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MS RESEARCH UPDATE

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MSAA's *MS Research Update* is published annually as a service to the MS community. This update provides an overview of the research behind the approved and experimental medications and therapies for the long-term treatment of multiple sclerosis. It does not include information on any symptom-management medications or therapies. For additional information about MS as well as MSAA's programs and services, please visit **mymsaa.org** or call **(800) 532-7667**.

MS RESEARCH UPDATE

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MS RESEARCH UPDATE

Published in February 2014, this update is a comprehensive overview of research findings on the FDA-approved disease-modifying therapies, as well as many experimental treatments

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INTRODUCTION

This year's expanded *MS Research Update* incorporates new information about the approved disease-modifying therapies (DMTs), as well as numerous experimental drugs currently under investigation for the long-term treatment of multiple sclerosis (MS). Highlights and recent research results are provided for each drug. **Please note that symptom-management drugs are not included in this report.**

This 2014 edition of MSAA's *MS Research Update* is being printed as a stand-alone issue, reflecting the incredible diversity and scope of research progress in MS. There is nonetheless far too much ongoing research in MS therapeutics for all of it to be covered here. This is therefore not a complete list, and not all study results could be included.

This information is based on a wide range of sources, including the extensive journal literature on MS and its management, a review of ongoing clinical trials, and papers presented at major national and international conferences. These include the 2013

Stephen Krieger, MD

conferences hosted by the American Academy of Neurology (AAN), the Consortium of Multiple Sclerosis Centers (CMSC), and the American and European Committees for Treatment and Research in Multiple Sclerosis (ACTRIMS and ECTRIMS).

The year 2013 marked the 20th anniversary of the United States Food and Drug Administration's (FDA) approval of Betaseron®, the first disease-modifying therapy for MS, and the beginning of the MS-treatment era. This medicine, and other available medications that followed, continue to show effectiveness over the long term. Importantly, these medications have also demonstrated a proven long-term

safety track record, which is crucial when considering that people with MS often require treatment for decades.

A recent review by Mark S. Freedman, MD, in the journal *Neurology*[1], summarized the positive long-term data for Avonex®, Betaseron®, Extavia®, Rebif®, and Copaxone®. These are the five FDA-approved drugs given via self-injection for the long-term treatment of MS. All five drugs (given individually, not in combination) reduce the frequency and severity of relapses. They also show that long-term treatment improves outcomes by delaying the time to significant disease progression. In addition, treatment begun early in the disease process is correlated with optimal outcomes over the long term.

Preferably, treatment is now often started when a person is diagnosed as having a clinically isolated syndrome (CIS). This is defined as a single attack (or the appearance of one or more symptoms characteristic of MS), with a very high risk of developing MS, when no other diseases or causes for symptoms are apparent. The use of MRI scans to identify lesions characteristic of MS has taken away the need to watch and wait for a second attack of MS in order to make this diagnosis. Numerous studies with multiple types of disease-modifying therapies (DMTs) have confirmed that early treatment at the time of CIS is beneficial in the long term.

Tysabri® is another important DMT option available for individuals with MS. Given via intravenous (IV) infusion, Tysabri is effective in reducing MS-disease activity, both in terms of relapses and lesions as seen on MRI scans. However, this medication does carry a small risk of a viral brain infection called PML (described on page 12), caused by the JC virus. A blood test to identify those who have been exposed to the JC virus, along with the recognition of other risk factors, allows clinicians to minimize this risk.

Three oral medications have been approved to treat MS in the past three years. In September 2010, Gilenya® (fingolimod) became the first oral DMT approved by the FDA for the treatment of relapsing forms of MS. Studies show that it reduces disease activity and the progression of disability, while offering the advantages of an oral medication to individuals who have difficulty with the injected DMTs. Particularly when starting this treatment, and at regular intervals afterwards, patients are monitored for potential adverse events.

September 2012 saw the FDA approval of the second oral DMT for relapsing forms of MS, Aubagio® (teriflunomide). As with all of the approved drugs for MS, information on this medication's clinical trial results, efficacy, and safety will be discussed in the pages to follow. Aubagio uses an entirely different mechanism of action, and presents another oral option to treat relapsing forms of MS.

The FDA approved the third oral DMT in March 2013, called Tecfidera™ (dimethyl fumarate or DMF; formerly known as BG-12). The data leading to its approval for relapsing MS, as well as ongoing studies, are included in this update. As MSAA Chief Medical Officer Dr. Jack Burks explains, "With the FDA approval of Tecfidera, a pill taken twice daily, another first-line oral treatment option for

people with relapsing forms of MS becomes available. The combination of robust effectiveness data with only transient side effects (consisting mainly of flushing and gastrointestinal symptoms) adds a valuable treatment to the list of options for patients and doctors to discuss."

Another new medication given by infusion, Lemtrada® (alemtuzumab, formerly known as Campath), was initially denied FDA approval in December, 2013. The pharmaceutical company Genzyme plans to appeal this decision. Please see details on these and many other new and emerging therapies in the pages to follow. As therapies for progressive forms of MS remain a crucial unmet need, **this Research Update highlights in bold those clinical trials that include or focus on primary- and secondary-progressive MS.** Past and present highlighted studies are listed on pages 6, 13, 18, 27, 29 through 35, and 40 through 43.

Individuals reading this update may also be interested in reading MSAA's cover story from the Winter/Spring 2010 issue of *The Motivator*, titled "MS Process and Targets for Treatment." This article may be easily accessed on MSAA's website at **mymsaa.org/publications** and by selecting "*The Motivator*" and the year of the issue. Anyone without internet access may call MSAA at **(800) 532-7667** to request a printed copy.

For more information on the specific symptoms of MS and treatments, please visit **mymsaa.org**, go to "About MS," and then select "Symptoms." For information on trial phases, please refer to the inside-back cover of this publication.

Please note that the authors have reported on the most recent study results available at the time of publication. While every effort has been made to provide meaningful, timely, and balanced information on each available agent, keeping the length of information equal for each medication is not possible. Please know that the different lengths of text should in no way be considered as favoritism toward any one product. Additionally, please note that references have only been cited for the newer study results.

Editor's note: Initial study results from therapeutic agents under investigation should be considered as preliminary, since additional studies and/or evaluations may be needed to prove the safety and efficacy of these agents. MSAA does not endorse or recommend any specific products or therapies. Readers are advised to consult their physician before making any changes to their medication, diet, exercise, or other treatment regimen.

This 2014 edition of MSAA's *MS Research Update* is dedicated to the memory of Diana M. Schneider, PhD, who passed away in September 2013. Dr. Schneider contributed mightily to the field of multiple sclerosis, using her extraordinary skills in writing and communication to disseminate advances in research and therapeutics to the MS community. This *MS Research Update* is written on the foundation that she herself wrote, and she is listed as a co-author again this year not merely symbolically, but because many of the words you will read are hers. This is but one of the many living testaments to her legacy of insight and MS education.

Avonex® (interferon beta-1a)

Company: Biogen Idec

- *Taken via weekly intramuscular injections; dosage is 30 mcg (micrograms)*
- *The FDA approved Avonex in 1996 for relapsing MS and more recently for individuals with clinically isolated syndrome (CIS)*

Avonex has been shown to reduce the number of relapses and lesions on an MRI, as well as slow the progression of physical disability. This drug has been shown to be both safe and effective.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and cells that decrease inflammation. They also reduce the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

In 2012, Avonex became available with a single-use, prefilled autoinjector called the Avonex Pen. The Avonex Pen incorporates the current Avonex Prefilled Syringe. Its needle is 25 gauge (width) and 5/8ths of an inch in length. Rather than a manual injection, the Avonex Pen injects with a click, using a covered needle that's half the length of the standard needle used with the Avonex Prefilled Syringe. In a Phase IIIb study, 94 percent of patients preferred the Avonex Pen over the Avonex Prefilled Syringe. This new option has the potential to make the weekly intramuscular self-injection process less stressful for people using this medication.

Long-term studies of Avonex include the ASSURANCE study, which evaluated 15-year data and showed that early suppression of clinical disease activity by Avonex is a marker of treatment response. This is associated with significant long-term benefits for quality of life as compared to patients who had received placebo. These results support other accumulating evidence that short-term responders to Avonex are also inclined to experience beneficial long-term outcomes.

A 10-year analysis of data from the CHAMPS trial – which treated patients with CIS and MRI findings consistent with MS – showed that although some had characteristics of disease progression, there was evidence of improved disease course with early treatment. These results again emphasize the value of early treatment. This effect remained evident in both the CHAMPIONS five- and 10-year extension studies.

Betaseron® (interferon beta-1b)

Company: Bayer HealthCare Pharmaceuticals

- *Administered by subcutaneous injection every other day; dose is 250 mcg*
- *Approved for relapsing forms of MS in 1993, and more recently, for individuals with CIS*

Betaseron reduces the number and severity of relapses (attacks) of MS. It also stabilizes the total lesion area as measured by MRI, compared to those without treatment.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and decrease inflammation. They also reduce the transport of damaging lymphocytes into the brain.

Follow-up data after 21 years from Betaseron's initial Phase III trial of RRMS[2]

show continued effectiveness and safety, as well as increased longevity. Following 21 years after the enrollment of this pivotal trial, Goodin and colleagues examined the effect of randomization to Betaseron versus placebo in the group of 372 patients on mortality. They found that patients originally assigned to Betaseron at random showed a 50-percent reduction in mortality over the 21-year period compared with placebo. The researchers conclude that the study provides evidence that early treatment with Betaseron (versus no treatment or delayed treatment) is associated with longer survival in patients with relapsing-remitting MS (RRMS). The results suggest that treatment was more effective when given early in the course of the disease, and a more favorable outcome can be seen for those patients who received the active drug in the very first trials when evaluated two decades later.

Improved effects of early treatment were also demonstrated in a group of 468 patients with CIS who were randomized to active treatment or placebo in the BENEFIT trial. In addition to the effect on preventing MS relapses and MRI lesions, by five years, the treated group showed greater improvement in scores on the Paced Auditory Serial Addition Test (PASAT), a measure of cognitive function. A follow-up BENEFIT trial extension study at eight years presented in 2013 showed both groups had stable or low disability levels, although the patients treated immediately with Betaseron following CIS had fewer relapses than those with delayed treatment.

The small START study of patients with RRMS was designed to identify immune markers of Betaseron therapy. Immune markers are tendencies or indicators observed across a population with a particular disease state. Immune markers in this study were compared in those patients with and without relapses during the first year of treatment.

The study revealed that the treated group showed significant changes in the levels of several immune-system markers. A trend toward higher levels of the pro-inflammatory cytokine interleukin-17 (IL-17) was found in patients who relapsed. (Cytokines are small proteins that may stimulate or inhibit the function of other cells, and can be studied in the blood.) Higher brain-derived neurotrophic factor (BDNF) levels were observed in the relapse-free group. (BDNF is a protein found in the brain that helps to support nerves and their development.)

The data suggest that the mode of action of the beta interferons may involve a shift in cytokines in favor of an anti-inflammatory/regulatory profile. Findings also suggest that elevated IL-17 may correlate with having relapses, while increased levels of another cytokine, BDNF, may be protective. These findings serve as a platform for further research of biomarkers predictive of responses to interferon therapy. More discussion on the potential role of biomarkers in the future of MS therapy is given later in this article.

Copaxone® (glatiramer acetate)

Company: Teva Neuroscience, Inc.

- *Given via daily (20 mg) or three-times-weekly (40 mg) subcutaneous injections*
- *Approved for RRMS and CIS*

Copaxone has been shown to significantly reduce the annual relapse rate in RRMS and reduce the risk of people with CIS for developing clinically definite MS (CDMS) at two years.

Copaxone is a synthetic polypeptide that mimics myelin basic protein, a key component of the myelin sheath (the protective covering of the nerves) that is damaged in MS. This therapy appears to decrease immune-system T cells that damage myelin, and may decrease inflammation by favorably shifting the balance among T-cell subtypes as well as by affecting several interleukins. (Interleukins are a type of cytokine, which are small proteins that may stimulate or inhibit the function of other cells.) Copaxone may also induce lymphocytes (immune-system cells produced to fight infection and disease) to produce factors that enhance the survival of cells that produce myelin, and may have a neuroprotective action that prevents damage to axons (nerve fibers).

An international European study called PreCISe was conducted to determine whether immediate treatment with Copaxone is better than delayed treatment in preventing conversion to clinically definite MS (CDMS). This study has shown that early treatment with Copaxone reduced the risk of converting to CDMS. The five-year extension data from this study were presented recently. The delay in the development of CDMS (resulting from early initiation of Copaxone) over placebo was maintained in the extension study with a CDMS risk reduction of 41 percent at five years. These results establish the importance of initiating treatment with Copaxone as early as possible to protect patients from the accumulation of disease activity.

In 2013, results were reported from the COPTIMIZE study,[3] a two-year observational survey of 672 patients with RRMS switching to Copaxone due to a lack of efficacy or treatment intolerability with a different disease-modifying therapy. Patients who switched to Copaxone from other disease-modifying drugs generally improved in measures of fatigue, cognition, quality of life, and depression; mobility remained stable, although the Expanded Disability Status Scale (EDSS) increased slightly from baseline. A total of 72.7 percent of the patients who switched to Copaxone remained relapse free.

Several years ago, the PROMISE study of 943 patients with primary-progressive MS (PPMS) failed to show that Copaxone was effective in this population of people with MS. Approximately 10 percent of the MS population is diagnosed with PPMS, where individuals experience a steady worsening of symptoms from the start, and do not have the periodic relapses and remissions found with relapsing-remitting MS (RRMS).

A smaller number of individuals are diagnosed with progressive-relapsing MS (PRMS), which begins as PPMS, but subsequently develops relapses. PRMS is similar to PPMS as it steadily worsens from the onset, but symptom flare-ups (with or without remissions) are also present. This is

considered the least common form of MS. There has been some debate as to whether categorizing PRMS separately from PPMS – in terms of clinical course and prognosis – can be justified. A sub-study of the PROMISE data[4] evaluated differences in baseline characteristics and disability progression between patients with PPMS and PRMS.

In this PROMISE sub-study, 42 of the 943 PPMS patients ultimately developed relapses and converted to PRMS. Although the numbers of PRMS patients analyzed in this study were small, the results suggested that disease progression is more rapid in this clinical sub-

Effects of Interferons and Copaxone on Pregnancy

Pregnancy outcomes with women on interferon beta-1b (Betaseron® and Extavia®) were examined in a large retrospective study presented in 2013.[5] The authors conclude that the data do not suggest an effect of interferon beta-1b on pregnancy outcomes after review of 1,045 pregnancy outcomes of women with an ongoing pregnancy at the time of reporting. Most pregnancies exposed to interferon beta-1b in utero resulted in healthy live births, and the spontaneous abortion rate was consistent with the rate seen in the general population. Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry[6] were also presented in 2013. Data were presented on 96 pregnancies, and no pattern was seen to suggest increased negative outcomes (such as fetal abnormalities) with Betaseron. Continued monitoring is recommended.

A German study looked at the effects of interferons and Copaxone on pregnancy and relapse rate. While these data support previous findings that the interferons and Copaxone do not present a major risk for birth defects, anyone who is pregnant or plans on becoming pregnant should discuss the risks and the benefits with her doctor before starting or continuing any disease-modifying therapy. This study also reconfirmed the reduced MS-relapse rate seen during pregnancy and the increased relapse rate particularly in the first three months after birth. Exclusive breastfeeding seemed to have beneficial effects on postpartum relapse-rate reduction.

