of Neurology at University Hospital Basel in Switzerland. "These data help provide further insight into teriflunomide's potential effects." ■

## Dimethyl Fumarate Shows Efficacy in Patients Newly Diagnosed With MS

*The drug may provide strong and sustained effects on relapses and disability progression.*

**BARCELONA**—Long-term treatment with delayed-release dimethyl fumarate demonstrated strong and sustained effects on relapses and disability progression among patients newly diagnosed with relapsing-remitting multiple sclerosis (MS), according to data presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

Delayed-release dimethyl fumarate demonstrated efficacy and safety in patients with relapsing-remitting MS in the phase III DEFINE and CONFIRM studies. ENDORSE is an eight-year extension of DEFINE and CONFIRM. In an integrated analysis of the DEFINE, CONFIRM, and ENDORSE trials, Jing Marantz, MD, PhD, and colleagues reported six-year outcomes with delayed-release dimethyl fumarate in newly diagnosed patients with relapsing-remitting MS.

### Five-Year Data

In ENDORSE, patients randomized in DEFINE or CONFIRM to delayed-release dimethyl fumarate 240 mg bid or tid continued on the same dosage. Patients randomized to placebo or glatiramer acetate (CONFIRM only) were rerandomized 1:1 to delayed-release dimethyl fumarate bid or tid. Results for the 240 mg bid dose were reported in the integrated analysis, as this represents the approved dosage. The glatiramer acetate arm was excluded from the parent analysis of newly diagnosed patients in DEFINE or CONFIRM.

“Newly diagnosed” was defined as MS diagnosis within one year prior to parent study entry, and patients were either treatment-naïve or previously treated with corticosteroids alone. Minimum follow-up (data as of May 14, 2014) was approximately five years; patients who received active treatment bid in previous studies (bid/bid) remaining on study received approximately five years or more of continuous delayed-release dimethyl fumarate treatment; patients receiving placebo bid remaining on study received two years of placebo in DEFINE or CONFIRM, followed by approximately three years of delayed-release dimethyl fumarate in the ENDORSE trial (ie, delayed treatment).

The newly diagnosed population included 144 bid and 85 placebo bid patients. At five years (ENDORSE year three), the annualized relapse rate in the newly diagnosed population was 0.137 in the bid patient group and 0.169 in the placebo bid group. Although the annualized relapse rate at five years was lower in the bid patient group, compared with those who received delayed treatment (ie, placebo followed by delayed-release dimethyl fumarate bid), those patients who switched to active treatment demonstrated improvements after switching to delayed-release dimethyl fumarate in ENDORSE: annualized relapse rate was 0.244 from years zero to two (DEFINE and CONFIRM), and 0.102 from years three to five (ENDORSE). The Kaplan–Meier estimated proportion of patients with 24-week confirmed disability progression at five years was 8.1% in those who remained on bid dosing and 20.4% in those who switched from placebo to active treatment.

### Six-Year Data

New long-term data from the six years of study—two years in DEFINE or CONFIRM followed by four years in the safety extension ENDORSE study—showed that the annualized relapse rate for the 144 newly diagnosed patients who started delayed-release dimethyl fumarate at the beginning of the study remained low (0.14). In those 85 patients who switched from placebo to active treatment, researchers saw that the annualized relapse rate was reduced from 0.26 during the placebo period to 0.1 in years three to six on delayed-release dimethyl fumarate treatment, which represents a 61% reduction. The proportion of patients with 24-week confirmed disability after six years of treatment was 15.7%, compared with 24.3% in those who switched to active treatment in year three.

The overall risk/benefit profile of delayed-release dimethyl fumarate remained consistent across all patients treated up to six years. “Early initiation of delayed-release dimethyl fumarate therapy does confer a long-term benefit for patients,” the researchers concluded. ■

## Daclizumab Reduces Brain Volume Loss, Compared With Interferon

*The results are consistent with research suggesting that the drug decreases inflammatory and lesion activity.*

**BARCELONA**—Patients with relapsing-remitting multiple sclerosis (MS) who receive daclizumab high-yield process (DAC HYP) for two years have significantly less brain volume loss than patients who receive intramuscular interferon beta-1a for two years, according to research presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). The effects of daclizumab, compared with those of interferon beta-1a, are not related to pseudoatrophy during the first 24 weeks of treatment, according to the investigators.

