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MEETING REPORT

HIGHLIGHTS FROM THE 5TH JOINT TRIENNIAL CONGRESS OF THE EUROPEAN AND AMERICAS COMMITTEES FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS/ACTRIMS)

S. Vasiliou

Thomson Reuters, Barcelona, Spain

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SUMMARY

With more than 7,000 active participants from 95 countries worldwide, the 5th joint triennial meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), held in Amsterdam on October 19-22, 2011, was the largest meeting on multiple sclerosis (MS) to date. Data were disclosed from several clinical studies on promising therapeutic modalities addressing relapsing forms of MS.

Key words: Oral therapeutics – Monoclonal antibodies – Interferon – Pain – Multiple sclerosis

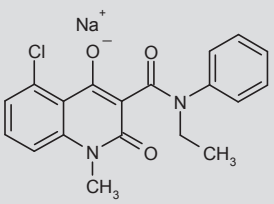
INTRODUCTION

ECTRIMS has served as Europe's largest professional organization dedicated to the understanding and treatment of multiple sclerosis (MS) for more than a quarter of a century. The vision of this independent organization is to create networking and collaboration opportunities among researchers and clinicians in an effort to advance basic and clinical research and to improve clinical outcomes in MS. Founded in 1995, ACTRIMS, the counterpart of ECTRIMS in the U.S. and Canada, is a nonprofit organization aiming to provide leadership in research and clinical care. The main focal points of the 5th joint triennial meeting of ECTRIMS/ACTRIMS included the importance of early treatment, risk management for new treatment modalities and ways to address the needs of patients with MS. This report summarizes updated findings on oral therapeutics that are expected to improve compliance to treatment, as well as monoclonal antibodies (MAbs). Results from clinical studies of other therapeutic modalities addressing the amelioration of neuropathic pain, as well as the treatment of optic neuritis associated with MS, are also included.

Correspondence: Sylvia Vasiliou, PhD, Thomson Reuters, Provença 398, 08025, Barcelona, Spain. E-mail: sylvia.vasiliou@thomsonreuters.com.

ORAL THERAPEUTICS

The oral immunomodulatory agent **laquinimod sodium** (Teva Pharmaceutical; licensed from Active Biotech) demonstrated the ability to obstruct the progression of disability and reduced the number of severe relapses in individuals with relapsing–remitting multiple sclerosis (RRMS) participating in the phase III ALLEGRO trial (1). Participants in the randomized, double-blind, placebo-controlled phase III study were randomized to receive treatment with laquinimod sodium (0.6 mg/day p.o.; n = 550) or placebo (n = 556) for a period of 24 months. Subjects treated with laquinimod demonstrated a reduction in the risk of progression based on Expanded Disability Status Scale (EDSS) scores by 36% after 3 months of ther-

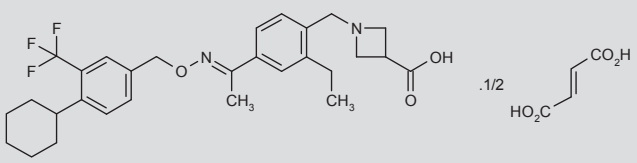


Laquinimod sodium

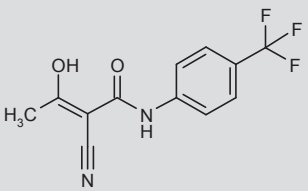
apy (*P* = 0.0122 versus placebo), with a 48% reduction in the risk for confirmed progression by EDSS at 6 months. The annualized rate of relapse requiring the use of intravenous steroids or hospitalization was reduced by 27% and 38%, respectively, in laquinimod-treated patients versus in subjects receiving placebo (*2*). At months 12 and 24 of the trial, laquinimod sodium reduced the mean cumulative number of gadolinium (Gd)-enhancing lesions and new T2 enlarging lesions by 37% and 30%, respectively, compared with placebo (*P* = 0.0003 and 0.0002, respectively). The active agent correlated with a significant reduction in the mean percent change of brain volume by 32.8% versus placebo (*P* < 0.0001) (3). Laquinimod therapy also resulted in significant improvements in the scores of the cognitive, physical and psychosocial subscales of the Modified Fatigue Impact Scale (MFIS) from baseline to 24 months compared with placebo (*P* = 0.05, 0.02 and 0.06, respectively) (4). Encouraging results were also presented from BRAVO, a trial aiming to assess the safety, efficacy and tolerability of laquinimod versus Avonex® (interferon beta-1a) in patients with RRMS (5). BRAVO was designed as a multicenter, randomized, rater-blind, parallel-assignment phase III study, in which participants were randomized to receive laquinimod sodium (0.6 mg p.o. once daily; n = 434), interferon beta-1a (30 µg once weekly; n = 447) or placebo (p.o. once daily; n = 450) for 24 months. Compared with placebo, laquinimod and interferon beta-1a resulted in significant reductions in the annualized rate of relapse of 21% and 29%, respectively (primary endpoint; *P* = 0.03 and 0.002, respectively). Treatment with laquinimod and interferon beta-1a also resulted in marked decreases in the risk of confirmed disease progression at 3 months of 33.5% and 28.7%, respectively, versus placebo. Headache was the most frequent adverse event (> 10%), with comparable frequency across treatment cohorts. Serious adverse events were reported in 7.2%, 8% and 5.7%, respectively, of patients receiving placebo, laquinimod and interferon beta-1a. No cases of liver failure were reported in the study. The findings from both trials support the use of laquinimod as a first-in-class treatment option in patients with MS (6).