Editor's Note: While the data presented on pregnancy were encouraging, as a limited number of women who became pregnant on DMTs did not see abnormalities in their babies, individuals with MS need to be strongly cautioned. These studies look at small numbers of pregnancies and do not suggest that getting pregnant is considered safe while taking DMTs. Interferons in particular have been associated with spontaneous abortion (miscarriage) in animal models, and are not recommended for women who are pregnant or attempting to conceive. The recommendations of the FDA and MS experts still stand for women on DMTs to take preventative measures to avoid pregnancy.

Copaxone® (continued)

group. Since PRMS falls under the category of "relapsing forms" of MS, the use of disease-modifying therapies may be considered for individuals with this type of MS.

The FDA-approved dose for Copaxone is 20 mg per day, given subcutaneously. The GALA trial was a randomized, placebo-controlled trial of Copaxone dosed at 40 mg given by subcutaneous injection three-times weekly versus placebo. Data from this trial were first presented in Fall 2012.[7] This three-times weekly dosing strategy of Copaxone reduced relapse rates by 34 percent compared with placebo, and reduced new MRI lesions by 35 percent. This is comparable with the expected efficacy of Copaxone given at the standard dose of 20 mg injected daily, and no new safety concerns were identified.

Teva Pharmaceutical Industries Ltd., the makers of Copaxone® (glatiramer acetate), announced in May 2013 that the FDA had accepted a supplemental New Drug Application (sNDA) for Copaxone at this higher dose and reduced frequency. The new dosing is double the concentration (40 mg) and is given three days per week (also via subcutaneous injection). On January 28, 2014, Teva Pharmaceutical Industries Ltd. announced that the three-times per week dosing of Copaxone (at the new, 40-mg dose) had been approved by the FDA. This new formulation enables individuals who take Copaxone to reduce their number of subcutaneous injections by 60 percent, once they are prescribed the new dosing regimen. Teva states that in addition to the newly approved dose, daily Copaxone (at the 20-mg dose) will continue to be available.

Combination Studies

Although in MS the standard of care has been to use one disease-modifying therapy at a time, many other conditions from high blood pressure to cancer are often treated with combinations of medicines to achieve the best outcome. Combining medications safely and effectively requires careful long-term studies, as drug interactions can be complex and difficult to predict.

Results were presented in 2012 for the Combi-Rx trial,[8] designed to assess if the combination of Copaxone and Avonex is more effective at reducing relapse rates than either agent alone. This National Institutes of Health (NIH)-funded trial recruited 1,008 patients, who were randomized to three study arms: combination of Copaxone and Avonex; Copaxone alone; and Avonex alone.

Although all participants were on one or both of the active treatments, the trial was placebo-controlled. This means that for individuals not given the combination of Copaxone and Avonex, they would receive either Copaxone and a placebo, or Avonex and a placebo. This allowed researchers to compare all three treatment groups equally.

Interestingly, the combination of Copaxone and Avonex taken together was not statistically superior to either therapy taken alone at preventing relapses. It is worth noting that these are the lowest relapse rates ever recorded in a clinical trial of these available agents, with the Combi-Rx trial continuing to support the excellent efficacy of these medicines, particularly when utilized early in the disease course. In this trial, the

treatment group that received Copaxone alone had the lowest number of relapses.

Interestingly, in the Combi-Rx trial,[9] the combination was found to be superior to individual drugs for new MRI lesion activity and the accumulation of total lesions. However, combination therapy failed to show an advantage on several other MRI outcomes.

A Phase II trial to study the effect of combining Copaxone and estriol (a naturally-occurring estrogen hormone) in RRMS on relapse rate is continuing. MS relapses are known to be significantly decreased during pregnancy. This trial is evaluating whether oral treatment with estriol, the major estrogen of pregnancy, induces a decrease in relapses in RRMS when used in combination with injectable Copaxone. If successful, this clinical trial could lay the groundwork for a larger, more definitive trial that might lead to a new oral treatment option for women with MS. A pilot trial was encouraging, and data from this study are expected in early 2014.

Extavia® (interferon beta-1b)

Company: Novartis Pharmaceuticals Corp.

- *Administered by subcutaneous injection every other day; dose is 250 mcg*
- *Approved for relapsing forms of MS and for individuals with CIS*

Extavia is an interferon beta-1b that is biologically identical to Betaseron and made in an identical process, but marketed by a different company. It was released in early 2010.

Extavia shares all prescribing, side effect, and safety information with Betaseron. The two pharmaceutical companies manage the patient-support programs differently; prices and copayments may also vary. The latest information is available through the patient-support programs at these two companies. For more information, visit **mymsaa.org**, and select "About MS," and "Prescription Assistance Programs."

Rebif® (interferon beta-1a)

Company: EMD Serono, Inc. and Pfizer Inc

- *Administered by subcutaneous injection three times weekly; dosage is 22 or 44 mcg (the 44 mcg dose appears significantly more effective than 22 mcg, and 44 mcg is the dose most often used in the United States)*
- *Approved for relapsing types of MS*

Rebif reduces the frequency of relapses and slows the progression of disability. It has also been shown to reduce MRI lesion area and activity compared to placebo.

Interferons appear to reduce inflammation

Rebif® (continued)

by modulating a favorable balance between cells that increase inflammation and cells that decrease inflammation. They also reduce the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

Two Phase IV observational clinical trials have been performed to evaluate ease of use and convenience of new injector devices for Rebif. These include The Multicenter, Open-label, Single-use Autoinjector Convenience Study of a device called Rebidose ®,[10] and a multi-center, observational, 96-week Phase IV study of the RebiSmart™ self-injection system.[11] Rebidose® is a single-use simplified autoinjector that provides ease of administration through a simple push-button injector. Rebidose became available in the United States in the first-quarter of 2013. The RebiSmart™ device, not yet approved in the United States, is an electronic autoinjector that stores several doses of Rebif at a time, and provides an interactive interface to help make injections more tolerable and reminders to stay on schedule with the medication. In a German study, it was found to have a 97-percent adherence rate at three months from the initiation of auto-injector use. These two new injector devices may improve compliance with Rebif in people with relapsing forms of MS.

The recent REFLEX study[12] of 517 patients compared the efficacy of two dosing frequencies (once or three times per week) of Rebif versus placebo. The effect studied is the conversion to definite MS in patients with clinically isolated syndrome (CIS), which is also referred to as a "first demyelinating event." The primary endpoint was the time to confirmed MS using the McDonald criteria, which is a set of guidelines used to confirm a diagnosis of MS. The secondary endpoint was time to clinically definite MS (CDMS). CDMS is confirmed only when a second neurologic event (indicative of MS) occurs in a patient who previously had one presenting symptom and was not yet diagnosed with MS.

Rebif, given at the standard dose of 44 mcg three times weekly, brought about a 51-percent reduction in the development of MS as compared with placebo. A 31-percent reduction in MS risk was seen with the once-weekly version of interferon beta-1a given subcutaneously, suggesting that the high-frequency interferon was more successful at prevention of disease activity in patients with CIS.

The Phase IV SKORE study continues to evaluate cognition and fatigue in people with RRMS treated with Rebif. Its primary outcome measure is the percentage of patients with stable or altered cognition status; secondary outcome measures include the proportion of relapse-free subjects and the proportion with defined Expanded Disability Status Scale (EDSS) changes. The study has 300 participants; it was initiated in June 2009 and was scheduled for completion in 2013; data are forthcoming.

A Phase IV observational study is ongoing, but is no longer recruiting participants. It is evaluating the effectiveness of Rebif therapy on quality of life, using two health-related, quality-of-life measures.

Novantrone® (mitoxantrone)

Company: EMD Serono, Inc.

- *Given via intravenous infusion, the dose varies according to an individual's weight. It is administered once every three months for a maximum of two-to-three years. The total dose is limited to avoid risking damage to the heart.*
- *Approved for use in SPMS, PRMS, worsening RRMS, and people who are not responding favorably to standard therapies.*

This drug appears to delay the time to a first-treated relapse, reduce the number of relapses, delay the time to disability progression, and decrease the number of new lesions that can be detected by MRI. It also appears to stabilize disease activity in some individuals with SPMS.

Novantrone is an immunosuppressant that has been used for many years to treat cancer. It targets rapidly dividing cells, including those believed to be involved in MS. Side effects may include cardiac disease and leukemia; patients must be closely monitored to minimize these risks. The risks of leukemia and cardiotoxicity limit the use to a maximum of two to three years and have dramatically reduced the use of Novantrone in the United States.

In June 2013, the FDA released a message regarding the potential harm that Novantrone can have on the heart's pumping action. Individuals who have or will be taking this drug must have their heart tested before treatment and every year thereafter, even after discontinuing with Novantrone. To view the full message, please visit **http://mymsaa.org/news-msaa/911-fda-statement-novantrone**.

Tysabri® (natalizumab)

Company: Biogen Idec and Elan Pharmaceuticals, Inc.

- *Administered via intravenous infusion every four weeks in TOUCH program-authorized infusion centers; dose is 300 mg*
- *Approved for individuals with relapsing types of MS*

This drug is generally recommended for patients who have not responded adequately to, or who cannot tolerate, another treatment for MS, although its use is evolving as described below.

This laboratory-produced monoclonal antibody acts against a molecule involved in the activation and function of lymphocytes (immune-system cells produced to fight infection and disease) and their migration into the central nervous system (CNS). Recent data suggest that it may also enhance remyelination and stabilize damage to the myelin sheath (the protective covering of the nerves).

A pivotal trial of Tysabri showed that this agent substantially reduces clinical and MRI activity in relapsing MS. Recent studies with Tysabri indicate that the drug may achieve a sustained improvement in disability for individuals with relapsing-remitting MS (RRMS). At 18 months and up to 24 months of treatment with Tysabri, 87 percent of RRMS patients previously treated with Avonex showed stable or improved MRI scans. In this same group, disability scores as measured by the Expanded Disability Status Scale (EDSS) were stable or improved in 59 percent of patients.

Tysabri® (continued)

Progressive Multifocal Leukoencephalopathy

Tysabri has been increasingly utilized as a disease-modifying therapy in RRMS, though clinical use of this drug has been limited from the outset by the risk of progressive multifocal leukoencephalopathy (PML). PML is a viral brain infection caused by the JC virus, which, when not discovered and treated early, can typically lead to severe disability or death. (Many people are exposed to the JC virus [JCV], which typically remains dormant; however, it may become activated and infect the brain when one's immune system becomes weakened, a condition that may result from immuno-suppressive drugs.)

Following a suspension of the drug in 2005 after two MS patients in Tysabri clinical trials developed PML, Tysabri was re-released in 2006. Once projected as a universal risk of approximately 1 in 1,000, based on Tysabri's pivotal trial data, new data presented and published in 2012 allow for the risk of Tysabri-associated PML to be estimated with increasing precision.

Three risk factors for Tysabri-associated PML have since been identified that allow for the classification of individuals by relative risk of PML.[13] The most important risk factor for PML is the presence of antibodies to the JC virus. Roughly 50 to 60 percent of adults carry the JCV antibodies, which can now be determined by a simple blood test.

The JCV Antibody Program (STRATIFY-2) began in April 2010, enrolling more than 30,000 people with MS, and will continue for several more years. Testing for JCV antibodies was added to the FDA label for Tysabri in 2012. The JCV antibodies assay is available through Quest Labs, at no charge to patients if ordered with the "STRATIFY JCV" test form (available from Quest and Biogen Idec). People testing negative for JCV antibodies are at risk for becoming JCV-positive by approximately 2 to 3 percent per year. Current recommendations are to re-test JCV antibodies status every six months in JC-virus negative people on Tysabri therapy.

The second risk factor for the development of Tysabri-associated PML is the duration of Tysabri treatment. Risk for PML in JCV-positive people increases the longer Tysabri is used. The risk is small in the first year of treatment with Tysabri, likely less than 1 in 1,000. In the second year, this increases to approximately 1 in 500, and beyond two years on Tysabri, the risk increases further.

The third risk factor for the development of Tysabri-associated PML is prior treatment with immune-suppressing medications such as Cytoxan® (cyclophosphamide), Novantrone® (mitoxantrone), or other chemotherapy agents. Standard injectable MS disease-modifying therapies (interferons and Copaxone, listed earlier) are not considered immune suppressants, and use of these prior to Tysabri does not increase the risk of PML.

As of Fall 2013, approximately 370 cases were reported of PML[14] with Tysabri, while more than 100,000 people have been treated with this medication. The FDA labeling of Tysabri has been updated to further quantify the risk. The new labeling also notes the increased risk from previous use of immunosuppressive medications.

Although PML is always serious, it is no longer always fatal. Early recognition and the quick removal of Tysabri using a procedure called plasmapheresis have improved the outcomes. Early PML diagnosis and treatment increases the survival rate to 80 percent (although often with disability). With risk-assessment based on the three risk factors, and careful consideration regarding how long someone with MS (who is JCV-positive) chooses to remain on Tysabri, the hope is that new cases of PML can be drastically minimized in the future.

A Phase IV trial, The Randomized Treatment Interruption of Natalizumab (RESTORE)[15] study, evaluated the impact of stopping Tysabri and switching to other disease-modifying therapies. This study enrolled 175 patients and found a high rate of recurrence of MS disease activity, both in terms of relapses and new lesions on MRI, beginning about three months after Tysabri was stopped. This study provides important information, especially for people on Tysabri who are weighing the risks and benefits of stopping this drug, particularly in light of the risk of PML. An informed, individualized treatment decision regarding duration of Tysabri therapy should be made in a collaborative manner between patients and their neurologists or MS specialists.

Current Study Information

As the use of Tysabri in early MS has not been widely studied, 300 individuals with early RRMS who are JC virus antibody negative will be followed over the course of four years while undergoing treatment with Tysabri.[16] The purpose of the study is to find out if any assessments might predict whether or not patients receiving Tysabri will remain free of disease, and also to determine how effective Tysabri is at keeping patients who are in the early stages of RRMS free of disease.

Final results of the Tysabri 24 PLUS study were presented in 2013. In this observational study, the clinical course of patients with RRMS receiving Tysabri 300 mg intravenously every four weeks for more than two years was assessed. Patients experienced reductions in relapse rates of more than 90 percent compared to their status before treatment. Eighty percent of patients experienced no relapses during the entire observation period after baseline. The mean EDSS scores remained stable at the level observed before the start of treatment. Safety data, including the number of cases of progressive multifocal leukoencenphalopathy (PML) were consistent with the known safety profile of Tysabri.

A small Phase II clinical trial, Natalizumab Treatment of Progressive Multiple Sclerosis (NAPMS), was performed at Copenhagen University Hospital to **study the safety and efficacy of Tysabri treatment of PPMS and secondary-progressive MS (SPMS)**.[17] It enrolled 24 patients and showed a reduction in markers of inflammation in the spinal fluid, as well as evidence of protection of brain tissue on modern MRI measures. This proof-of-concept study provides encouraging evidence that Tysabri may have beneficial effects in progressive forms of MS.

To continue this line of investigation, a large, **randomized trial of Tysabri in SPMS called ASCEND**[18] is ongoing, and will evaluate the effects on the accumulation of disability in

Tysabri® (continued)

people with SPMS. As of Fall 2013,[19] all 889 SPMS patients have been enrolled. This trial is expected to conclude in 2015.

A small study of 20 individuals with RRMS is evaluating the role of Tysabri on cognition and neurodegeneration (the breakdown or cell death of nerve cells). Its objective is to further establish the role of Tysabri in preventing neurodegeneration in MS and to establish new markers for such damage.