“These results are consistent with other MRI outcomes from DECIDE that showed significantly lower inflammatory and chronic brain MRI lesion activity for DAC HYP, compared with intramuscular interferon beta-1a,” said Douglas Arnold, MD, a neurologist at Montreal Neurological Institute and Hospital, and colleagues.

Compared with the general population, people with MS have more rapid brain volume loss that may lead to the accumulation of disability. Previous data suggest that intramuscular interferon beta-1a reduces brain volume loss at year two.

To compare the effects of DAC HYP and intramuscular interferon beta-1a on brain volume change, Dr. Arnold and colleagues examined data from the DECIDE study, which compared these two drugs in people with relapsing-remitting MS. Participants in the randomized, double-blind trial received 150 mg of subcutaneous DAC HYP every four weeks or 30 mg of intramuscular interferon beta-1a once weekly for at least 96 weeks. Some participants continued in the study for as long as 144 weeks. Whole brain volume change was evaluated as the percentage brain volume change (PBVC) over the prespecified intervals of weeks zero to 24, 24 to 96, and zero to 96 using the structural image evaluation, using

**The median annualized percentage brain volume change from baseline to week 96 was -0.580 for interferon beta-1a and -0.553 for daclizumab high-yield process, according to an analysis of data from the DECIDE study.**

normalization, of atrophy (SIENA) method. The researchers performed subgroup analyses according to patients’ baseline demographics and clinical characteristics.

A total of 1,841 patients were enrolled in DECIDE. Patients’ mean age was 36, and 68% of participants were female. Mean duration of disease was approximately four years, the mean number of relapses in the previous year was approximately 1.5, and mean Expanded Disability Status Scale score was 2.5. Median brain volume was 1,498 cm<sup>3</sup>.

Annualized PBVC was significantly reduced in the DAC HYP group between baseline and week 96, compared with the intramuscular interferon beta-1a group. The median annualized PBVC from baseline to week 96 was -0.580 for interferon beta-1a and -0.553 for DAC HYP. Subgroup analyses indicated that annualized percentage brain volume loss between baseline and week 96 was lower in the DAC HYP group than in the interferon beta-1a group across all subgroups, except in subgroups of patients who were male, had baseline T2 lesion volume equal to or above the median, and with MS diagnosis within three to 10 years.

Annualized percentage brain volume loss also was lower in the DAC HYP group, compared with the interferon beta-1a group in the period from baseline to week 24 (-0.674 vs -0.745). Annualized PBVC also was reduced between weeks 24 and 96 for DAC HYP, compared with interferon beta-1a (-0.511 vs -0.549). ■



## Anti-JCV Antibody Index and L-Selectin Hone PML Risk Stratification During Natalizumab Therapy

**Adherence to a risk-stratification algorithm could prevent as much as 85% of cases of PML.**

**BARCELONA**—The anti-JCV antibody index and L-selectin (CD62L) have merit for risk stratification and share a potential biological relationship with implications for general progressive multifocal leukoencephalopathy (PML) etiology, according to research presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). “A risk algorithm incorporating both biomarkers could strongly reduce PML incidence,” said Nicholas Schwab, PhD, of the Department of Neurology at the University of Münster in Germany.

Natalizumab treatment is associated with PML development, with more than 541 cases as of March 3, 2015. Treatment duration, prior immunosuppressant use, and JCV serostatus are currently used for categorical risk stratification, but PML incidence continues to rise steadily. Anti-JCV antibody index and CD62L have previously been proposed as additional risk-stratification parameters. Dr. Schwab and his research colleagues aimed at verifying and integrating both parameters into one applicable algorithm for risk stratification.

The research team gathered international cohorts of patients with multiple sclerosis who were treated with natalizumab. The participants were assessed for JCV index (1,921 control patients and nine pre-PML patients) and CD62L (1,257 control patients and 17 pre-PML patients).

Low CD62L in natalizumab-treated patients was retrospectively confirmed and prospectively validated as a biomarker for PML risk. The risk factor “CD62L low” increased a patient’s relative risk 55-fold. Validation efforts established an 86% sensitivity and 91% specificity for CD62L and a 100% sensitivity and 59% specificity for JCV index as predictors of PML.