Results were presented from a phase II study assessing the safety and efficacy of Novartis' **BAF-312,** a next-generation lysophospholipid $S1P_1$ and $S1P_5$ receptor modulator, in subjects with RRMS. BAF-312 at 5 dose levels was compared with placebo in 2 consecutive periods in a total of 297 patients with RRMS enrolled in a randomized, double-blind, dose-ranging phase II study. In period 1, participants (n = 188) were randomized to receive BAF-312 0.5, 2 or 10 mg p.o. or placebo for 3 months. In period 2, patients (n = 109) were randomly assigned to placebo or BAF-312 (doses of 0.25 and 1.25 mg were selected in order to define the final dose–response curve). Dose–response relationships were analyzed using Multiple Comparison Procedures with Modeling (MCP-Mod) methodology. The number of combined unique active magnetic resonance imaging (MRI) lesions was established as the study's primary outcome measure. Treatment with BAF-312 resulted in a reduction in combined unique active MRI lesions by up to 80% versus placebo, with the 2- and 10-mg doses forming an upper plateau of the dose–response curve. The dose of 0.5 mg correlated with a 50% decrease in combined unique active MRI lesions versus placebo. The annualized rate of relapse was estimated at 0.61, 0.20 and 0.30, respectively, at doses of 0.5, 2 and 10 mg of BAF-312 versus 0.58 with placebo (*P* < 0.05 for the 2-mg BAF-312 dose versus placebo). Toxicities included five transient symptomatic bradyarrhythmic events without sequelae seen following treatment with BAF-312 at the two highest doses in period 1. No bradyarrhythmic events were reported following the introduction of the initial dose titration scheme in period 2 or in the extension phase of the study. Other safety findings included transient and asymptomatic increases in the levels of liver enzymes (7, 8).

Teriflunomide (Sanofi) is an orally available immunomodulator undergoing clinical development for the treatment of relapsing forms of MS. The agent, which acts by reversibly inhibiting the activity of dihydroorotate dehydrogenase (quinone), mitochondrial (*DHODH*), has shown favorable safety and efficacy at 2 years in the phase III TEMSO (TEriflunomide Multiple Sclerosis Oral) study (9). Results were disclosed describing the effects of the agent on cognitive performance at 96 weeks during the multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-assignment trial. Participants were randomized 1:1:1 to receive once-daily oral treatment with teriflunomide 7 or 14 mg (n = 355 and 358, respectively) or placebo (n = 363) for 2 years. At week 96 of the study, a significant difference was observed between the cognitive function Z-score of patients receiving teriflunomide and those receiving placebo (mean change from baseline to week 96 in least squares of +0.075, +0.073 and –0.022, respectively, in subjects treated with the 7- and 14-mg doses of teriflunomide and placebo; *P* = 0.04 for both teriflunomide groups versus placebo) (10). Patients who completed the core TEMSO trial were eligible to participate in the extension phase of the study, which is currently ongoing and is aiming to