Other studies are exploring the effects of Tysabri on ambulation (walking and mobility), cognition, fatigue, depression, bladder function, sexual function, disability, and health-related quality of life. Some of these studies are completed with generally favorable results. One study indicated that Tysabri-treated patients had fewer MS-related hospitalizations and emergency-room visits over one year of treatment, suggesting that it may reduce the economic burden of MS.

In December 2013, the FDA approved a label change for Tysabri. Some of the more notable changes include: indications of approval for first, second, and third-line therapy are the decision of the provider; updated data includes patients on treatment for up to six years; an increased risk of developing herpes encephalitis and meningitis – patients need to be instructed by the provider to immediately report if they experience fever, headache, or confusion; and one patient with acute liver failure is noted.

Aubagio® (teriflunomide)

Company: Genzyme and Sanofi

- *Oral medication (tablet form) taken daily; two doses approved: 7mg and 14 mg*
- *Approved for relapsing forms of MS*

Aubagio (teriflunomide) contains the same active ingredient as leflunomide, which has been used in the treatment of rheumatoid arthritis since 1998. This drug is an immunomodulator that affects the production of T and B cells. It inhibits rapidly dividing cells, including activated T cells, which are thought to drive the disease process in MS. Unlike some drugs that modulate the immune system, Aubagio is thought to leave the immune system's response to infection intact, so it may still fight against infection while a patient is taking this drug. It may also inhibit nerve degeneration by reducing the production of free radicals. (Free radicals are unstable molecules [or atoms] produced in the body that can damage cells in the brain and other organs.)

Aubagio was the second oral medication to be FDA approved for relapsing forms of MS, and became available in October 2012. Both a 7-mg and 14-mg daily dose were approved, although the 14-mg dose proved to be more effective in Aubagio clinical trials, as discussed below.

People taking Aubagio are advised to be checked for exposure to tuberculosis (TB) prior to starting this medication, as several cases of TB occurred in the clinical trials. In addition, liver function tests must be performed monthly for the first six months while on Aubagio, and

periodically thereafter. Hair loss is another potential side effect of Aubagio, though this can be transient.

Aubagio is considered Pregnancy Category "X," and both men and women of child-bearing potential should use effective birth control while taking Aubagio. As the drug can remain in the body for up to two years, this is an important consideration to plan in advance. If pregnancy is contemplated, a rapid decrease of Aubagio levels in the blood can be induced by taking cholestyramine or activated charcoal. The process takes 11 days.

Prior to approval, Aubagio successfully completed several large clinical trials. The TEMSO trial for RRMS compared 7 mg and 14 mg of Aubagio in 1,088 individuals. Both doses significantly reduced the annualized relapse rate by approximately 31 percent. The 14-mg dose also reduced the risk of sustained disability progression by 29.8 percent relative to placebo. Aubagio (7-mg dose) resulted in a 39.4-percent reduction in brain lesion volume on MRI compared with placebo; the 14-mg dose resulted in a 67.4-percent reduction. The number of gadolinium-enhancing lesions were also reduced with both doses compared with placebo, and a trend toward a greater effect was observed with the higher dose. Importantly, no difference in the rate of serious infection, opportunistic infection, or malignancy was found between patients taking Aubagio and those on placebo.

A Phase III extension study TEMSO is ongoing. Patients who completed the original study and who received the drug are being maintained on the same dose; those who received placebo are randomized to Aubagio 7 mg or 14 mg. The study remains double-blinded, and will evaluate long-term safety and efficacy of the drug. Preliminary data presented in 2013[20] found no new or unexpected adverse events (AE) associated with long-term (up to nine years) exposure to Aubagio in the TEMSO extension trial. Adverse events were consistent with the two-year core trial, and incidence of adverse events generally decreased and remained low over time.

Results of the TOWER study of 1,169 individuals with RRMS were reported in the fall of 2012.[21] This study also evaluated the 7-mg and 14-mg doses of Aubagio versus placebo. Its primary endpoint was the annualized relapse rate (ARR); the secondary endpoint was time to disability progression. The results showed a 36.3-percent reduction in ARR with Aubagio, 14 mg, versus placebo. There was also a significant 37-percent risk reduction in the number of patients who were relapse-free during the trial and a 31.5-percent reduction in the risk for 12-week sustained accumulation of disability vs placebo. Results for the 7-mg dose showed a significant but smaller reduction in relapse rate but not in sustained accumulation of disability.

A third Phase III study called TENERE[22] compared two oral doses of Aubagio (7 mg and 14 mg once daily) to standard-dose treatment with Rebif (interferon beta-1a). The primary endpoint was time to the first occurrence of

Aubagio® (continued)

confirmed relapse or permanent treatment discontinuation for any reason, whichever came first. In the study, 48.6 percent of patients receiving the 7-mg dose of Aubagio and 37.8 percent of those on the 14-mg dose relapsed or discontinued treatment over the course of the trial, compared to 42.3 percent of patients on Rebif. However, the rate of permanent treatment discontinuation was lower with Aubagio (18.3 and 19.8 percent) than in the Rebif group (28.8 percent).

The secondary endpoint was the difference in annualized relapse rate (ARR). This was not statistically significant for the 14-mg dose of Aubagio compared with Rebif (0.259 vs. 0.216, respectively). At Week 48, treatment satisfaction was higher for both Aubagio doses compared with Rebif.

The Phase III TOPIC study[23] of 618 individuals with clinically isolated syndrome (CIS) reported data in 2013. This study also compared 7-mg and 14-mg doses of Aubagio versus placebo. The study's primary endpoint was the time to conversion to clinically-definite MS (CDMS) after CIS. The study was ended early as revised diagnostic criteria have enabled earlier diagnosis of MS.

The 14-mg dose of Aubagio reduced the risk of second MS relapse (and thus reduced the risk of conversion from CIS to "clinically definite MS") by 43 percent. Results of the study were consistent with safety and efficacy of the other Phase III Aubagio studies and highlighted the ability of early treatment with this disease-modifying therapy (DMT) to delay the onset of MS attacks.

Gilenya® (fingolimod, FTY720)

Company: Novartis Pharmaceuticals Corp.

- *Oral medication; 0.5 mg capsule taken once daily*
- *Approved for relapsing forms of MS*

Gilenya (pronounced as "Jil-EN-ee-ah") is the first in a new class of immunomodulatory drugs, called "S1P-receptor modulators." It is similar in structure to a naturally occurring component of cell-surface receptors on white blood cells. (White blood cells are produced by the immune system to fight infection and disease.) Gilenya blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues. It may reduce damage to the central nervous system (CNS) and enhance the repair of damaged nerves within the brain and spinal cord. Study data suggest that Gilenya may have neuro-protective effects.

Some adverse events with Gilenya include: an initial reduction in heart rate; infrequent changes in the conduction of electricity in the heart (atrioventricular [AV] block); macular edema (a condition that can affect vision, caused by swelling behind the eye); and infections, including reactivation of herpes infections. Following the death of a patient within 24 hours after taking a first dose of Gilenya in November 2011, the FDA conducted an investigation, and in April 2012, updated the prescribing guidelines for Gilenya.

Other deaths from cardiac causes have been reported from among the many thousands of people in several countries who have been treated with this medication. Contraindications now include a history or presence of cardiac conditions (such as myocardial infarction or

stroke in the previous six months, second-and third-degree atrioventricular block, or other serious cardiac rhythm disturbances) or in patients treated with certain antiarrhythmic drugs.

The updated prescribing information recommends that all patients starting treatment should undergo electrocardiography immediately before the first dose and at the end of the initial six-hour observation period, along with hourly measurement of blood pressure and heart rate. Continuous cardiac monitoring must be performed in some cases. This "First Dose Observation" is part of a set of monitoring requirements that need to be completed when Gilenya is prescribed.

Study Information

The FREEDOMS Phase III study of Gilenya compared with placebo showed the drug to be safe and well tolerated. Gilenya reduced the risk of confirmed disability progression by 30 to 32 percent versus placebo, and significantly increased the proportion of patients who were disease-free over two years. It also resulted in a 30-percent reduction of brain-volume loss as compared with placebo at one and two years, suggesting a possible direct neuroprotective effect. A second Phase III study, FREEDOMS II, evaluated safety, tolerability, and efficacy of Gilenya compared with placebo, and reported similar results.

Two deaths from herpes virus infections occurred in the FREEDOMS trials; both of these individuals received a higher dose of fingolimod that is not FDA-approved or prescribed. No deaths from infections were reported in those individuals treated with the FDA-approved lower dose, which is the only dose available for MS patients.

The TRANSFORMS Phase III trial was a 12-month study of the efficacy of Gilenya as compared to weekly intramuscular injections of Avonex in individuals with RRMS. In summary, Gilenya was more effective in reducing the annual relapse rate, resulted in less deterioration in the ability to independently perform daily activities, was associated with a lower rate of brain atrophy, and showed a greater effect on reducing MRI measures of lesion activity. No difference in progression of disability was demonstrated in this 12-month study.

In both the FREEDOMS and TRANSFORMS studies, Gilenya significantly reduced the frequency of severe relapses and those that required intervention (steroids or hospitalization), and reduced the number of relapses with no or partial recovery. In the TRANSFORMS trial, Gilenya also consistently reduced the annualized relapse rate in patients with highly active MS as compared to Avonex.

Interim data was presented in 2013 from LONGTERMS,[24] a single-arm, open-label extension study that began in June 2010 and will continue with annual interim analyses through June 2016. Clinical disease activity remained low for up to five years in patients treated with Gilenya, an interim data analysis indicates. Most patients remained relapse free and disability remained stable for up to five years. Approximately 70 percent of patients remaining on Gilenya were relapse-free. As with many extension trials, individuals dropping out may have caused a "selection bias" favoring long-term use of the drug.

Gilenya® (continued)

Several analyses[25] of Gilenya's clinical trials have demonstrated that Gilenya has significant effects on slowing brain atrophy in MS. In the TRANSFORMS trial, Gilenya significantly reduced brain volume loss over one year compared with Avonex, and in the FREEDOMS trials, Gilenya reduced brain volume loss over two years compared with placebo. Intriguingly, in new research presented in 2013,[26] patients on Gilenya who remained disease-free over 48 months were shown to have less brain-volume loss over the four-year study than those who were not disease-free.

In addition, reduced brain-volume loss was associated with better clinical outcomes at month 48. These data suggest that the effect of Gilenya on slowing brain atrophy may have a meaningful clinical impact on preventing disability.

Results of an Italian study[27] confirm that the first-dose administration of Gilenya is generally safe and well tolerated; these results are consistent with results from previous clinical trials. Data were collected from 812 Italian patients who were undergoing the required six-hour first-dose observation period following administration of Gilenya. Most patients (95.2 percent) did not have any adverse events during the six hours. Cardiovascular adverse events occurring in 18 patients were all self-limiting, and did not require intervention.

The six-month Phase IV EPOC[28] study also presented data in 2013. This study was designed to evaluate: patient-reported outcomes; physician assessment of a change; as well as safety and tolerability in patients with relapsing MS, who had also been previously treated with other DMTs and are now receiving Gilenya. This study found that, based on the Treatment Satisfaction Questionnaire for Medication (TSQM), people with relapsing multiple sclerosis (MS) reported greater treatment satisfaction after starting the oral treatment Gilenya vs. switching to, or staying on, injectable interferon beta or glatiramer acetate.

Although Gilenya was approved for RRMS in 2010, several large clinical trials of this medication are still ongoing. **The 36-month INFORMS study will evaluate the effect of Gilenya relative to placebo on delaying the time to sustained disability progression in patients with PPMS.** It will also evaluate safety, tolerability, and the effects on MRI parameters. As there is presently no FDA-approved medicine for PPMS, this is an important study for the field. The enrollment of 969 PPMS patients into the INFORMS trial was completed in 2011, and it is expected to be completed in the fall of 2014.

Another ongoing Gilenya clinical trial is a Study Evaluating Safety and Efficacy of Two Doses of Fingolimod Versus Copaxone.[29] This 12-month trial will compare the marketed dose of Gilenya with one-half this dose, using Copaxone as a comparison, on annual MS relapses and several MRI measures of disease. The goal of this study, which was required by the FDA, is to assess if a lower dose of this medication may be equally effective at preventing relapses. This study is expected to run through 2014.

Tecfidera™ (dimethyl fumarate)

Company: Biogen Idec

- *Oral medication taken twice daily*
- *Tecfidera is approved for relapsing forms of MS*

The United States Food and Drug Administration (FDA) announced in March 2013 that it had approved Tecfidera™ (dimethyl fumarate or DMF, formerly known as BG-12) as a first-line therapy for the long-term treatment of relapsing forms of multiple sclerosis (MS). Tecfidera became the 10th drug to be approved as a disease-modifying therapy. It is administered in pill form orally (by mouth), and the approved dosage is 240 mg taken two-times daily.

Tecfidera™ is an oral fumaric acid ester, related to a medication called Fumaderm®, which was previously shown to be effective in patients with psoriasis, and used for this indication in Germany for many years. The mechanism of action in MS is still under investigation, however, Tecfidera may have a distinct dual mechanism of action. First, it is an immunomodulator with anti-inflammatory properties. This induces anti-inflammatory cytokines (small proteins that may stimulate or inhibit the function of other cells) and appears to suppress damaging macrophage cell activity. Macrophages are a type of white blood cell that can damage both myelin in the central nervous system and the nerves themselves. Second, Tecfidera may also have neuroprotective effects. This is due to its activation of a substance that is critical for resistance to cellular damage (from what is termed "oxidative stress") as well as for normal immune function.

Completed Studies with Tecfidera

Two large Phase III trials were conducted with Tecfidera; both showed positive outcomes. The Phase III DEFINE study, which compared two doses of Tecfidera against placebo in 1,200 patients, was completed in February 2011. The Phase III CONFIRM study, which enrolled 1,232 patients, tested two dose levels against placebo, and also compared Copaxone against the same placebo group; the study was completed in September 2011.

The Phase III DEFINE study was a multicenter, double-blind trial of Tecfidera. In this study, 240 mg of Tecfidera was given either twice or three times daily versus placebo for two years. The study met its primary endpoint with a 49 to 50-percent reduction in the proportion of patients who relapsed during the study period. One of the secondary clinical endpoints was confirmed disability progression. Each of the two Tecfidera doses reduced the risk of sustained disability progression (for at least 12 weeks) by 34 to 38 percent.

The Phase III CONFIRM study was also a multicenter, double-blind trial. For two years, it compared the same two doses of Tecfidera with placebo (as done in the DEFINE study) and also compared the same placebo group to a group receiving daily subcutaneous injections of Copaxone. (Please note that the study was not designed to compare the effectiveness of Tecfidera to Copaxone.) The study met its primary endpoint with a reduction in relapse rates of 44 to 51 percent for Tecfidera compared to placebo. No statistically significant difference was observed in the remaining clinical endpoint of confirmed disability progression, possibly due to the unexpectedly low rate of progression in

Tecfidera™ (continued)

the placebo group. In both studies, compared to placebo, individuals given Tecfidera had significantly reduced disease activity as shown on magnetic resonance imaging (MRI) scans. These included significant reductions in the number and size of new and enhancing brain lesions (areas of disease activity, inflammation, and potential damage to the myelin and nerves).

Continuation Studies

A continuation study of 1,736 patients who participated in the DEFINE and CONFIRM studies called ENDORSE is evaluating the long-term safety profile of Tecfidera as well as its long-term efficacy on clinical outcomes, MRI scans, and quality-of-life. The study continues as of 2013, although initial data were presented in 2012 and 2013.[30] No new safety concerns were identified, and no deaths were thought to be related to the medication. Although malignancies have been observed in this patient population, at an incidence of less than 1 percent, it was not apparent that these were directly caused by Tecfidera.