Low CD62L values were also found in various other PML associations and stages (ie, lupus, lymphopenia, HIV, and acute natalizumab-PML). CD62L values correlated with JCV serostatus, so the lower the CD62L value of a patient was, the higher the probability that he or she was JCV positive. The researchers ultimately found that 26 out of 27 (96%) patients with low CD62L were JCV positive. Additionally, CD62L values negatively correlated with JCV index values.

“The combined use of JCV serology and CD62L level found 2% of patients studied to be at highest risk,” Dr. Schwab reported. “Adherence to the risk-stratification algorithm might prevent up to or over 85% of PML cases,” he said. ■

### Suggested Reading

Schwab N, Schneider-Hohendorf T, Pignolet B, et al. PML risk stratification using anti-JCV antibody index and L-selectin. *Multi Scler*. 2015 Oct 5 [Epub ahead of print].

## Do Attitudes Toward Marijuana Differ Between Men and Women With MS?

***Men with MS are more likely to report current and past use of marijuana than their female counterparts.***

**BARCELONA**—Among people with multiple sclerosis (MS), more men than women report current and past use of marijuana, according to the results of a survey presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

More men have spoken to their doctor about marijuana use than women, but fewer men thought that marijuana improves symptoms associated with MS.

“Gender differences in [marijuana] use and perceptions about use should be considered in discussions about use,” said Stacey Cofield, PhD, Associate Professor of Biostatistics at the University of Alabama at Birmingham and North American Research Committee on MS (NARCOMS) Coordinating Center Deputy Director. NARCOMS conducted the survey to investigate patients’ perceptions about the effectiveness of marijuana for treating MS symptoms.

**The researchers found no gender difference in the proportion of respondents who thought that marijuana should be legal. Overall, 91.5% of respondents supported the drug’s legality.**

NARCOMS is a participant-driven registry with semiannual, self-reported information about MS treatments and symptomatic therapies, financial status, insurance status, and MS disease status.

Participants in NARCOMS are invited to take part in additional research separate from the semiannual updates.

In August 2014, Dr. Cofield and colleagues invited 12,260 active participants in NARCOMS to complete an anonymous online questionnaire about current behaviors and attitudes toward marijuana use and legality. For the purpose of the survey, “marijuana” referred to smoked and ingested forms of the drug, as well as any controlled substance derived from marijuana or synthetic marijuana. Questions included

whether participants had used marijuana before their MS diagnosis, whether they used or considered using marijuana to treat MS symptoms, and whether they had discussed marijuana with their doctor. In addition, participants were asked what symptoms they thought marijuana might improve in MS and whether they had any of those symptoms.

A total of 5,665 participants responded to the survey, and 78.3% of respondents were women. Men were older than women at the time of the survey, but the researchers found no difference in age at diagnosis between genders. A higher proportion of men than women described their MS status as progressive without a history of relapse.

More men than women reported having used marijuana before their MS diagnosis. When examining data for marijuana users, the researchers saw no difference between genders in the number of days of marijuana use in the previous 30 days. The median number of days of use was 20 for both genders. Similarly, the researchers found no gender difference in the proportion of respondents who thought that marijuana should be legal. Overall, 91.5% of respondents supported the drug’s legality.

A higher proportion of men than women reported having muscle spasms, cramps, and spasticity, but a lower proportion of men thought that marijuana was effective for treating these symptoms. Similarly, a higher proportion of men than women reported tremor, but the researchers found no difference between genders in the perceived improvement of tremor with marijuana treatment. Also, more men than women (9.5% vs 5.9%) thought that marijuana did not improve any symptoms.

A higher proportion of women than men reported having migraines or headaches, anxiety, and nausea or gastrointestinal issues and thought that marijuana improved these symptoms. Gender differences persisted when the investigators adjusted the data for type of MS, age, duration of disease, and current marijuana usage. ■

## Long-Term Efficacy of Fingolimod Reinforced by New NEDA-4 Analysis

*The research suggests that NEDA-4 is a comprehensive and balanced measure for relapsing-remitting MS.*

**BARCELONA**—Data presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) show that 31.2% to 44.8% of patients continuously treated with fingolimod in the FREEDOMS core and extension trials achieved NEDA-4 in each of the years three to seven. NEDA-4—no evidence of disease activity in the four areas of relapses, MRI lesions, brain atrophy, and disability progression—is a comprehensive measure of MS disease control. A separate analysis confirmed that NEDA-4 status in the first year is a better predictor of

**In the first year, 27.1% of patients on fingolimod achieved NEDA-4, a comprehensive measure of MS disease control, compared with 9.1% on placebo.**

long-term outcomes than an assessment of three parameters (relapses, MRI lesions, and disability progression).