BAF-312

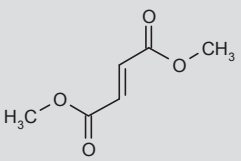


Teriflunomide

assess the long-term safety and efficacy of teriflunomide in relapsing forms of MS. Interim findings from this study were made available. A total of 742 subjects entered the extension phase of TEMSO to receive teriflunomide at doses of 7 or 14 mg/day p.o. (n = 381 and 361, respectively). Among the participants who had received placebo in the core study, 129 and 108, respectively, were administered the 7- and 14-mg dose of teriflunomide. Individuals who had been randomized to therapy with the active agent in the core phase of the trial maintained treatment at the same dose level in the extension study (252 and 253 patients, respectively, were treated continuously with the 7- and 14-mg dose of teriflunomide). The treatment was well tolerated at up to 4 years of follow-up. Preliminary safety analysis identified neutropenia and leukopenia, as well as reductions in neutrophil count and white blood cell count, as the most frequent adverse events (seen in < 5% of patients). Infections and infestations (mostly upper respiratory tract infections, urinary infections and infestations) occurred with similar frequency with the 7- and 14-mg teriflunomide doses (3.1% and 2.5%, respectively) (11, 12). MRI data obtained at 5 years following the initial randomization indicated that the change from baseline in total lesion volume (T2 and T1 hypointense lesions) was lower in subjects treated with teriflunomide at doses of 7 or 14 mg throughout the core and extension phase of TEMSO than in patients switching from placebo to teriflunomide in the extension phase of the trial. Gd-enhancing T1 lesions were significantly fewer in number per MRI scan in individuals receiving the active treatment than in those receiving placebo during the core part of the study, with a greater change from baseline seen with teriflunomide than with placebo. This change from baseline became comparable across treatment groups during the extension phase of TEMSO, when all participants were administered the active treatment (13).

Long-term (8-year) efficacy data were also disclosed from the open-label extension part of a phase II trial of teriflunomide in relapsing forms of MS (14). In the initial placebo-controlled, 36-week phase II study, a total of 179 patients were randomized 1:1:1 to receive treatment with oral teriflunomide 7 or 14 mg/day (n = 61 and 57, respectively) or placebo (n = 61). Participants who completed the 36-week treatment period were eligible to receive open-label teriflunomide at a dose of 7 or 14 mg/day in the extension study (n = 81 and 66, respectively). Of the patients who participated in the extension study, 29 and 26 were switched from placebo to the 7- and 14-mg dose of teriflunomide, respectively, whereas the remaining patients continued treatment with the preassigned dose of the active agent. Annualized relapse rate (ARR) was the primary efficacy parameter of the study. Assessments of relapse-free patients and MRI scans were performed every 48 weeks, whereas EDSS scores were evaluated every 24 weeks from the beginning of the extension study. At week 408, the adjusted ARR was estimated at 0.316 and 0.200, respectively, in subjects receiving continuous therapy with doses of 7 and 14 mg teriflunomide, whereas patients switching from placebo to the 7- or 14-mg dose of the active agent displayed respective adjusted ARR values of 0.252 and 0.212. The mean change from baseline in EDSS scores was calculated at 1 and 0.14, respectively, in individuals switching from placebo to the 7- and 14-mg dose of teriflunomide, whereas the respective values for patients receiving continuous therapy with teriflunomide 7 or 14 mg/day were calculated at 0.83 and 0.63, respectively (15). Exposure to teriflunomide for a follow-up period of up to 9 years was well tolerated. The most common treatment-emergent adverse events reported in ≥ 20% of patients receiving therapy at doses of 7 or 14 mg (n = 81 and 66, respectively) were identified as nasopharyngitis, hypoesthesia, fatigue, headache, back pain and muscular weakness. The incidence of infection was comparable across treatment groups (16).

Several poster presentations described the phase III DEFINE (Determination of the Efficacy and safety of oral Fumarate IN rElapsing-remitting MS) trial. The data support the safety, tolerability and efficacy of BG-12 (**dimethyl fumarate**; Biogen Idec) in RRMS. The agent acts as an activator of nuclear factor erythroid 2-related factor 2 (*NFE2L2/NRF2*) and suppresses the activation of nuclear factor NF-κB. The multicenter, randomized, double-blind, placebo-controlled trial included a total of 1,234 patients with RRMS who were randomly assigned to treatment with BG-12 240 mg p.o. b.i.d. or t.i.d. (n = 410 and 416, respectively) or placebo (n = 408). The overall incidence of adverse events was similar across treatment groups. The most common adverse events included flushing, MS relapse, nasopharyngitis, headache, diarrhea and fatigue. Serious adverse events (most commonly MS relapse) were seen in 21%, 18% and 16% of subjects, respectively, receiving placebo and BG-12 twice or three times daily. Infections and infestations were observed with comparable frequency across treatment groups (64-68%; 2-3% severe infections/infestations) (17). MRI data from the DEFINE study indicated potent antiinflammatory effects for BG-12 on focal white matter lesions. MRI analysis was performed in the intent-to-treat population of the DEFINE study, comprising 180 subjects receiving placebo, 176 receiving BG-12 twice daily and 184 receiving BG-12 three times daily. Treatment with BG-12 correlated with a reduction in the mean number of newly enlarging T2 lesions over 2 years by 85% and 74%, respectively, when administered twice and three times daily ($P < 0.001$ for both vs. placebo), with respective reductions in the mean number of Gd-positive lesions of 90% and 73% ($P < 0.001$ for both compared with placebo). The number of new T1 hypointense lesions developing over a period of 2 years was reduced by 73% and 63%, respectively, in patients treated with BG-12 given twice or three times daily compared with placebo ($P < 0.0001$ for both BG-12 cohorts) (18). Following 2 years of therapy with BG-12, improvements in the Physical Component Summary (PCS) scores of the Short Form-36 (SF-36) health survey were reported by 21% and 24% of patients, respectively, receiving the agent twice and three times daily (n = 400/group), compared with 16.2% in the placebo