Side Effects and Adverse Events

In the large studies leading up to the approval of Tecfidera, flushing and gastro-intestinal events, such as diarrhea, nausea and vomiting, and abdominal pain, were the most commonly reported side effects. Flushing and gastrointestinal events occurred in approximately 30 to 40 percent of patients and occurred more often at the beginning of treatment, decreasing in frequency after the first one to two months on this medication.

Other adverse events, which were mild or moderate in severity, included upper respiratory infection, pruritus (chronic itching), and erythema (skin redness or rash). The only serious adverse events (aside from MS relapses) to occur in two or more patients taking Tecfidera during these large studies were gastroenteritis (an inflammation of the lining of the intestines) and gastritis (an inflammation of the stomach lining).

In terms of long-term health risks, reduced white-blood cell (lymphocyte) counts were seen during the first year of treatment. However, the incidence of infection did not differ between the treated and placebo groups during the studies. Because of the reduced white-blood cell counts, the FDA recommends that prior to starting Tecfidera, and annually thereafter while still on the treatment, patients be given a complete blood count to monitor their ability to fight infection.

During the first six months of therapy in the DEFINE study, liver enzymes were elevated in 6 percent of individuals taking Tecfidera, compared to 3 percent of the placebo group. No cases of liver failure were reported in either study. Excess protein in the urine (proteinuria) was observed slightly more often in the treated groups versus the placebo group of the DEFINE study. No cases of kidney failure were reported in either study.

Pregnancy data on Tecfidera was provided in 2013 from the BG-12 development program. Pregnancy outcomes are known for 25 of the 35 pregnancies exposed to Tecfidera. To date, pregnancy data indicate no increased risk of fetal abnormalities or adverse pregnancy outcomes associated

with exposure to Tecfidera during the first trimester. Further data regarding pregnancies will be collected through a pregnancy registry. As with DMTs discussed previously, the recommendations of the FDA are for women on DMTs including Tecfidera to take preventative measures to avoid pregnancy.

Ongoing Studies

The Phase II EXPLORE trial is evaluating oral Tecfidera as a combination therapy with an injectable medication. It will determine the safety and tolerability of Tecfidera when administered in combination with interferons or Copaxone to 100 people (who continue to have evidence of disease activity despite receiving consistent treatment for at least one year). Efficacy endpoints (determining the effectiveness) will also be assessed in a subset of participants. Although the study concluded in 2012, the results are still anticipated as of early 2014.

EXPERIMENTAL MEDICATIONS: A NEW INTERFERON

Plegridy® PEGylated interferon beta-1a, also known as BIIB017)

Company: Biogen Idec

- *Administered by subcutaneous injection once every two weeks at a dose of 125 mcg (micrograms)*
- *Plegridy is being studied for relapsing forms of MS*

PEGylation is a chemical modification that has been performed on the interferon beta-1a molecule that allows it to be given subcutaneously (under the skin) every two or four weeks, in contrast to the more frequent injections utilized by the currently approved forms of interferon. The goal is to reduce the number of injections, while maintaining the positive effect of the drug. Studies have tested this experimental therapy for safety and effectiveness. If approved by the FDA, this would give patients the option of using a single-dose auto-injector with a prefilled syringe less frequently.

The Phase III clinical trial (ADVANCE) enrolled patients with relapsing-remitting MS (RRMS) to determine the safety and efficacy of Plegridy as compared to placebo. Results were presented in 2013[31] from the first year of this Phase III study, where 1,512 patients were randomized to one of three groups: one group receiving placebo; a second group receiving Plegridy given by subcutaneous injection once every two weeks; and a third group receiving Plegridy by subcutaneous injection once every four weeks.

Plegridy dosed every two weeks significantly reduced MS disease activity versus placebo. Relapses were reduced by 36 percent, and new brain lesions by 67 percent, compared to placebo at one year. Disability outcomes were also positive in this one-year trial. In total, the proportion of disease activity-free patients over one year was significantly higher in the two treatment groups compared to placebo.

The overall incidence of serious adverse events (SAE) and adverse events (AE) was

Plegridy® (continued)

similar among the Plegridy and placebo groups. The most common serious adverse event was infection, which was balanced across all treatment groups (less than or equal to 1 percent per group). The most commonly reported adverse events with Plegridy treatment were redness at the injection site and influenza-like illness. Flu-like illness was reported in 47 percent of both treatment groups compared to 13 percent in the placebo group. These safety data are consistent with the established safety profile of interferon beta-1a therapies for MS.

After the first year, study participants who were taking the placebo were re-randomized to one of the two treatment groups (taking the active drug either once every two weeks or once every four weeks), and will continue on their new treatment for the remainder of the second year in the study. Once the study is completed, participants will be given the option to enroll in the ATTAIN open-label (no longer blinded) extensions study. Participants will be followed for up to four years in this second study.

In a subgroup of ADVANCE participants, up to 120 were enrolled in a sub-study that involves optical coherence tomography (OCT). This is a rapid, noninvasive, office-based imaging technique that allows objective evaluation of the thickness of the retinal axon (the nerve behind the eye) and nerve layers that atrophy (shrinking due to nerve cell death) in MS. Preliminary evidence supports the use of OCT as an objective tool to monitor the effectiveness of a therapy, and it is hoped that OCT may be used as an outcome measure in future studies.

In May 2013, Biogen Idec submitted a new treatment application for multiple sclerosis to the United States FDA for approval, and the application was accepted for review. A decision regarding the approval of Plegridy is expected in 2014.

Laquinimod

Company: Teva Neuroscience, Inc. and Active Biotech

- *Oral medication taken once daily; dosing is still under investigation*
- *Laquinimod is being studied in RRMS*

Although its exact mechanisms of action are unknown, laquinimod is an immunomodulator, apparently through its effects on cytokines and interleukins (immune-system signaling chemicals). It enhances T-regulatory cell activity, which reduces Th1-inflammatory T-cell activity. It also appears to reduce white blood cell penetration of the central nervous system (CNS). In addition to its immunomodulatory actions, laquinimod increases levels of the brain-derived neurotrophic factor (BDNF), possibly contributing to neuroprotection (protecting the nerves and myelin from damage) in MS patients. BDNF is a protein found in the brain that helps to support nerves and their development.

The Phase III ALLEGRO study of 1,106 individuals with RRMS showed that, compared to placebo, laquinimod reduced the annualized relapse rate by 23 percent and the progression of disability by 36 percent. It also was effective on several MRI outcomes, including a reduction in brain atrophy by 33 percent.

The BRAVO Phase III trial was another global, 24-month, double-blind study with 1,300 participants designed to evaluate laquinimod's efficacy, safety, and tolerability versus placebo. In August 2011, the sponsors announced that the study had failed to achieve its primary goal of reducing the annualized relapse rate, although there was a trend in that direction if the data are adjusted for differences in MRI characteristics at the start of the study.

Because the effect of laquinimod on relapses was more modest than has been seen with other disease-modifying therapies for RRMS, the drug was not considered for approval in the United States in 2012. In 2013, the results of two separate analyses of pooled data from the Phase III ALLEGRO and BRAVO trials studying laquinimod were presented.[32] The first analysis compared the expected risk of disability progression (given a particular relapse rate) with that seen in the pooled data. In this analysis, the effect of laquinimod on reducing the risk of disability progression was larger than predicted. The second analysis examined the relationship between relapses and disability by looking at disability progression in both relapsing and relapse-free patients in the two trials. About one third of the patients who progressed were relapse-free, suggesting that these two outcome measures are mediated through different pathways.

Since laquinimod may have more of an effect on disability than on relapses, a new trial looking primarily at laquinimod's disability-preventing impact was designed. This 24-month trial, The Efficacy and Safety and Tolerability of Laquinimod in Subjects With Relapsing Remitting Multiple Sclerosis (CONCERTO[33]), is comparing two doses of laquinimod (including a 1.2-mg dose, higher than that which was tested in prior Phase III studies) with placebo, looking at confirmed disease progression as the primary outcome. This is the first modern RRMS trial to prioritize prevention of disability over prevention of relapses. The trial began enrollment of 1,800 patients in 2013, and is expected to run into 2018.

Cladribine

Company: Merck Serono, Inc.

- *Given orally, as one or two courses per year, depending on the study regimen*
- *Although the parent company is not currently seeking approval, cladribine continues to be studied in RRMS*

Cladribine predominantly affects peripheral blood lymphocytes (immune-system cells produced to fight infection and disease), with relative preservation of other cell types and components. It causes a preferential and sustained depletion of certain T cells in the immune system, as well as a decrease in B cells. (T and B cells are two types of lymphocytes.) Cladribine also seems to directly influence the overall T-cell response, which is believed to play a major role in the MS process.

Cladribine (continued)

The two-year Phase III CLARITY trial of two levels of cladribine versus placebo involved 1,326 patients with RRMS. Each course consisted of once-daily administration for four-to-five consecutive days, and study patients took cladribine for a total of eight-to-20 days of treatment during the year. It met its primary endpoint, showing 55-to-58-percent reductions in annualized relapse rates and 31-to-33-percent reductions in disability progression, as well as a substantial reduction in lesion burden.

The ONWARD Phase II study of 200 individuals who have experienced at least one relapse while taking Rebif combines oral cladribine with Rebif. This study will determine whether the combination is more effective than Rebif alone.

The Phase III ORACLE MS study was designed to assess whether cladribine can delay the time to a second clinical demyelinating attack in 600 individuals who have had a first clinical demyelinating event, also referred to as clinically isolated syndrome (CIS).

In March 2011, after an increase in malignancies was observed in patients in the cladribine clinical trials, the FDA announced that it would not approve oral cladribine for MS without more safety information. In June 2011, Merck Serono announced that they will not currently pursue global approval for cladribine tablets for the treatment of RRMS, but would continue existing clinical trials. The company may consider a reapplication if safety concerns are lessened. The experience with cladribine, while a setback for MS therapy, provides an important lesson in medication development – and a reminder that risks are as important as benefits in developing medications, and in offering these medications to people with MS.

Lemtrada®

(alemtuzumab, formerly Campath)

Companies: Genzyme, a Sanofi company, and Bayer HealthCare Pharmaceuticals

- *Administered in one course yearly by intravenous infusion over three-to-five consecutive days*
- *Lemtrada is being studied in RRMS*

Lemtrada is a humanized monoclonal antibody that targets a protein present on the surface of mature lymphocytes, and results in a rapid depletion/suppression of T and B cells. This agent has been approved for the treatment of B-cell leukemia, although since 2012 it is being developed solely for MS.

A Phase II study of 334 individuals with early, active RRMS compared Lemtrada to high-dose Rebif (44 mcg) in RRMS. In this three-year safety and efficacy trial, Lemtrada was more effective than Rebif at reducing the relapse rate and the risk for six-month sustained accumulation of disability in patients with RRMS. In a multi-year extension study of the 334 individuals who participated in the original Phase II study, Lemtrada yielded a 73-percent reduction in risk

for sustained accumulation of disability, while 77 percent of Lemtrada-treated patients were relapse-free. A five-year assessment showed that 87 percent were free of sustained disability accumulation, 72 percent were relapse-free, and 65 percent were free of clinical-disease activity. These data indicate that Lemtrada's treatment effect is durable; it halts clinical-disease activity in a significant proportion of RRMS patients through five years – even though many of those patients did not require subsequent re-treatment with the drug.

Lemtrada has since successfully completed two Phase III trials: CARE-MS I and II. The CARE-MS I study[34] compared the clinical and MRI results of treatment with Lemtrada, to treatment with subcutaneous Rebif (interferon beta-1a) in patients with RRMS who had not received prior treatment with any disease-modifying therapies. Rebif was given according to the regular dosing of three times per week, while Lemtrada was given intravenously for five days, and then a second time one year later for three days. CARE-MS I was a multicenter international trial. Data were collected for each patient during a two-year period from the time of the first infusion.

The ARR (annual relapse rate) was 0.18 (or slightly less than one relapse every five years) for Lemtrada-treated patients. This was as compared with 0.39 (or slightly less than one relapse every two-and-a-half years) for Rebif-treated patients. This means that Lemtrada reduced the ARR by 55 percent compared to Rebif. Individuals taking Lemtrada had a 59-percent reduction in severe relapses requiring steroid treatment. These clinical data were supported by MRI outcomes. Through year two, fewer Lemtrada patients developed new gadolinium-enhancing lesions (areas of active inflammation and myelin damage in the brain) than Rebif-treated patients (15.2 percent versus 27.2 percent).

CARE-MS II[35] is the third study to compare Lemtrada with Rebif. It was designed to evaluate the effect of Lemtrada on relapse and disability as compared to Rebif in people with RRMS who had relapsed on prior therapy – people for whom a first-line injectible medication was insufficient. The study design was otherwise the same as that in CARE-MS I. The co-primary efficacy

About Monoclonal Antibodies

Monoclonal antibodies are derived from cells that are identical (cloned from a single cell and then replicated). They are produced from animal tissue, most commonly laboratory mice. Humanized monoclonal antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. Monoclonal antibodies are an important type of medication, as they can be specifically targeted to perform a particular action, which is desirable when trying to impact a complex structure like the immune system. The name of all monoclonal antibodies ends with "mab," including natalizumab (Tysabri), which is already approved for MS. Several other monoclonal antibodies have shown promise in MS, and these are reviewed in this section.

Lemtrada® (continued)

endpoints were the ARR and time to six-month sustained accumulation of disability as measured by the Expanded Disability Status Scale (EDSS).

Relapse data showed that 65 percent of patients treated with Lemtrada were relapse-free at two years, as compared to 47 percent with Rebif. These data also showed a 49-percent reduction in relapse rate as compared to Rebif. The group treated with Lemtrada showed a decrease in the mean disability score, versus a slight worsening of disability in those treated with Rebif. Approximately 29 percent of patients treated with Lemtrada experienced a six-month sustained *improvement* in disability, as compared to 13 percent with Rebif.

In addition to the new goal of identifying improvement in disability achieved by some participants in clinical trials, looking at the percent of patients who are "disease activity free" during a clinical trial is another important aspirational goal of our increasingly powerful therapies for MS. Along these lines, subsequent analyses of the Lemtrada clinical trial data were presented in 2013.[36] In a subset of patients with highly active disease in the CARE-MS II trial (patients with multiple relapses and enhancing MRI lesions in the year prior to enrolling in the trial), 24 percent of individuals treated with Lemtrada were free of disease activity at the end of the two-year study, while none of these study participants treated with Rebif (interferon beta-1a) achieved that outcome.

Several safety concerns have been raised by the above studies, including infusion reactions to the medication, and an increased risk of infection and emergent autoimmune diseases in patients treated with Lemtrada. All three studies showed a modest increase in the incidence of infections, though no opportunistic infections occurred. (These types of infections are a result of microorganisms found in the body that only infect a person when the immune system has been weakened.) No treatment-related fatalities were reported in the Phase III studies.

In the CARE-MS I and II studies respectively, approximately 18 percent and 16 percent of Lemtrada patients developed an autoimmune thyroid disorder, and 0.8 percent and 1 percent developed a potentially severe bleeding disorder called immune thrombocytopenic purpura (ITP). In ITP, the blood does not clot as it should, and this can result in internal bleeding. It is important that patients treated with Lemtrada commit to monthly lab and self-monitoring because, if not detected and treated, ITP can have grave consequences. When addressed promptly, ITP caused by drug treatments such as Lemtrada, responds readily to treatment. A program to monitor for the development of thyroid issues and immune thrombocytopenia was successful in early detection of these known complications from Lemtrada in the clinical trials.