A follow-up analysis of pooled data from the FREEDOMS and FREEDOMS II core and extension trials was conducted to assess NEDA-4 each year for seven years in patients with relapsing-remitting multiple sclerosis (MS). Bruce Cree, PhD, MD, of the University of California San Francisco, and colleagues found that in the first year, 27.1% of patients on fingolimod achieved NEDA-4, compared with 9.1% on placebo. Switching from placebo to fingolimod after year two doubled the proportion of patients achieving NEDA-4 (12.7% to 27.4%) in year three. Of those patients on continuous fingolimod treatment, 31.2% to 44.8% reached NEDA-4 status in each of the years three to seven.

“Fingolimod showed sustained efficacy in achieving NEDA-3 and NEDA-4 over seven years,” Dr. Cree and colleagues reported. “Patients who were on placebo for the first two years demonstrated substantial improvements in NEDA-3 and NEDA-4 outcomes after switching to fingolimod. However, patients who received fingolimod from the start appeared to derive more benefit throughout the first five years.”

A separate follow-up analysis of data from the FREEDOMS and FREEDOMS II trials also confirmed for the first time that assessment of relapsing-remitting MS based on NEDA-4 allowed physicians to better predict long-term disability and brain shrinkage outcomes than just assessing relapses, MRI lesions, and disability progression. Ludwig Kappos, MD, of University Hospital in Basel, Switzerland, and colleagues found that NEDA-4 status over the first year was a significantly better predictor of disability and brain atrophy over the subsequent five years, as measured by patients reaching a stage of severe disability (EDSS of 6 or more) or having more than 0.4% mean annual brain volume loss. According to the researchers, these findings support the importance of assessing relapsing-remitting MS with NEDA-4 to enable a more reliable prediction of long-term disease outcomes.

“NEDA-3 status seems to correlate more with subsequent relapse and focal inflammatory MRI activity, while NEDA-4, which adds an imaging outcome that captures tissue destruction as a result of both focal and diffuse pathology, tended to be a better predictor of subsequent disability-related outcomes and brain volume loss,” Dr. Kappos and colleagues said. “These findings support use of NEDA-4 as a more comprehensive and balanced measure for relapsing-remitting MS.” ■



## Minocycline for MS?

*The antibiotic appears to reduce the risk of developing multiple sclerosis by 44.6%.*

**BARCELONA**—The tetracycline antibiotic minocycline reduces the relative risk of multiple sclerosis (MS) in patients experiencing their first clinical demyelinating event by 44.6%, according to the results of a phase III double-blind placebo-controlled Canadian multicenter clinical trial reported at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

“Current proven therapies for patients experiencing their first clinical demyelinating event show benefit the earlier they are introduced. However, payment coverage varies throughout the world, often delaying treatment until patients have demonstrated a second clinical attack,” said Luanne M. Metz, MD, Professor and Head of the Division of Neurology and Director of the MS Program at the University of Calgary in Canada, and her research colleagues. “Current oral therapies may not be ideal options because of safety concerns. Minocycline is an inexpensive oral anti-

**In a phase III trial, the absolute risk reduction was 27.4%, the relative risk reduction was 44.6%, and the number needed to treat was four.**

biotic with a recognized safety profile. It is widely available, often in generic formulation. Preclinical and preliminary clinical studies suggest it may be a therapeutic option in MS as both monotherapy and as an add-on treatment.”

Dr. Metz and colleagues enrolled subjects between ages 18 and 60, with onset of their first demyelinating symptoms within the previous 180 days and at least two

T2 hyperintense lesions on brain MRI. The study subjects were randomized to oral minocycline 100 mg bid or identical placebo. Treatment continued for 24 months or until MS diagnosis by 2005 McDonald criteria was confirmed. Follow-up visits were scheduled at one, three, six, nine, 12, 15, 18, 21, and 24 months. MRI scans were scheduled at screen; months three, six, 12, and 24; and at early end of study. The primary outcome was the proportion of participants who developed MS by six months. Risk estimates, absolute risk reductions, and relative risk reductions were calculated from actuarial life table analysis.