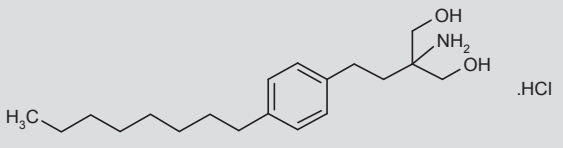


Dimethyl fumarate

group (n = 389; *P* = 0.0013 and < 0.0001, respectively). Significant improvements in the Mental Component Summary (MCS) of the SF-36 questionnaire were seen only in patients treated with the 240-mg t.i.d. dose of BG-12 versus with placebo (30% vs. 20.6%, respectively; *P* < 0.0001) (19).

Avanir Pharmaceuticals' Nuedexta® (**dextromethorphan hydrobromide/quinidine sulfate**) capsules are the first and only FDA-approved treatment for pseudobulbar affect (PBA), a neurological condition causing involuntary, sudden and frequent episodes of laughing and crying in patients with certain underlying neurological conditions, including MS and amyotrophic lateral sclerosis (ALS). A phase III trial was designed to investigate the efficacy, safety and tolerability of two different doses of the treatment in individuals with PBA secondary to ALS or MS. Researchers from Avanir Pharmaceuticals and the Cleveland Clinic presented data on a subgroup analysis of this study involving subjects with MS. Of the total 326 participants in the randomized, double-blind, placebo-controlled, 12-week phase III trial, 129 exhibited MS and were randomly assigned to oral dextromethorphan hydrobromide/quinidine sulfate 30/10 mg or 20/10 mg (n = 45 and 39, respectively) or placebo (n = 45). Safety data revealed the incidence of one or more adverse events in 68.9%, 71.8% and 82.2% of subjects, respectively, treated with doses of 30/10 mg or 20/10 mg of the active treatment and placebo. The most frequent adverse events observed in ≥ 5% of subjects across treatment groups were headache and fall. Transient, mild to moderate dizziness and diarrhea were the most common adverse events with active treatment versus placebo (20, 21).

Data were disclosed from a 6-month phase II study and its 6-month extension phase assessing the immunosuppressant Gilenya® (**fingolimod hydrochloride,** FTY-720; Novartis, Mitsubishi Tanabe Pharma) in Japanese subjects with MS. Patients with RRMS (n = 167) or secondary progressive MS (SPMS; n = 4) were randomized 1:1:1 to receive fingolimod hydrochloride 0.5 or 1.25 mg p.o. q.d. or placebo for 6 months (n = 57/group). The study was completed by 147 participants. At 3 and 6 months, significantly more subjects receiving fingolimod were free of Gd-enhancing lesions (70% and 86%, respectively, of those receiving fingolimod 0.5 and 1.25 mg vs. 40.4% of participants receiving placebo). Compared with placebo, fingolimod correlated with marked reductions in ARR at month 6 of 49% and 58%, respectively, at the 0.5- and 1.25-mg doses relative to placebo (22). Participants who entered the extension phase of the trial (N = 143) either continued treatment with their preassigned dose of fingolimod (n = 47 and 46, respectively, in the 0.5- and 1.25-mg groups) or were switched from placebo to receive the active agent (0.5 or 1.25 mg p.o.; n = 27 and 23, respectively). At months 9-12, the majority of patients across treatment groups were free of Gd-enhancing lesions (68.4-85.7%). Similar results were obtained at months 7-12 in assessments of patients free from new/newly enlarged T2 lesions (61.9-88.1%). Using data obtained during months 7-12, the ARR was estimated at 0.23 and 0.28, respectively, in subjects treated continuously with the 0.5- or 1.25-mg dose of fingolimod. The respective values in subjects switching from placebo to the 0.5- or 1.25-mg dose of fingolimod were 0.26 and 0.21. The most frequent adverse events seen during months 7-12 in patients who switched from placebo to fingolimod included nasopharyngitis, abnormal results in tests of liver function and leukopenia, which were also reported in individuals receiving continuous therapy with fingolimod for 12 months. In the latter cohort, bradycardia, diarrhea and dental caries were also observed in > 5% of patients (23).