With the side effects and adverse events in mind, the significant reduction in relapses with Lemtrada compared with Rebif suggest that there is potential for Lemtrada to be a meaningful addition to the presently available treatment options for RRMS. In June 2012, the parent company announced that Lemtrada was submitted to both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for approval. In September 2013, the EMA granted marketing authorization for Lemtrada for the treatment of

multiple sclerosis. In Europe, the drug is indicated for the treatment of adult patients who have relapsing-remitting MS with active disease defined by clinical or imaging features.

In November 2013, the FDA held a meeting to discuss Lemtrada. Despite raising concerns over the drug's safety as well as study design, the FDA's advisory committee voted to recommend the drug for approval. Unlike the EMA's decision, the committee recommended that the treatment be approved only as a second-line therapy, when other disease-modifying therapies fail or are not tolerated well by a patient. However, on December 30, 2013, Lemtrada was denied FDA approval. The issue lies in the design of the Phase III studies. According to a press release from Genzyme, the FDA has requested more trial data utilizing a "different design and execution" plan before they will consider approval of Lemtrada. Genzyme will appeal that FDA decision.

Daclizumab (also known as Zenapax®)

Companies: Biogen Idec and Abbott Laboratories

- *Administered via intravenous infusion every four weeks; also studied when given in subcutaneous injections*
- *Daclizumab is being studied in both RRMS and secondary-progressive MS (SPMS)*

Daclizumab is a genetically engineered monoclonal antibody that binds to CD25, a receptor on T cells that is thought to become activated in response to MS. Daclizumab is believed to work by selectively targeting these activated T cells without causing general T-cell depletion. It is approved by the FDA for use in rheumatoid arthritis and other autoimmune diseases. Daclizumab high yield process (DAC HYP) is administered subcutaneously once every four weeks, rather than via intravenous infusion.

Participants in the **Phase II CHOICE study had either RRMS or SPMS**, with worsening disease activity while taking one of the approved interferon therapies. The study showed that DAC HYP was well tolerated when added to an interferon. A statistically-significant 72-percent reduction in the frequency of gadolinium-enhancing MRI lesions was seen in the high-dose group (300 mg every four weeks).

The Phase IIb SELECT trial, with 600 participants who have RRMS, was a one-year study of treatment with DAC HYP. This study was subsequently extended for a second year as the SELECTION trial. The study included three treatment arms, with two dose levels (at 150 mg and 300 mg) and a placebo group.

Results of the SELECT trial announced in August 2011 indicated that the annualized relapse rate was decreased by 54 percent in the 150-mg-dose group and by 50 percent in the 300-mg-dose group. It also met its secondary endpoints: the number of new gadolinium-enhancing lesions was reduced by 69 percent and 78 percent; the number of new or newly enlarging T2-hyperintense lesions was reduced by 70 percent and 79 percent; and the proportion of patients who relapsed was reduced by 50 percent and 51 percent. These results were all for the low- and high-dose groups respectively. Sustained disability progression at one year was reduced by 57 percent with the lower dose and 43 percent

Daclizumab (continued)

with the higher dose.

Participants who completed this trial were enrolled in an extended trial called SELECTION to evaluate long-term safety and efficacy. One-year results of the SELECTION trial were presented[37] at the ECTRIMS meeting in the fall of 2012. Patients who were on placebo and began treatment with DAC HYP in the extension trial had a 59-percent reduction in annualized relapse rate compared to the year prior, while patients who continued on DAC HYP saw their low relapse rate from the prior year maintained.

In 2013, further data from this trial was presented;[38] patients who received two years of treatment with DAC HYP in the SELECT trial and its one-year extension study, SELECTION, were evaluated to determine the rate of brain atrophy (brain-volume loss). During the second year of treatment, the percentage of brain-volume loss was 27-percent lower in the treated groups compared with the placebo group at year one, and 24-percent lower than year one of the treated groups. The authors of the study note that this reduction in the rate of brain atrophy in people with MS may be consistent with neuroprotection.

DAC HYP is being further studied in the DECIDE trial,[39] a Phase III study with 1,500 participants that will compare DAC HYP to Avonex. DAC HYP will be administered subcutaneously once every four weeks for 96 to 144 weeks in a dose of 150 mg as compared to a weekly 30-mcg intramuscular injection of Avonex. The study began in March 2010, is fully enrolled, and is scheduled for completion in the spring of 2014. Outcome measures include relapse rate, functional decline, and disability progression, as well as quality of life.

Daclizumab appears to be generally well-tolerated. Reported side effects in the Phase II studies include infections and abnormal liver function tests, diarrhea or constipation, and swelling of the extremities. One death in a daclizumab-treated patient was due to complications of a muscle abscess, and a second death was due to autoimmune liver inflammation. The safety profile of this medication will be closely followed in the ongoing Phase III trial.

Rituxan® (rituximab)

Companies: Genentech and Biogen Idec

- *Administered via intravenous infusion*
- *Rituxan is being studied in both RRMS and SPMS*

Rituxan is a monoclonal antibody (CD20, from mouse tissue) that binds to a receptor on the surface of B cells. These cells are then destroyed and their levels in the circulation are decreased. It is approved for use in the treatment of lymphomas, leukemias, and autoimmune disorders.

A Phase II trial, completed in 2006, examined the effect of a single course of Rituxan treatment in RRMS, with two infusions of 1,000 mg each, administered two weeks apart. At 24 and 48 weeks, the number of active lesions was reduced by 91 percent and relapses were reduced by 58 percent.

The drug was also tested in a study of 30 people with RRMS who had experienced

continued clinical activity despite treatment with one of the approved disease-modifying therapies. Participants received two doses of Rituxan, two weeks apart, while continuing to take their usual medication. Results showed gadolinium-enhancing lesions were reduced after treatment with Rituxan: 74 percent of post-treatment MRI scans were free of gadolinium-enhancing activity as compared with 26 percent free of gadolinium-enhancing activity at baseline. There was an 88-percent reduction in the average number of these lesions.

A Phase I/II double-blind study of 80 people with low-inflammatory SPMS, sponsored by the National Institute of Neurologic Diseases and Stroke, is testing Rituximab versus placebo (RIVITaLISe). The study is recruiting participants[40] and is expected to run until 2016. The primary outcome measure will be the progression of brain atrophy after two years of treatment, unless predetermined analysis shows that the secondary outcome measures of MRI and clinical assessment are more reliable measures of effectiveness than brain atrophy.

Serious adverse events have been reported in Rituxan-treated patients with other diseases, including Progressive Multifocal Leukoencephalopathy (PML), the same viral infection of the brain that has been seen with Tysabri. While no PML has been diagnosed in MS patients taking Rituxan, the number of individuals with MS treated with Rituxan is relatively small to date.

Rituxan is not likely to be further developed for FDA approval. However, next-generation anti-CD20 monoclonal antibodies have been developed to build on the encouraging data from Rituxan's MS studies, including ocrelizumab, as discussed in the following entry.

Ocrelizumab

Companies: Genentech and Roche Pharma AG

- *Administered via intravenous infusion*
- *Ocrelizumab is being studied in RRMS and in primary-progressive MS (PPMS)*

Like Rituxan, this drug is an anti-CD20 monoclonal antibody. It has the potential advantage of being a more humanized antibody than Rituxan. As noted in the introduction to this section, humanized monoclonal antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. "More humanized" refers to a protein sequence that is more similar to antibodies produced in humans, compared to another humanized monoclonal antibody (Rituxan in this instance).

In a Phase II study of ocrelizumab[41] in 220 individuals with RRMS, reductions in the total number of brain lesions detected by MRI scans (the primary endpoint of the study) were highly significant at 96 percent for 2,000-mg ocrelizumab and 89 percent for 600 mg compared to placebo. The annualized relapse rate was significantly lower versus placebo at week 24, with a reduction of 73 percent for ocrelizumab 2,000 mg, and 80 percent for ocrelizumab 600 mg. Ocrelizumab's effectiveness was maintained through week 72 (about two weeks less than one year and five months); the proportion of relapse-free patients at week 72 was 84 percent for the 600-mg group, and 82 percent for the 2,000-mg ocrelizumab group.

Infusion-related symptoms, which were generally mild to moderate, were seen in the

Ocrelizumab (continued)

ocrelizumab-treated groups. The number of serious adverse events was small and similar among the groups. However, one patient in the ocrelizumab 2,000-mg group died of a systemic inflammatory response of unknown etiology (e.g., the reason why this response occurred is not known). Although Phase III trials in rheumatoid arthritis had significant rates of serious and opportunistic infections, none were identified in this trial of 220 people with MS. Please note that the number of MS patients studied in this Phase II trial is small in comparison to the number of rheumatoid arthritis patients studied in the larger Phase III studies that have already been completed.

Several Phase III trials of ocrelizumab are now underway. OPERA I[42] and II[43] are comparing ocrelizumab (600 mg) to Rebif (44 mcg of interferon beta-1a given via subcutaneous injection three times per week) in RRMS and plan to enroll approximately 800 patients in each study. These trials are anticipated to run through mid-2015. The primary outcome measure is annualized relapse rate; secondary measures include time to onset of sustained disability progression, the proportion of relapse-free patients, MRI measures of disease activity, and change in Multiple Sclerosis Functional Composite (MSFC) scale, which measures upper and lower limb function as well as cognition.

In addition, because subgroup analysis of Rituxan in the OLYMPUS study suggested a benefit to younger PPMS patients and those with gadolinium-enhancing lesions, ocrelizumab is also being studied in primary-progressive MS (PPMS). **The Phase III ORATORIO[44] safety and efficacy study of ocrelizumab in 630 patients with PPMS is currently recruiting participants.**

Patients will receive either ocrelizumab (300 mg given intravenously in two infusions separated by 14 days in each treatment cycle) or placebo. The study is scheduled to run through late 2017. The primary outcome measure is time to onset of sustained disability progression (for at least 12 weeks); secondary outcome measures include the time to sustained disability progression (for at least 24 weeks), change in the total volume of T2 lesions (as seen on MRI), as well as safety, tolerability, and the incidence of adverse events.

Ofatumumab (also known as Arzerra®)

Companies: GlaxoSmithKline and Genmab

- *Administered via intravenous infusion and will also be studied via subcutaneous injection*
- *Ofatumumab is being studied in RRMS*

Like Rituxan and ocrelizumab, this drug is an anti-CD20 monoclonal antibody. It has the potential advantage of being a human monoclonal antibody (versus antibodies from non-human species that have been modified).

Ofatumumab has a unique target on the CD20 molecule and is approved for certain forms of leukemia. Genmab announced positive interim results for a Phase II safety and pharmacokinetics (how the body processes the drug) study of ofatumumab in 2010. This study had 38 patients who were randomized to ofatumumab or placebo in a cross-over

design. Statistically, the number of gadolinium-enhancing lesions and new or enlarging T2 lesions was significantly less in patients treated with ofatumumab compared to placebo.

Another Phase II study, MIRROR[45], will compare several doses of ofatumumab administered subcutaneously to placebo in RRMS and plans to enroll approximately 200 patients. This study is expected to run through 2015.

EXPERIMENTAL MEDICATIONS: OTHER THERAPEUTIC STRATEGIES

New S1P Receptor Modulators

Data were presented in 2012 on two new investigational oral agents now in ongoing clinical trials that have a mechanism similar to that of Gilenya (fingolimod). Both drugs were well tolerated and reduced lesions related to RRMS. It is hoped that these agents, siponimod (BAF312) and ONO-4641, will maintain or improve on the efficacy and safety of Gilenya. However, both were still associated with cardiovascular effects, such as bradycardia (slowed heart rate).

Siponimod (BAF312)

Data from a Phase II dose-finding study of siponimod in people with RRMS were also reported in 2012. Siponimod has a relatively short half-life compared to Gilenya, which means that the drug does not stay in the body as long. Researchers hope that this will minimize cardiac issues.

The trial had a complex design whose goal was to determine the most appropriate dosing regimen. One group of 188 patients received placebo or once-daily siponimod in doses of 10 mg, 2 mg, or 0.5 mg for six months. A second group of 109 patients were given one of two additional intermediate doses of 1.25 mg or 0.25 mg for three months.

At six months, the proportion of relapse-free patients as compared to placebo was 84 percent for the 10-mg group, 92 percent for the 2-mg group, and 77 percent for the 0.5-mg group. In the placebo group, 72 percent were relapse-free. After six months, the ARR (annual relapse rate) was lower with the three higher doses than the two lower doses and placebo. Additionally, MRI findings indicated that treatment with siponimod was associated with a reduction in active lesions on MRI. The 2-mg dose reached statistical significance versus placebo, with a reduction in active lesions of approximately 80 percent.

A Phase III trial of siponimod in secondary-progressive MS (the EXPAND trial)[46] began recruitment in 2013, and is expected to run through Fall 2016. This is the first S1P receptor modulator to be studied in SPMS, and joins fingolimod, which is being studied in PPMS as potential future options for patients with progressive disease.

ONO-4641

In the Phase II DreaMS trial, 407 patients with RRMS were randomly assigned to placebo or one of three different doses of ONO-4641 (0.05 mg, 0.10 mg, or 0.15 mg once daily for 26 weeks). The primary endpoint was the number

New S1P Receptor Modulators (continued)

of T1 gadolinium-enhancing lesions on MRI; secondary endpoints included new and enlarging T2 lesions.

All three treatment groups showed a substantial decrease in MRI disease activity as measured both by gadolinium-enhancing lesion numbers and new or enlarging T2 lesions. Compared to placebo, lesion counts were reduced by 82 percent in the 0.05 mg/day group; 92 percent in the 0.10 mg/day group, and 77 percent in the 0.15 mg/day group. The study was not designed to evaluate relapse rates or disability progression, but there was a statistically significant decrease in relapse rate (with the 0.10-mg dose).

Adverse events were similar to those seen with Gilenya, including bradycardia and lymphopenia (a reduction in circulating lymphocytes) in some patients. These were dose-related and did not result in drug discontinuation. The drug may advance to a Phase III study.

Ponesimod

Ponesimod is another selective S1P receptor modulator that completed a Phase II trial, with results reported in 2012.[47] In this study, 462 people with RRMS were randomized to placebo or 10 mg, 20 mg, or 40 mg of ponesimod. Reductions in annualized relapse rate and new lesions were seen for all groups as compared with placebo, though the 40-mg dose generated an increase in adverse events that included swelling of the extremities and difficulty breathing. With an 83-percent decrease in gadolinium enhancing lesions and a favorable adverse event profile, the 20-mg dose of ponesimod may have the best benefit-to-risk profile in this trial. An extension trial[48] over two years presented in 2013 demonstrated continued efficacy and no new safety issues emerged. A decision has not been made as to whether this agent will advance to further trials.

Masitinib

(also known as Kinavet® and Masivet®)

Masitinib is termed a protein kinase inhibitor. It selectively inhibits molecules (kinases) that play a major role in the activation of mast cells. Masitinib has a role in both veterinary and human medicine. Mast cells are involved in the immune response, in the recruitment of lymphocytes to the brain (lymphocytes are immune-system cells produced to fight infection and disease), and also in inflammatory processes associated with MS. **A small Phase II trial of masitinib in progressive MS**[49] showed a trend towards benefit, however, the results were not statistically significant.[50]

In 2012, results from a Phase II study of 30 patients with masitinib were released. These indicated what is termed "proof of concept," showing that **this agent may have potential in treating both PPMS and relapse-free SPMS.** The study investigated the hypothesis that masitinib's action of targeting and inhibiting mast cells may delay the onset of symptoms associated with progressive forms of MS. The results showed that for the primary endpoint of Multiple Sclerosis Functional Composite (MSFC) score, which measures upper and

lower limb function as well as cognition, 32 percent of patients treated with masitinib showed a response to treatment versus none of those receiving a placebo. Responses were seen in the third month and were sustained over the 18-month duration of the study.