Starting in December 2008, 236 patients were screened at 12 Canadian sites; 143 were randomized. Intention to treat analysis included 142 subjects, as one subject was randomized in error; 72 received minocycline. Mean age was 35.8; 68.3% were women. Onset was monofocal in 76.8%, median Expanded Disability Status Scale score was 1.5, mean duration since onset of demyelinating symptoms was 84.5 days, 69% had more than eight T2 lesions, and 34.5% had enhancing lesions at screen. The risk of conversion to MS by six months was 61.4% in the placebo group and 34.0% in the minocycline group. The absolute risk reduction was 27.4%, the relative risk reduction was 44.6%, and the number needed to treat (NNT) was four. At 12 months, the absolute risk reduction was 25.1%, the relative risk reduction was 37.6%, and the NNT was four.

Based on their findings, the researchers concluded that minocycline 100 mg bid reduces conversion of the first clinical demyelinating event to MS. “Given its known safety and low cost, minocycline should be considered for initial treatment as well as for combination therapy trials.” ■

## Fampridine May Improve Walking and Quality of Life in Patients With MS

*The drug may reduce the number of walking aids necessary for some patients.*

**BARCELONA**—Prolonged-release fampridine improves objective and subjective measures of walking in patients with multiple sclerosis (MS), according to research presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). The drug also may improve patients' quality of life.

Rachel Farrell, PhD, a consultant at the National Hospital for Neurology and Neurosurgery in London, and colleagues enrolled 133 patients (93 females) with MS and severe walking impairment into a study to examine the long-term efficacy of prolonged-release fampridine on walking, quality of life, and functional ability when used in routine clinical practice. Participants were examined by neurologists and specialist physiotherapists in a specialist ambulation clinic. Study outcomes included Timed 25-Foot Walk (T25FW), MS Walking Scale (MSWS-12), the

**At two weeks, mean T25FW speed improved by 83.3% from baseline in the responder group, compared with a deterioration of 2.73% among nonresponders.**

EuroQol 5-dimension instrument (EQ-5D-5L), functional goals of treatment, and walking aid use. Patients whose T25FW speed increased by 20% or more from baseline and whose MSWS-12 scores also improved were considered responders.

Participants' mean Expanded Disability Status Scale score at baseline was 6.41. In all, 105 patients achieved responder status at two weeks. Mean baseline T25FW speed was 0.822 ft/s for responders and 0.934 ft/s for nonresponders.

At two weeks, mean T25FW speed improved by 83.3% from baseline in the responder group, compared with a

deterioration of 2.73% among nonresponders. Responders continued to walk faster at 22 months (0.920 ft/s) than at baseline. The researchers also observed significant improvements in the MSWS-12 among responders (-21.7), but not among nonresponders (+5.7).

In addition, the EQ-5D-5L index improved significantly among responders (+0.114), compared with nonresponders (-0.046). Responders reported more anxiety or depression on EQ-5L-5D at baseline than nonresponders, but scored better on the other four domains of the index. After four months, 79% of patients had achieved their goals (eg, walking to the corner shop, reducing falls, increasing social activities, or doing housework). After 10 months, 55% of patients had maintained their goals, and a further 38% had achieved their goals.

The majority of patients required the same walking aids at the end of the study period. A total of 17 patients required fewer aids, and three patients required more assistance. "This [result] suggests that prolonged-release fampridine responders perform better functionally for up to 22 months of treatment," said Dr. Farrell.

Side effects reported in the study were the same as those described in phase III and IV trials of fampridine. They included insomnia, urinary tract infections, gastrointestinal side effects, dizziness, and headaches.

"This cohort has a higher responder rate than that of pivotal trials. This [result] may be due to the severity of their walking impairment and the open-label nature of this study," said Dr. Farrell. "This [finding] brings into question the current practice of using a 20% improvement as the threshold for clinical significance." Overall, "the results of this study validate the utility of prolonged-release fampridine in improving walking of people with MS in routine clinical practice," she concluded. ■

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