Fingolimod hydrochloride

MONOCLONAL ANTIBODIES

Data were described in support of the long-term beneficial effects of **daclizumab** (Abbott, Biogen Idec), a humanized IgG_1 MAb targeting interleukin-2 receptor subunit alpha (CD25), in RRMS. DAClizumab High-Yield Process (DAC HYP) is currently being assessed in the double-blind, multicenter phase II SELECT (Safety and Efficacy study of daLizumab HYP to trEat relapsing-remitting mulTiple sClerosis) study (24). A total of 600 individuals with RRMS were randomized to receive treatment with DAC HYP 150 or 300 mg s.c. (n = 201 and 203, respectively) or placebo (n = 196) every 4 weeks for a period of 52 weeks. The study's primary endpoint was established as the ARR. Treatment with daclizumab at 150 or 300 mg resulted in ARR reductions of 54% and 50%, respectively, compared with placebo. At 52 weeks, 81% and 80% of subjects, respectively, receiving the 150- and 300-mg doses of daclizumab were free of relapse, versus 64% of those receiving placebo. Significant improvements in Multiple Sclerosis Impact Scale-29 (MSIS-29) physical scores by 4.1 and 1.4 points were observed, respectively, with the 150- and 300-mg doses of daclizumab relative to placebo. Confirmed disability progression at 3 months was reported in 5.9% and 7.8% of subjects, respectively, receiving doses of 150 and 300 mg daclizumab, compared with in 13.3% of those receiving placebo. Between weeks 8 and 24, new or enlarged Gd-positive T1 lesions were reduced by 69% and 78%, respectively, in patients treated with daclizumab 150 and 300 mg (*P* < 0.0001 for both versus placebo), with respective reductions in new Gd-positive lesions by 79% and 86% seen at week 52. MS relapse and nasopharyngitis were the most frequent adverse events reported in > 10% of subjects across treatment groups (25). An extension trial of SELECT is currently under way (26).

In a study conducted by researchers from the National Institute of Neurological Disorders and Stroke (NINDS), the antibody exhibited long-term benefits in reducing brain atrophy in subjects with RRMS. The study involved the retrospective analysis of 1.5T and 3T brain MRI scans obtained from individuals with RRMS who were treated with daclizumab or other disease-modifying therapies. A total of 982 scans were analyzed from 27 patients receiving daclizumab for at least 12 consecutive months, with or without adjunctive interferon

beta therapy for 6 months. In the comparator arm, 440 scans were analyzed from 44 patients receiving other disease-modifying therapies (predominantly interferon). Treatment with daclizumab correlated with significant decreases in the loss of supratentorial volume compared with other therapies (annual rate of volume loss was estimated at 3.3 cc in daclizumab-treated patients versus 5.1 cc in subjects not receiving daclizumab; $P < 0.002$). Daclizumab was also associated with specific reductions in atrophy in the thalamus and the caudate nucleus of 38% and 43%, respectively, but not in the cortex or the supratentorial white matter. A marked reduction of 60% was also reported in the rate of ventricular enlargement in daclizumab-treated individuals. The findings support the potential long-term neuroprotective effects of daclizumab (27).

Biogen Idec and Elan's Tysabri® (**natalizumab**), a humanized $IgG_{4\kappa}$MAb targeting human integrin alpha-4, was launched in 2006 for the treatment of MS. Results have been presented from several clinical studies of the product.