A Phase IIb/III multicenter, randomized, double-blind, placebo-controlled trial[51] is currently underway. **The investigators planned to recruit 450 people with PPMS or SPMS without relapses.** The primary endpoint will be an improvement in the MSFC scale at 96 weeks; results are expected after December 2014.

Ibudilast

Ibudilast (MN-166) is an oral agent with novel immune modulating and potential neuroprotective properties that is being studied in progressive MS. Launched in Fall 2013, the **Phase II Secondary and Primary Progressive Ibudilast NeuroNEXT trial (SPRINTMS)[52] will include 28 enrolling clinical sites across the United States and is designed to evaluate the safety, tolerability and efficacy of MN166 (ibudilast) administered twice daily to individuals with primary- or secondary- progressive MS.** Primary outcomes of this trial will be MRI findings including brain atrophy, as this is felt to be an important aspect of progression in MS. There will also be several other imaging and clinical disability outcomes evaluated. The NIH and National MS Society are supporting the study along with a commercial partner, MediciNova. The trial is expected to require approximately three years for enrollment, treatment, and data analyses, and will run through the end of 2016.

Tcelna™ (formerly Tovaxin®)

Tcelna is a T-cell vaccine. In the process of administering this vaccine, myelin-reactive T cells are removed from a small amount of the patient's blood, inactivated, and then injected back into the patient. The body's immune system may then potentially protect the myelin from these cells.

The TERMS placebo-controlled, one-year study in 150 people with CIS and RRMS to evaluate Tcelna's efficacy, safety, and tolerability has been completed. The treatment was found to be safe, but did not achieve statistical significance in the primary endpoint, which was a reduction in the cumulative number of gadolinium-enhancing lesions.

There was an annualized relapse rate of 0.34 per year (or one relapse roughly every three years) in the placebo group and 0.21 per year (or roughly one relapse every five years) in the Tcelna group, representing a 37-percent decrease. The drug was well tolerated with mild skin reactions in some patients; no serious safety concerns were raised by this study. In a subgroup of 70 patients who had at least one relapse in the 12 months prior to enrolling in the study and who had no previous exposure to MS therapy, Tcelna reduced their annualized relapse rate by 64 percent compared to placebo. Additionally, 76 percent of Tcelna-treated patients remained relapse-free at one

Tcelna™ (continued)

year compared with 60 percent of placebo patients.

After re-branding this agent as Tcelna, a new clinical trial initiative was launched in 2012. **Tcelna is being studied in a Phase II trial in SPMS in the Abili-T study.**[53] This is a placebo-controlled two-year trial, evaluating brain atrophy on MRI as the primary outcome, and delay in accumulation of sustained disability as the secondary outcome. The trial is planned to enroll 180 patients and is expected to run through the end of 2015.

Amiloride

It is hypothesized that accumulation of salt and potassium within the cells of MS lesions may contribute to cellular injury and neurodegeneration. This hypothesis would suggest that by blocking certain channels in these cells, the buildup of these molecules can be prevented and neurodegeneration can be prevented. This strategy was tested and data presented in 2013[54] looking at the use of amiloride – a potassium-sparing diuretic approved for the treatment of high blood pressure and congestive heart failure – that may have this neuroprotective activity.

The effect of amiloride was studied in 14 people with primary-progressive multiple sclerosis (PPMS) using MRI markers of neurodegeneration as outcome measures of neuroprotection. Patients with PPMS underwent MRI scans before and during amiloride treatment for a period of three years. Researchers found a significant reduction in the development of brain atrophy, and a slowing of the development of disability during the treatment phase, suggesting that amiloride may exert neuroprotective effects in patients with progressive multiple sclerosis. This pilot study was the first translational study on neuroprotection using amiloride, and supports further investigation of this drug as a potential neuroprotective agent in MS. A phase II trial studying this agent in optic neuritis[55] was initiated in 2013 and is expected to run through 2015.

Statins

Statins are oral medications that are most commonly prescribed to lower cholesterol. Current interest is based on a non-controlled observational study (a study without a placebo group) suggesting that the risk of developing new brain lesions was reduced by about half if patients with early forms of MS were taking atorvastatin (Lipitor®). However, a three-year Danish study of patients with RRMS failed to find any beneficial effect for simvastatin as an add-on therapy to Avonex. The use of statins to lower cholesterol in patients on interferons should be discussed with a healthcare professional to consider the potential benefits versus risks.

At the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) annual meeting in fall 2012, Chataway and colleagues presented the results of the MS-

STAT trial.[56] **This Phase II study evaluated whether high-dose simvastatin can slow the rate of whole-brain atrophy, and/or disability, in secondary-progressive MS (SPMS).** In this study, 140 patients were randomized, and the simvastatin group had a statistically significant benefit over the placebo group on the Expanded Disability Status Scale (EDSS) at two years, and the rate of brain atrophy was decreased. This serves as a positive proof-of-principle project that may allow for a larger trial, which can look at the clinical outcomes as the primary outcomes measure. As effective treatments for SPMS remain an unmet need, and since these are readily available drugs, this is a tantalizing possibility.

Tetracycline Antibiotics

The tetracycline antibiotics, including minocycline and doxycycline, have immunomodulatory and neuroprotective activities. They appear to decrease the passage of lymphocytes across the blood-brain barrier. A small Phase II trial of Copaxone plus minocycline showed favorable magnetic resonance imaging (MRI) data, with minocycline decreasing gadolinium-enhancing activity by 50 percent over a period of six months. A subsequent 24-month trial showed a significant decrease in lesion activity and clinical status.

In a larger study of 305 patients called RECYCLINE, minocycline was used as an add-on to Rebif in people with RRMS. Patients being treated with Rebif were randomized to oral placebo (n = 155) or minocycline 100 mg (n = 149) twice daily for 96 weeks. Data were presented at ECTRIMS in the fall of 2012,[57] and disappointingly, minocycline did not provide significant improvement to either clinical or MRI outcomes. Further studies of minocycline are not thought to be warranted.

Another Phase III trial with 200 participants looking at minocycline is still ongoing. This trial will evaluate the effect of 100 mg of oral minocycline twice daily on the conversion of clinically isolated syndrome (CIS) to a diagnosis of MS at six and 24 months. It began in January 2009 and is scheduled for completion in December 2015. It will determine whether 100 mg of oral minocycline twice daily reduces the conversion of clinically isolated syndrome (CIS) to clinically active MS and if any treatment benefit seen after six months is maintained at two years.

Vitamin D3

Vitamin D is a type of hormone and a powerful mediator of immune function. The data documenting an association between low Vitamin D and high MS risk, relapses, disability, and CNS inflammation now appear to be strong, consistent, and reproducible, including new data presented in 2013.[58] Data from a number of areas of investigation suggest that Vitamin D may be one underlying common factor that begins to make sense of the large amount of data on the geographic distribution of susceptibility to MS.

Genetically, a link appears to exist between changes in the genes involved in the synthesis of

Vitamin D3 (continued)

the Vitamin D hormone and the Vitamin D hormone receptor, and the risk of developing MS. The strongest genetic risk factor for MS is a specific gene (HLA DRB1*1501), whose activity appears to be influenced by Vitamin D.

A finding in animal models of MS that Vitamin D directly terminates production of disease-causing proteins may shed light on the mechanism of Vitamin D in MS. When Vitamin D is given to mice with EAE (an animal model of MS), it blocks the gene that encodes IL-17, stopping its production. IL-17 appears to be a major inflammatory component in MS. This study also demonstrates that Vitamin D increases suppressive T cells that combat inflammation.

An important longitudinal cohort study presented in 2012 by Mowry and colleagues[59] found that in people with MS, each 10 ng/ml higher Vitamin D level was associated with a 15-percent lower risk of a new T2 lesion, and a 32-percent lower risk of a gadolinium-enhancing lesion. Higher Vitamin D levels were associated with lower, but not statistically significant, relapse rates. While this was not a randomized treatment trial, it suggests that higher levels of Vitamin D may exert a protective role against MS disease activity.

Similar data was presented in 2013, as researchers looked at how Vitamin D may play a role in MS development and disease activity on a molecular level. The BENEFIT trial, as discussed above, studied the effects of interferon beta-1b (Betaseron) in patients with CIS. Blood samples were taken at various intervals, along with MRIs. This study found that individuals with higher Vitamin D levels had lower numbers of gadolinium-enhancing lesions. These individuals generally experienced less disease activity, and genes associated with these higher Vitamin D levels appear to be involved. Studies indicate that roughly 350 genes are "significantly associated" with MS activity, and of these 350 genes, 155 are associated with Vitamin D regulation. The authors of this study explain that Vitamin D may directly and indirectly regulate gene expression in a manner that reduces MS activity.

A number of new clinical trials, mostly using Vitamin D as an add-on to existing therapies in Phase IV studies, are ongoing to assess if supplemental Vitamin D can exert such disease-modifying effects. To follow are examples of these types of investigations.

Mowry and colleagues at Johns Hopkins have initiated a multi-center clinical trial in which patients with relapsing-remitting MS will receive high-dose (5,000 IU/day) or low-dose (600 IU/day) oral Vitamin D in addition to Copaxone.[60] Patients will be evaluated for two years, and the effect of high-dose Vitamin D supplementation on the rate of MS attacks as well as on the number of new lesions and change in brain volume on MRI will be determined. This trial is presently enrolling, with a goal of 172 participants, and is expected to run through December 2014.

A Phase II study that is currently recruiting[61] participants is investigating whether Vigantol® oil, a form of Vitamin D hormone supplement (cholecalciferol), provides any added benefit when given in conjunction with Rebif. The study

will have 348 participants; it began in February 2011 and is scheduled for completion in March 2014. Primary outcome measures are the mean change from baseline in the total volume of T2 lesions at week 48 and the proportion of relapse-free subjects at week 96. Secondary outcome measures include sustained disability progression, MRI measures of disease progression, the proportion of subjects free from disease activity at 96 weeks, and changes in cognitive function.

The French CHOLINE Phase II study[62] of 250 individuals with RRMS who are receiving ongoing treatment with Rebif began in January 2010 and is scheduled for completion in July 2014. The aim of this study is to evaluate the efficacy and safety of supplementary treatment with Vitamin D3 in people with RRMS treated with Rebif. The study participants will be divided into two groups, one receiving Vitamin D3 100,000 IU twice monthly along with Rebif treatment, and the other group will be on placebo along with Rebif treatment. Its primary outcome measure is a reduction in relapse rate; secondary outcome measures include the time to a first documented relapse, the mean number of relapses per subject per year, the number of relapse-free patients after two years of treatment, MRI measures of progression and lesion load, and change in quality of life.

Please note that while no major safety issues have been reported with these larger daily doses of Vitamin D3 (such as 5,000 to 10,000 IU/day), as with all medications and supplements, individuals should always consult their physician before making any changes to their treatment plan.

Salt

An array of recent research ranging from molecular studies to animal models and even some preliminary human data has implicated levels of dietary salt – sodium chloride, or NaCl – as potentially affecting MS outcomes. In research presented in 2013,[63] high dietary salt was found to increase autoimmune neuro-inflammation by markedly boosting a Th17 helper T-cell driven autoimmune response in EAE (an experimental disease used to simulate MS in mice). Th17 is an immune-system cell (lymphocyte) involved with the inflammation that causes damage to the myelin and nerves with MS. This Th17-boosting property of dietary salt was also seen in humans.

In a separate study,[64] higher salt consumption was associated with increased clinical and MRI disease activity in people with MS. Seventy patients with RRMS were followed over two years, tracking sodium intake, in conjunction with clinical and MRI assessment every three to six months or at the time of relapse. Researchers found that individuals with high-sodium intake had 3.4 times greater odds of developing a new lesion on the MRI, and on average, had eight more T2 lesions on MRI. MS relapse rates were higher among those with high-sodium intake as well.

The theory that salt may increase MS inflammation remains to be proven, and interventional studies will need to be performed to establish causality, but this theory could have far-reaching practical dietary implications for MS patients.

Chronic Cerebrospinal Venous Insufficiency (CCSVI)

Over the past several years, the Chronic Cerebrospinal Venous Insufficiency (CCSVI) theory of MS pathogenesis received considerable attention, and remains an area of ongoing research. The evidence continues to increase that occlusions/obstructions of the vascular system in cerebrospinal veins (certain veins located in the head and neck) imaged with ultrasound and magnetic resonance venography do not appear to be related to MS.

Reports from an ongoing study at the University of Texas Health Sciences Center in Houston showed that people with and without MS had abnormalities consistent with CCSVI, and that this abnormality was not found to be more common in people with MS. The group used strict ultrasound criteria definitions, and concluded that their tests – using neurosonography and magnetic resonance venography – did not support the concept that CCSVI is causally involved in MS.

Several vascular-intervention procedures to address the reported venous narrowing in MS are being studied, however, these procedures have also been offered in clinical practice, outside of the safety oversight inherent in clinical trials. Shortly after the American Academy of Neurology's (AAN) meeting in mid-2012, the FDA issued an alert about risks, including death, associated with these surgical treatments of CCSVI.

The FDA Safety Communication regarding CCSVI treatment in MS stated that, as of May 2012, the FDA believes there is no reliable evidence from controlled clinical trials that this procedure is effective in treating MS. Data to support CCSVI as a clinical entity on its own or its relationship with MS are inconclusive and at times, contradictory. The FDA believes that using these medical devices in CCSVI treatment procedures poses a risk to patients for several reasons. First, there is no clear diagnostic evidence that CCSVI exists as a distinct clinical disorder or is linked to MS. Second, the venous stenoses seen on imaging tests may be normal variants and not related to a disease process. Furthermore, the safety and effectiveness of using balloon angioplasty devices or stents in the internal jugular or azygos veins have not been established, and that major risks, including death, have been associated with these procedures.

The largest CCSVI study to date was presented at ECTRIMS in the fall of 2012. In the CoSMo study, Comi and Italian colleagues studied nearly 2,000 people with MS and other neurological diseases, as well as healthy controls. They used both trained local sonographers, as well as review by three central imaging experts. The three imaging experts were all "blinded," meaning that they did not know which patients had MS and which were the healthy controls.

The CoSMo study found evidence of CCSVI in 3.3 percent of MS patients, 3.1 percent of other neurological diseases, and 2.1 percent of healthy controls. Interestingly, the central reviewers found less evidence of CCSVI than the local sonographers, which speaks to the importance of blinding and rigorous trial design to yield meaningful results. Differences in

CCSVI between MS and other neurologic conditions and healthy participants were not statistically different, and the study group concluded that the data did not support that CCSVI is a disease connected to MS.

Several other CCSVI research projects are still in progress, including research in Europe and the United States. A study for the Evaluation of Angioplasty in the Treatment of Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis[65] is being coordinated at Albany Medical Center, and is still ongoing.

MSAA enthusiastically but cautiously supports the investigation of any plausible causes and treatments for MS, striving to communicate such research to the MS community as soon as any information becomes available. However, at the same time, MSAA's policy is to consider patient safety as the top priority – recognizing that all prospective theories and experimental treatments need to be thoroughly studied through rigorous clinical trials.

As with any unproven theory and treatment, interested patients are strongly encouraged to first talk with their doctor. Without a tested and proven protocol for the diagnosis and treatment of CCSVI, individuals could be putting themselves at risk by undergoing a procedure in a non-research, "commercial" setting. Caution and skepticism is advised pertaining to research projects that have not been reviewed by the FDA, are not listed on **clinicaltrials.gov**, and charge "retail prices" or require travel to a foreign country for the procedure.

For more information on CCSVI and the FDA's 2012 warning, please refer to MSAA's online news articles, "FDA Issues CCSVI Treatment Warning" and "CCSVI Update." These may be accessed by visiting MSAA's website at **mymsaa.org** and selecting "News from MSAA" under "MS News," and then scrolling down to the articles on CCSVI.

EXPERIMENTAL MEDICATIONS: NEW THERAPIES UNDER INVESTIGATION

New Therapies under Investigation

The earlier listing of approved and experimental drugs is only a fraction of the many treatments currently being studied. Some of the following are among the most exciting potential therapies under investigation. These very brief snapshots of highly technical concepts will warrant more in-depth explanations in the future, if pilot clinical trials are encouraging.

Anti-LINGO: LINGO-1 itself is a protein in the central nervous system whose role is to halt myelination and prevent the survival of neurons. The cells making up all organs in the body receive such "instructions" regarding when to grow and when to cease growing. Without these sorts of cellular "checks and balances," tissues could grow without restraint, as seen in some malignancies. Anti-LINGO-1 (BIIB033) is an agent with potential remyelinative properties, after animal studies showed that it blocks this protein responsible

for stopping the growth of myelin. It was shown to promote spinal cord remyelination and axonal integrity in the animal model of MS (EAE).

The first trials of experimental anti-LINGO to stimulate myelin repair – human Phase I trials[66], involving 64 healthy adult volunteers and 42 people with relapsing or secondary-progressive MS – have been completed. In these trials, intravenous doses of anti-LINGO were well tolerated, and there were no serious adverse events; headache was the most frequent adverse event reported. The authors concluded that the results support advancing this myelin repair strategy into a Phase II clinical trial. The first Phase II trial of anti-LINGO launched in 2013,[67] recruiting patients with newly-diagnosed MS involving the visual pathways (optic neuritis) to evaluate its effect on remyelination.

A second, larger Phase II trial[68] looking at this drug in combination with Avonex will recruit approximately 400 patients and examine the degree to which patients have an improvement in disability with anti-LINGO. Since this agent does not reduce relapses or prevent new MRI lesions, further studies with anti-LINGO, and other potential remyelination therapies, will need to utilize new endpoints such as this to prove efficacy. This includes measurements of recovery or improvement on physical, visual, cognitive, and other functional assessments of the effects of MS.

For a detailed review of the science behind anti-LINGO-1, please see the article in *CNS Drugs*, "Blocking LINGO-1 as a Therapy to Promote CNS Repair: From Concept to Clinic," Mi et al, 2013.[69]

Erythropoietin: Erythropoietin is a hormone produced by the kidneys that promotes the formation of red blood cells in the bone marrow. It has shown neuroprotective effects in animal studies. A German Phase I/IIa pilot study suggests that high-dose treatment, but not a lower-dose regimen, leads to clinical improvement of motor function. Cognitive performance was also improved. Studies are ongoing, including one evaluating erythropoietin as an adjunct treatment for optic neuritis.[70]

Idebenone (Catena®, Sovrima®): This experimental drug, similar to coenzyme Q10, was initially developed to treat Alzheimer's disease and other cognitive defects. Coenzyme Q10 is produced within your own body and is necessary for cells to grow and remain healthy. This substance also works as an antioxidant, helping to prevent injury from the oxidation process. It is being explored in MS because oxidative stress has been postulated to play a role in the death of myelin-producing cells, which has been linked to MS progression. Oxidation is the body's natural metabolism of oxygen. When disturbances occur in this process, "oxidative stress" can result, causing damage to the body's cells and tissues. Oxidative stress is believed to be a contributing factor in many diseases, including those affecting the nerves and the immune system.

A double-blind, placebo-controlled Phase I/II clinical trial of idebenone[71], sponsored by the National Institute of Neurological Disorders and Stroke, is currently recruiting participants with PPMS with little to moderate disability. It began in July 2009 and is scheduled for completion in September 2016.

MIS416: This "therapeutic vaccine" is a potent activator of the innate immune system, which provides immediate defense against infection but does not result in long-lasting or protective immunity. It has been primarily tested in cancer and acquired infections, with the goal of enhancing the inherent capability of a person's immune system to fight disease. **A Phase I/II study to evaluate the safety and tolerability of IV-administered MIS416 in people with either PPMS or SPMS presented interim results in 2012.** This open-label, dose-escalation/confirmation trial showed MIS416 to be well tolerated and identified a clinical dose for further evaluation. Moreover, during the dose confirmation portion of the study, eight of 10 patients with SPMS who were treated with MIS416 for 12 weeks showed some improvement. Further Phase II studies are planned, but are not as yet enrolling.

Transdermal Administration of Peptides: A small Polish study of 30 individuals[72] with RRMS evaluated the efficacy and safety of transdermal (skin patch) administration of two dose levels of three myelin peptides: MBP 85-99, PLP 139-151 and MOG, versus controls. In the lower-dose group, which received 1 mg each of the three peptides, the annual relapse rate at one year was reduced by 65 percent compared with placebo, progression in the Expanded Disability Status Scale (EDSS) was slightly lower, and 56 percent were relapse-free versus 10 percent in the placebo group. The treated group also showed a decrease in gadolinium-enhancing lesion volume and T2-lesion volume. The treatment was safe and well-tolerated. This approach may be pursued in future studies.

Other Agents in Development

A number of other agents have shown some encouraging immunomodulatory effects and have been studied in humans. These agents are under investigation for possible future use in MS and include the following experimental treatments:

Secukinumab (AIN457) is a humanized monoclonal antibody to IL-17. A preliminary study[73] administered AIN457 to a very small number of patients with psoriasis, rheumatoid arthritis, and uveitis with variable results. A proof-of-concept trial in RRMS[74] enrolled 73 patients and showed a reduction in gadolinium-enhancing MRI lesions compared with placebo.[75] A larger, Phase II trial has been planned to enroll approximately 380 patients with relapsing MS; the design was presented at ECTRIMS in Fall 2013.

RTL1000 is a protein that inhibits the activation of myelin-reactive T cells, preventing the release of inflammatory cytokines and causing the release of anti-inflammatory cytokines. This molecule is related to the pathways studied transdermally (through the skin), as discussed earlier with peptides. A preliminary safety/tolerability dose-finding study of RTL1000 was reported in 2012.[76]

SB-683699 (firategrast) is an oral agent thought to reduce the number of active white blood cells entering the brain via a similar mechanism to Tysabri. It had positive results in a placebo-controlled Phase II trial[77] using gadolinium-enhancing lesions as the primary outcome.

Stem Cells

Based on encouraging results from a variety of studies, clinical trials are now starting to enroll patients using three different broad classes of stem-cell-based approaches.

The first stem-cell approach is hematopoietic stem-cell transplantation (HSCT). This form of stem-cell therapy first requires a wiping out or "ablation" of the immune system, typically with high-dose chemotherapy. This intensive course of chemotherapy destroys most blood cells as well as the bone marrow, where blood cells are formed. Then a patient's own hematopoietic stem cells can be transplanted, in an effort to completely reset the immune system in the hopes of abolishing the autoimmunity responsible for MS.

One trial of this technique is the High-Dose Immunosuppression and Autologous (stem-cell) Transplantation for Multiple Sclerosis (HALT MS) Study, for poor prognosis multiple sclerosis. The HALT Phase II study was conducted in 25 patients with highly active RRMS who had failed conventional therapy. The two-year follow-up results of the HALT study were reported in 2013.[78] The treatment induced profound immune suppression and a high rate of sustained remissions at two years. One patient died within three years of transplantation. Study participants will be followed for five more years to see how long the benefits of this treatment may continue.

Another study in Sweden[79] found a high proportion of patients with aggressive, relapsing forms of MS were free from disease activity following hematopoietic stem-cell transplantation (HSCT). A group of 41 patients participated in this study. They had a mean annualized relapse rate of 4.1 in the year preceding treatment, which means that on average, these individuals with very active disease were each experiencing four relapses in one year. With a mean average follow-up time of nearly four years (47 months) after receiving the HSCT procedure, 89 percent of the participants were relapse-free and 77 percent of the participants had no disability progression, as measured by the EDSS. In addition to the serious though expected side effects, including sepsis and fever, a small number of patients experienced other adverse events, such as a reactivation of herpes zoster in seven patients and thyroid disease in four patients; no deaths occurred in this trial.

A second type of stem cell therapy utilizes mesenchymal stem cells, which can be derived from tissues other than bone marrow and do not require a "wiping out" of the immune system for their use. In a phase IIa study,[80] **10 patients with SPMS with involvement of the visual system** were infused with self-derived (autologous) mesenchymal stem cells. The researchers found an improvement in visual function, as well as an improvement in other laboratory and imaging measures of optic nerve function. There were no serious adverse events or deaths. Although the mechanism by which mesenchymal stem cells exert their beneficial effects has not been fully worked out, these cells do not need to penetrate into the nervous system and grow at the site of lesions, such as the optic nerve. The results of this study were suggestive of a more generalized neuroprotective effect; this effect is discussed in the next section.

A third approach to investigating stem cell therapy, and perhaps the one most in-line with

the commonsense notions about the potential uses of stem cells, is to utilize them for the purpose of directly regenerating myelin that has been damaged by MS. This approach requires multiple complex steps in order to be successful. Techniques must be utilized to harvest a patient's stem cells, grow and multiply them, administer them to the patient, ensure that they get into the central nervous system, ensure that they are not destroyed by the body's own immune system, ensure that they grow to become the correct type of cell (for instance, to restore myelin), and to ensure that they do not overgrow or cause damage to the nervous system.

This approach to stem cell therapy is being investigated in an open-label Phase I clinical trial[81] announced in Fall 2013. **This single-center trial plans to enroll 20 patients with progressive MS**, and will infuse doses of stem cells harvested from the patients' own bone marrow directly into the cerebral spinal fluid (CSF), typically done via lumbar puncture, repeatedly over six months. As an open-label study, the primary endpoint will be to determine the safety of this approach. Potential subsequent investigations may pursue efficacy, ascertain the optimal dose and route of administration, and identify patients most likely to benefit from this therapeutic approach. It is important to recognize that, as a Phase I study, this project is at the earliest stages of experimental human research.

Neuroprotective Agents

The term "neuroprotection" refers to strategies designed to prevent irreversible damage from a variety of cell types in the central nervous system (CNS), as well as to promote regeneration after MS-related damage has occurred. These have the goal of preventing the development of disability. A variety of neuroprotective strategies are now being studied.

- One that seems especially promising is to identify the role that the neurotoxic transmitters glutamate and nitric oxide play in the development of neuronal damage, with the goal of preventing this process.
- At the same time, studies are focusing on stimulating growth factors that promote neural function, such as brain-derived neurotrophic factor (BDNF). This combination – decreasing factors that cause damage while at the same time increasing factors that stimulate growth – holds significant potential for preventing MS-related damage and stimulating neuronal function.

Biomarkers

In medicine, the term biomarker refers to anything that can be used as an indicator of a particular disease state; in effect, a biomarker is a surrogate for the disease state. It often refers to a protein measured in blood, whose concentration reflects the severity or presence of disease and/or that can be used to measure therapeutic effectiveness. Many types of biomarkers are being researched in MS, and are likely to grow in importance in the coming years.

Although the term itself is relatively new, biomarkers have long been used in medicine. For example, body temperature is a well-known biomarker for fever, blood pressure helps determine the risk of stroke, and cholesterol levels are a biomarker and risk indicator for

coronary and vascular disease. Biomarkers are often seen as the key to the future of what is termed "personalized medicine." This refers to treatments that can be individually tailored to specific patients for highly efficient intervention in disease processes.

The concept of personalizing MS care has been implemented in a general way by the use of disease-modifying therapies based on someone's clinical course – CIS, RRMS, SPMS, PRMS, or PPMS – categories that are entirely based on a patient's clinical history. This approach has been refined as clinicians may recommend "more aggressive" therapies based on markers of disease severity (such as MRI lesions), as well as on demographic factors that may be concerning for a more difficult disease course.

The search for biomarkers of MS is referred to throughout this article, and studies are ongoing with all major MS drugs to find markers that will help determine who should be treated with that drug as well as how effective the drug is after therapy is begun. We already utilize one type of blood test to help predict ongoing therapeutic response – neutralizing antibodies to the interferons and Tysabri. A major goal of biomarker studies is to be able to decide which patient is most likely to respond to which therapy before it is started, so the decision about which medication to start can be optimized.

For example, current studies are showing that it may soon be possible to determine who might be a suboptimal responder to interferons, based on immune system-related substances that can be measured in the blood. Another study was designed to evaluate whether the type of cytokine present prior to treatment with Copaxone might act as a biomarker to identify those individuals with RRMS who are more likely to respond to immunomodulating treatments. It showed that people who responded to Copaxone secreted higher levels of specific inflammatory cytokines prior to treatment. A genetic study, with results reported in 2012, looking at the response to Copaxone, also suggested that multiple genetic markers may predict a favorable response to this medication.

An additional use of biomarkers will be to predict and minimize the risk of medication-related adverse events. This approach has already proved effective for new infectious biomarkers, such as the development of a blood test for JC virus antibodies, to identify who is at greater or lesser PML risk when treated with Tysabri. Based on this blood test, the option of using Tysabri can be more precisely personalized to maximize the benefit/risk ratio for this medication in practice. This type of biomarker strategy may also prove useful in predicting the risk on an individual basis of non-infectious adverse events to some of the investigational medicines reviewed.

A strong link exists between biomarkers and genetics, and the line between them may sometimes appear blurred. This is because many of the biomarkers that are being discovered relate to the activity of specific genes that code for proteins involved in inflammation, or are otherwise linked to the response to disease-modifying therapies. Studies of the gene expression signature, through global gene expression analysis, reveals the pattern of the entire DNA in an individual. This type of study has become possible due to recent advances in high-speed genetic pattern analysis. For example:

- Genes found to be expressed differently in MS, effectively become biomarkers for disease progression and may change as the result of treatment. A recent study identified several candidate genes that could potentially serve as biomarkers of interferon treatment or targets for therapeutic intervention in MS.
- A study using gene expression analysis of whole blood showed significant differences in expression profiles of patients with optic neuritis compared with healthy controls.
- Another study showed that interferon therapy induces the expression of genes involved in interferon regulation and signaling; a subgroup of patients with a higher risk for relapses showed a different expression of specific genes.

An ongoing clinical trial sponsored by the National Institutes of Health is studying more than 1,000 people with RRMS participating in the CombiRx study (described on page 8); this includes patients on interferon only, Copaxone only, or a combination of both. Samples of serum and white blood cells are being obtained from each patient prior to the study and at regular intervals thereafter.

Although Copaxone and Avonex did not differ greatly in their efficacy in the CombiRx trial, certainly both drugs work well for some people and less well for others. This study will identify biomarkers (genes and the proteins they encode) and link them to clinical- and MRI-based outcomes, such as the extent of inflammation and rate of disease progression. It will examine how the biomarkers may be related to disease development and progression as well as differences among patients' symptoms and response to treatment. Based on these genetic biomarkers, likely best-responders to either form of therapy can be identified.

Genetic Studies

As discussed in this article in previous years, there has been a growing body of evidence for the genetic component in MS. The studies on biomarkers have arisen as the result of this work, and a number of genes that are linked to the development of MS have been identified.