Natalizumab was previously demonstrated to lead to a significant reduction in the rates of clinical relapse in patients with RRMS participating in the phase III AFFIRM (nAtalizumab safety and eFFicacy In Relapsing-remitting Multiple sclerosis) trial. AFFIRM enrolled 942 patients who were randomized to treatment with placebo or natalizumab 300 mg i.v. given once every 4 weeks. Data on long-term clinical outcomes were obtained from subjects who remained free of disease activity over the 2-year AFFIRM trial and were subsequently included in the STRATA study. STRATA is an ongoing, multinational, open-label, single-arm phase III trial conducted in subjects who completed the AFFIRM, SENTINEL, GLANCE and STARS feeder trials (N = 1,094). A total of 592 completers of AFFIRM, including 177 individuals who were free of disease activity and 415 subjects who were not free of disease activity during the 2-year AFFIRM trial, were enrolled in STRATA. During STRATA, relapses were reported by fewer patients who were free of disease activity in AFFIRM than by subjects who were not (20% vs. 33%). At 192 weeks following the initiation of STRATA, participants who were free of disease activity during AFFIRM exhibited improvement in mean EDSS scores compared with individuals who were not free of disease activity in AFFIRM (mean EDSS scores of 2.34 and 3.23, respectively; $P < 0.0001$). Following completion of 24-48 weeks in STRATA, patients enrolled at U.S. sites were included in TYGRIS, a longer-term follow-up study. Irrespective of the length of follow-up, sustained disability progression during STRATA and TYGRIS was seen less frequently in patients who had been free of disease activity in AFFIRM than in those who had exhibited active disease (28). Interim safety analysis revealed an incidence of serious adverse events in 14% of participants in STRATA, most commonly infections and infestations (3%), gastrointestinal disorders (2%), neoplasms (2%), urinary tract infection and progressive multifocal leukoencephalopathy (PML; < 1% each). Efficacy data showed that the ARR in the overall STRATA population, including patients entering TYGRIS, remained low (0.17) during treatment with natalizumab. The ARR was lower in subjects originally randomized to natalizumab than in those originally randomized to placebo in the feeder trials (0.15 vs. 0.22, respectively) (29).

TRUST was designed as an open-label, single-arm, 24-week, proof-of-concept study. Participants (N = 30) received natalizumab 300 mg i.v. every 4 weeks for 6 months. The trial was completed by 28 subjects. Natalizumab correlated with significant improvements in incontinence-related Quality of Life (QoL) measures, as assessed in the Urogenital Distress Inventory-6 (UDI-6) questionnaire and the Incontinence Impact Questionnaire-7 (IIQ-7). At week 24 of the study, improvement from baseline in the UDI-6 score was reported in 85.7% of patients, whereas 3.6% and 10.7%, respectively, exhibited stable or worsening scores ($P < 0.0001$). At the same time point, IIQ-7 scores exhibited an improvement from baseline in 78.6% of participants; 17.9% and 3.6% of patients, respectively, experienced worsening or stable scores ($P = 0.0011$) (30).

The ongoing noninterventional TYSABRI 24 PLUS trial is aiming to document data on the clinical outcomes, MRI changes and patient management in an estimated 1,000 subjects with RRMS recruited in Germany who are treated with natalizumab 300 mg i.v. every 4 weeks for 2 years or longer. The study was designed as a multicenter, prospective, open-label, observational program. Interim analysis of follow-up data from 835 patients demonstrated a decline in the mean ARR from 2.2 to 0.4 following therapy with natalizumab for 24 months. A total of 12 serious adverse events were reported, including 1 confirmed and 1 suspected PML, as well as MS relapse (n = 2), exacerbation of MS, exacerbation of ataxia, increased leukocytosis, syncope, mumps and spinal disc herniation (n = 1 each) (31).

A prospective, single-center, controlled, randomized, rater-blind pilot trial aimed to generate the first prospective data on the possibility of de-escalating natalizumab-treated subjects with RRMS to therapy with interferon beta-1b (IFN-β-1b). A total of 19 individuals with RRMS who had received natalizumab for ≥ 12 months and exhibited stable disease while receiving the treatment were randomized to continue therapy with natalizumab (n = 10) or de-escalate to IFN-β-1b (n = 9). Within a period of 6 months, none of the participants in the natalizumab cohort experienced a relapse, whereas two of the participants receiving IFN-β-1b did. MRI analysis at 6 months revealed new T2 lesions in five of eight patients receiving IFN-β-1b and in two of eight natalizumab-treated individuals. The small number of participants, short observation period and the lack of a placebo arm constitute the main limitations of this trial (32, 33).

Preliminary findings were presented from RESTORE, a randomized, partially placebo-controlled study assessing the effects of a 24-week interruption of treatment with natalizumab on immune parameters and disease activity in subjects with MS. Participants (N = 175) were randomized 1:1:2 to receive natalizumab (n = 45), placebo (n = 42) or other immunomodulatory therapies (including intramuscular IFN-β-1a, glatiramer acetate or methylprednisolone; n = 17, 17 and 54, respectively). During the randomized period, clinical relapses were reported in 4% of natalizumab-treated patients and in 17%, 29%, 27% and 15%, respectively, of participants receiving placebo, IFN-β-1a, glatiramer acetate and methylprednisolone. MRI data revealed that interruption of therapy with natalizumab resulted in recurrence of disease activity by week 12 in subjects receiving placebo, glatiramer acetate or methylprednisolone and by week 24 in IFN-β-1a-treated patients (34).

Alemtuzumab is a humanized MAb targeting CAMPATH-1 antigen (CD52) that was launched in 2001 by Bayer HealthCare Pharmaceuticals and Bayer Schering Pharma for the treatment of B-cell chronic lymphocytic leukemia. The product is currently under-

going clinical development by Sanofi and its subsidiary Genzyme for the treatment of RRMS. Updated findings were disclosed from CARE-MS I (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, study one [I]), as well as results from the phase III study CARE-MS II (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, study two [II]) (35, 36). CARE-MS I was a randomized, single-blind, parallel-assignment phase III trial conducted in patients with active MS exhibiting onset of symptoms within 5 years of the initiation of the study and experiencing one or more relapses in the year prior to entry in the trial. Participants (N = 581) were randomized to receive alemtuzumab 12 mg i.v. (n = 376) given as 5 consecutive daily doses at month 0, followed by 3 consecutive daily doses at month 12 of the trial, or Rebif® (interferon beta-1a, IFN-β1a) 44 µg s.c. (n = 187) administered 3 times per week for 2 years. The rate of relapse, as well as the time to sustained accumulation of disability (SAD) in a time frame of 2 years constituted the coprimary outcome measures of the study. The trial was completed by 97% and 93% of patients receiving alemtuzumab and IFN-β1a, respectively. Treatment with alemtuzumab versus IFN-β1a correlated with a significant reduction of 55% in annualized rate of relapse over the 2-year study period ($P < 0.0001$). The proportion of subjects remaining free of relapse at year 2 was estimated at 78% and 59%, respectively, with alemtuzumab and IFN-β1a. No marked difference was observed in the time to 6-month SAD between the alemtuzumab and IFN-β1a cohorts (8% vs. 11%). Following 2 years of alemtuzumab therapy, new T1 hypointense lesions were reported in 24% of the recipients and Gd-enhancing lesions in 15.4%. These respective values were 31.4% and 27% after 2 years of IFN-β1a therapy ($P = 0.054$ and 0.0008, respectively). Brain atrophy, as assessed by the median percent change in the parenchymal fraction of the brain over 2 years, was significantly lower in patients receiving alemtuzumab than in those receiving placebo ($P < 0.0001$). Autoimmune thyroid disorders (most commonly hyperthyroidism) were seen in 18.1% of patients treated with alemtuzumab and in 6.4% of subjects receiving IFN-β1a (37). A total of 840 patients with RRMS who relapsed while on therapy have been enrolled in CARE-MS II. Participants in that global, randomized, rater-blinded phase III trial were randomly assigned treatment with alemtuzumab 12 or 24 mg/day i.v. or IFN-β1a 44 µg s.c. three times/week. Prior treatment regimens included IFN-β, glatiramer acetate, natalizumab, immunoglobulin, azathioprine or other therapeutics (78.6%, 32.5%, 3.2%, 1.5%, 1.3% and 0.8%, respectively). Topline efficacy and safety data from CARE-MS II are expected to be disclosed later in the year (38).

Long-term (96-week) data were presented on the safety and efficacy of **ocrelizumab** (Genentech, Roche) in subjects with RRMS. The product is a humanized MAb targeting B-lymphocyte antigen CD20 and was previously reported to decrease the ARR of patients with RRMS by ≥ 73%. In a multicenter, randomized, double-blind, placebo-controlled phase II study, participants (N = 220) were randomized 1:1:1:1 to treatment with ocrelizumab on days 1 and 15 at a total dose of 600 or 2000 mg intravenously (cohorts A and B, respectively), placebo (cohort C) or open-label IFN-β1a at a dose of 30 µg intramuscularly (cohort D). At week 24 of the trial, all subjects were switched to open-label ocrelizumab at a dose of 600 mg/cycle (cohorts A, C and D) or 1000 mg given at weeks 24 and 48 followed by 600 mg at week 72 (cohort B). Four subjects in cohort B continued treatment at the 1000-mg dose. The 96-week treatment period was completed by 183 individuals. The ARR for weeks 0-96 was estimated to be 0.18 and 0.22, respectively, in cohorts A and B. No relapses and no confirmed progression in EDSS scores from week 0 to 96 were reported in 67.3% of subjects in cohort A and in 76.4% of participants in cohort B. Exploratory analysis revealed reductions in ARR at weeks 24-96 in subjects switching from placebo or IFN-β1a to ocrelizumab of from 0.64 to 0.20 and from 0.36 to 0.16, respectively. At week 96, there were no Gd-enhancing T1 lesions in any patient treated with ocrelizumab. The mean reduction in total brain volume for weeks 12-96 was estimated at 1.1% and 1.2%, respectively, in individuals treated with the 600- and 2000-mg dose of ocrelizumab. The antibody was well tolerated, with no imbalance in the number of serious adverse events reported across treatment arms throughout the 96-week study. Ocrelizumab is currently being evaluated in the phase III trial ORCHESTRA (39, 40).