This field of research saw a major breakthrough in August 2011, when the journal *Nature* published the results of the largest MS genetics study ever undertaken. A global collaboration of scientists identified 29 new genetic variants associated with MS, and confirmed 23 others that had been previously associated with the disease. The study confirmed that the immune system plays a major role in the development of MS: most of these genes are related to immune function, and more than one-third of them have previously been confirmed to be associated with other autoimmune diseases, such as Crohn's disease and type 1 diabetes.

The study involved nearly 10,000 people with MS and more than 17,000 controls without MS, in 15 countries. The research was carried out by approximately 250 investigators. The results are now to be confirmed and expanded in a second, large-scale study.

The team found that a large number of these genes are related to T-cell function; they were mainly associated with T-cell activation and proliferation. This was particularly important because these are the cells believed to be the major mediators of the early immune attack on the brain and

spinal cord in MS. Two of the genes are linked to Vitamin D, and low Vitamin D levels have already been implicated as a risk factor for developing MS. As noted earlier, more than one third of the genes are known to be associated with other autoimmune diseases such as Crohn's disease and type 1 diabetes; MS is believed to be an autoimmune disease as well.

These and other genetics studies do not as yet significantly improve our ability to provide genetic counseling to individuals concerned about their risk of developing MS. However, they should help researchers to better define the biological pathways that lead to the development of MS. It is also hoped that they will enhance our ability to design better treatments for early MS.

CLOSING NOTES

In summary, the future of disease-modifying therapies (DMTs) for MS continues to be promising, both in terms of new information about currently approved DMTs and exciting results for emerging therapies. Advances in genetic and biomarker studies hold the promise that, in the future, it will be possible to personalize the decisions about MS therapy in a precise, biologically-driven manner. And ongoing clinical trials in PPMS and SPMS, as well as investigations into neuroprotection, remyelination, and repair, offer great promise for the treatment of progressive MS and the goal of reversing the damage caused by this disease.

In recent years, our arsenal of MS therapies has grown considerably. Along with these new therapies come a host of new challenges and risks, which will require vigilance and a thoughtful approach to medication selection and management. The new generation of MS medications will undoubtedly enhance both the benefits, and the complexity, of the MS therapy decision-making process.

As clinicians have more numerous and more complex treatment options to offer patients, the need for patient education and awareness has become more crucial. Now more than ever is the age of empowered, highly-informed patients, who can be true participants in their MS care in collaboration with their treatment team. We hope this update is a valuable part of that process. For more information about clinical trials, please visit **www.clinicaltrials.gov**. For more information about MS and its treatments, please contact MSAA at **(800) 532-7667**, or visit **mymsaa.org**.

REFERENCES

[1] Freedman MS. "Long-term follow-up of clinical trials of multiple sclerosis therapies." *Neurology*. 2011 Jan 4;76(1 Suppl 1):S26-34.

[2] Goodin DS, et al. "Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial." *Neurology*. 2012 Apr 24;78(17):1315-22.

[3] Ziemssen T, et al. ECTRIMS 2013 [Abstract 973]

[4] Fabian, et al. Presented at the AAN Thursday, April 14, 2011. See http://www.mssm.edu/departments-and-institutes/neurology/news/mount-sinai-researchers-help-identify-differences-in-disease-progression-in-two-subtypes-of-ms

[5] Snow S, et al. "Pregnancy outcomes in patients exposed to interferon beta 1b." Presented at ECTRIMS 2013.

[6] Coyle P, et al. Presented at CMSC 2013 Poster SC06

[7] Khan, et al. "A phase 3 trial to assess the efficacy and safety of glatiramer acetate injections 40mg administered 3 times a week compared to placebo." Presented at ECTRIMS 2012.

[8] Lublin F, et al. "The CombiRx Trial: A Multi-Center, Double-Blind, Randomized Study Comparing the Combined Use of Interferon Beta-1a and Glatiramer Acetate to Either Agent Alone in Participants with Relapsing-Remitting Multiple Sclerosis – Clinical Outcomes." Presented at AAN; April 21-28, 2012; PL02.003.

[9] Wolinsky J, et al. "The CombiRx Trial: A Multi-Center, Double-Blind, Randomized Study Comparing the Combined Use of Interferon Beta-1a and Glatiramer Acetate to Either Agent Alone in Participants with Relapsing Remitting Multiple Sclerosis – MRI Outcomes." Presented at AAN; April 21-28, 2012; S11.002.

[10] ClinicalTrials.gov Identifier: NCT00958009

[11] ClinicalTrials.gov Identifier: NCT01036165

[12] Comi G, et al. "Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial." *Lancet Neurol.* 2012 Jan;11(1):33-41. Epub 2011 Dec 4. Erratum in: *Lancet Neurol.* 2012 Feb;11(2):125.

[13] Bloomgren G, et al. Presented at ECTRIMS 2011; Amsterdam, Netherlands. [P995] Fox and Rudick, *Neurology*, 2012.

[14] Gold R and Kieseier B. Presented at ECTRIMS 2013, Session: Management of Risk in MS Therapy.

[15] Fox R, et al. "5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS): Abstract 150." Presented October 22, 2011.

[16] ClinicalTrials.gov Identifier: NCT01485003

[17] Christensen JR, et al. Presented at ECTRIMS 2012; October 9–13, 2012; Lyon, France. [Abstract 170]

[18] ClinicalTrials.gov Identifier: NCT01416181

[19] Nikol, et al. Presented at ECTRIMS 2013, P1087

[20] Freedman M, et al. ECTRIMS 2013 [Poster 544]

[21] Kappos, et al. "28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)." Abstract 153. Presented October 12, 2012.

[22] http://en.sanofi.com/Images/29301_20111220_TENERE_en.pdf

[23] Miller A, et al. ECTRIMS 2013 [Abstract 99]

[24] Kappos L, et al. ECTRIMS 2013 [Poster 1052]

[25] Cohen J, et al. Presented at AAN 2013, Abstract S51.006.

[26] Barkhof F, et al. ECTRIMS 2013 [Poster 518] and Radue E, et al. ECTRIMS 2013 Session: Long-term Treatment Monitoring.

[27] Laroni, et al. "Safety of the first dose of fingolimod for multiple sclerosis." Presented at ECTRIMS 2013.

[28] ClinicalTrials.gov Identifier: NCT01216072

[29] ClinicalTrials.gov Identifier: NCT01633112

[30] Phillips JT, et al. ECTRIMS [Poster 996]

[31] Calabresi P, et al. ECTRIMS 2013 [Poster 514] and Calabresi P, et al. AAN 2013; Abstract S31.006.

[32] Vermersch P. ECTRIMS 2013 [Abstract 107] and Comi G, et al. ECTRIMS 2013. Session: Long-Term Treatment Monitoring.

[33] ClinicalTrials.gov Identifier: NCT01707992

[34] Cohen JA, et al. "Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial." *CARE-MS I investigators. Lancet.* 2012 Nov 24;380(9856):1819-28.

[35] Coles AJ, et al. "Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial." *CARE-MS II investigators. Lancet.* 2012 Nov 24;380(9856):1829-39.

[36] Krieger S, et al. "Alemtuzumab Is Efficacious In Highly Active RRMS Patients In CARE-MS II." Presented at CMSC 2013, Platform DX01.

[37] Giovannoni G, et al. Presented at ECTRIMS 2012; October 9–13, 2012; Lyon, France. [Abstract P169]

[38] Radue EW, et al. ECTRIMS 2013 [Poster 977]

[39] ClinicalTrials.gov Identifier: NCT01064401

[40] ClinicalTrials.gov Identifier: NCT01212094

[41] Kappos L, et al. "Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial." *Lancet*. 378 (9805), 1779-87 (2011).

[42] ClinicalTrials.gov Identifier: NCT01412333

[43] ClinicalTrials.gov Identifier: NCT01247324

[44] ClinicalTrials.gov Identifier: NCT01194570

[45] ClinicalTrials.gov Identifier: NCT01457924

[46] ClinicalTrials.gov Identifier: NCT01665144

[47] Olsson T, et al. [Abstract 152]; Freedman MS, et al. [Abstract P923]; Fernandez O, et al. [Abstract 919] All presented at ECTRIMS 2012; October 9–13, 2012; Lyon, France.

[48] Pozzilli, et al. Presented at ECTRIMS 2013, P995

[49] ClinicalTrials.gov Identifier: NCT01450488

[50] Vermersch P, et al. "Oral Masitinib in Patients with Primary and Secondary Progressive Multiple Sclerosis." Presented at American Academy of Neurology Annual Meeting. Seattle, WA, USA, 25 April-2 May 2009.

[51] ClinicalTrials.gov Identifier: NCT01433497

[52] ClinicalTrials.gov Identifier: NCT01982942

[53] ClinicalTrials.gov Identifier: NCT01684761

[54] Arun T, et al. "Targeting ASIC1 in primary progressive multiple sclerosis: evidence of neuroprotection with amiloride." *Brain*. 2013 Jan;136(Pt 1):106-15.

[55] ClinicalTrials.gov Identifier: NCT01802489

[56] Chataway J, et al. "The MS-STAT trial: high dose simvastatin demonstrates neuroprotection without immune-modulation in secondary-progressive multiple sclerosis (SPMS) – a phase II trial." [London, Brighton, GB]

[57] Sorensen PS, et al. "No beneficial effect of minocycline as add-on therapy to interferon-beta-1a for the treatment of relapsing-remitting multiple sclerosis: results of a large double-blind, randomised, placebo-controlled trial." On behalf of the RECYCLINE Study Investigators.

[58] Ascherio A, et al. ECTRIMS [Abstract 96]

[59] Mowry EM, et al. "Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis." *Ann Neurol*. 2012 Aug;72(2):234-40. doi: 10.1002/ana.23591.

[60] ClinicalTrials.gov Identifier: NCT01490502

[61] ClinicalTrials.gov Identifier: NCT01285401

[62] ClinicalTrials.gov Identifier: NCT01198132

[63] Linker R, et al. "High Dietary Salt Aggravates Experimental Neuroinflammation in Mice Via Induction of Th17 Cells." Presented at AAN, 2013.

[64] Farez MF, et al. ECRIMS 2013 [Abstract 119]

[65] ClinicalTrials.gov Identifier: NCT01201707

[66] ClinicalTrials.gov Identifier NCT01244139

[67] ClinicalTrials.gov Identifier: NCT01721161

[68] ClinicalTrials.gov Identifier: NCT01864148

[69] Mi S, Pepinsky BS, Cadavid D. "Blocking LINGO-1 as a Therapy to Promote CNS Repair: From Concept to the Clinic." *CNS Drugs* (2013) 27:493–503.

[70] ClinicalTrials.gov Identifier: NCT00355095

[71] ClinicalTrials.gov Identifier: NCT00950248

[72] Juryńczyk M, et al. "Immune regulation of multiple sclerosis by transdermally applied myelin peptides." *Ann Neurol*. 2010 Nov;68(5):593-601. doi: 10.1002/ana.22219.

[73] Hueber W, et al. "Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis." *Sci Transl Med*. 2(52), 52ra72 (2010).

[74] ClinicalTrials.gov Identifier: NCT01051817

[75] Rudick, et al. Presented at ECTRIMS 2013

[76] Yadav V, et al. "Recombinant T-Cell Receptor Ligand (RTL) for Treatment of Multiple Sclerosis: A Double-Blind, Placebo-Controlled, Phase 1, Dose-Escalation Study." *Autoimmune Dis*. 2012;2012:954739. Epub 2012 Apr 5.

[77] Miller DH, et al. "Firategrast for relapsing remitting multiple sclerosis: a phase 2, randomised, double-blind, placebo-controlled trial." *Lancet Neurol*. 2012 Feb;11(2):131-9. doi: 10.1016/S1474-4422(11)70299-X. Epub 2012 Jan 5.

[78] CMSC 2013: P20 "2-Year Follow-Up Results Of The HALT MS Clinical Trial." (ITN033AI).

[79] Burman J, et al. ECTRIMS 2013 [Poster 1017]

[80] Connick P, et al. "Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study." *Lancet Neurol*. 2012 February; 11(2): 150–156. PMCID: PMC3279697.

[81] ClinicalTrials.gov Identifier: NCT01933802

Trial Phases for Investigating Drugs and Treatments

Every approved treatment for MS has undergone extensive study prior to receiving approval by the United States Food and Drug Administration (FDA). The process of testing a new drug therapy for MS is time-consuming, and all drugs must undergo several phases of investigation in order to be deemed both safe and effective.

PHASE I: Phase I studies are primarily concerned with assessing the drug's safety. This initial phase of testing in humans is done in a small number of healthy volunteers, and is designed to determine what happens to the drug in the human body – how it is absorbed, metabolized, and excreted.

Phase I trials are referred to as "open label" and "unblinded," because everyone – the patient, medical staff, and investigators – knows the drug and dose that each participant is receiving. A Phase I study will investigate side effects that occur as dosage levels are increased. Phase I trials can take several months to one year to complete.

PHASE II: Once a drug has been shown to be safe, it must be tested for efficacy. This second phase of testing may last from several months to two years, and involve up to several hundred patients. Phase II studies are often "double-blinded," meaning that the participants, medical staff, and investigators are not told who is receiving the drug and who is receiving the placebo.

These studies are also "randomized," so that participants are assigned to treatment groups (or "treatment arms") based on chance. One group of patients receives the experimental drug, while a second "control" group will receive a standard treatment or placebo. In this manner, the study can provide the pharmaceutical company and the FDA information about the relative safety of the new drug, and its effectiveness. Only about one-third of experimental drugs successfully complete both Phase I and Phase II studies.

PHASE III: In a Phase III study, a drug is usually tested in several hundred to several thousand patients, usually in multiple medical facilities around the world. Phase III studies typically last several years. This large-scale testing provides the pharmaceutical company and the FDA with a more thorough understanding of the drug's effectiveness, benefits, and the range of possible adverse reactions.

Most Phase III studies are randomized and blinded trials. Only after a Phase III study is successfully completed can a pharmaceutical company request FDA approval for marketing the drug.

PHASE IV: Phase IV clinical trials are conducted after a drug has been approved. Participants are enrolled to further monitor safety and side effects, while evaluating long-term efficacy.

MS poses a specific set of challenges for clinical research. It is a highly-variable condition that affects everyone differently. Choosing the correct population of MS patients to study poses formidable challenges to clinical research, and is a major reason why accurately comparing the results of different MS drug trials (in order to answer the question "which drug is better?") is impossible.

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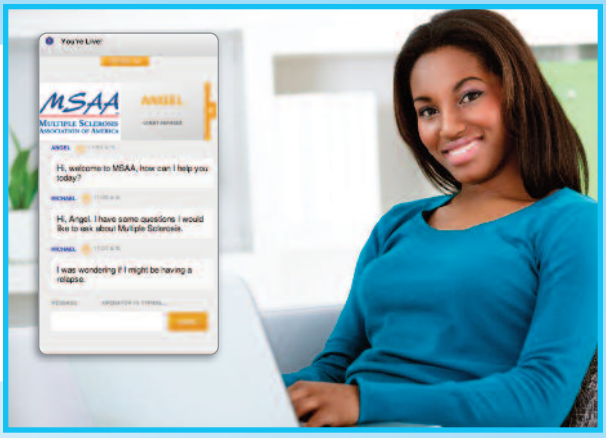

MS Relapse Resource Center

MSAA's **MS Relapse Resource Center** provides detailed information on relapses and treatments. Found under the "Manage Your MS" tab on our homepage, you'll find relapse tools, a relapse media center, a survey section, and more. *The Relapse Resource Center has been developed through an unrestricted grant provided by Questcor Pharmaceuticals.*

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