OTHER THERAPEUTIC MODALITIES IN CLINICAL DEVELOPMENT

The dual sodium-dependent serotonin transporter (*SLC6A4*/*SERT*) and sodium-dependent noradrenaline transporter (NET; *SLC6A2*/*NET1*) inhibitor **duloxetine hydrochloride** (Lilly) was evaluated for its potential use in the amelioration of central neuropathic pain in individuals with MS. Findings from this study were disclosed by scientists from Lilly and the University of Colorado. Patients with central neuropathic pain associated with MS (N = 239) were randomly assigned to treatment with duloxetine (n = 118) or placebo (n = 121) in a randomized, double-blind, placebo-controlled trial. In the acute, 6-week period of the study, duloxetine was administered at 30 mg/day for 1 week followed by a dose of 60 mg/day for the remaining 5 weeks. In the optional, open-label, flexible-dose part of the trial, participants received duloxetine at doses of 30-120 mg/day for 12 weeks followed by a taper period of 2 weeks. The majority of patients (64%) were Caucasian females with RRMS who exhibited median EDSS and median average pain intensity (API) scores of 4 and 6.4, respectively, at baseline. Results were presented from the acute part of the study. At week 6, a significant improvement in mean weekly API was observed with duloxetine versus with placebo (–1.8 vs. –1.1, respectively; $P < 0.001$). A decrease in weekly API by ≥ 30% from baseline was achieved by 41% of subjects treated with duloxetine compared with 27% of those receiving placebo ($P = 0.027$). Marked improvements with duloxetine over placebo were also observed at secondary efficacy endpoints, including night pain intensity ($P < 0.001$). Fatigue, nausea, dizziness (7.6% each), constipation, decreased appetite, dry mouth (5.9% each), somnolence (5.1%) and headache (4.2%) were the most frequently reported treatment-emergent adverse events in the cohort receiving duloxetine (41, 42).

Atacicept (EMD Serono, Merck Serono) is a fully humanized recombinant fusion protein comprising the extracellular ligand-binding portion of TNF receptor superfamily member 13B (*TNFRSF13B*/*TACI*) receptor fused to the Fc domain of human Ig. Increased disease activity seen in patients with MS treated with the product in the phase II ATAMS (ATAcicept in MS) trial resulted in the termination of ATAMS and of a concurrent phase II study, ATON (ATacicept in Optic Neuritis) (43, 44). Results from the ATON trial have been made avail-

able. ATON was a 36-week, randomized, double-blind, placebo-controlled phase II trial conducted in 34 patients with optic neuritis. Participants received atacicept 150 mg s.c. twice weekly for a loading period of 4 weeks, followed by once-weekly administration for 32 weeks, or placebo (n = 17/group). After premature termination of enrollment/dosing of patients, the protocol of ATON was amended to include a 60-week safety follow-up period. The study's primary endpoint was established as the change in the thickness of the retinal nerve fiber layer (RNFL) from baseline to week 36 as assessed by ocular coherence tomography (OCT). A total of 28 individuals entered the 60-week follow-up part of the trial. Maximal loss of RNFL was detected in the affected eye at week 12 compared with baseline (mean change from baseline to week 12 in RNFL thickness of –9.4 μM with atacicept versus –17 μM with the control), whereas no marked changes in RNFL were noted in the unaffected eye. No serious adverse events occurred during the double-blind period of the trial. During the 60-week follow-up part of the study, 3 serious adverse events were identified in each treatment group: myelitis, pyrexia and blistering with placebo, and bacterial pyelonephritis, MS and transverse myelitis with atacicept. Conversion to clinically definite MS was more frequently seen with atacicept than with placebo during the double-blind part of the trial, with similar occurrence of the condition reported between the two treatment groups during follow-up (45).

Promising data have been presented on **interferon beta-1a** (IFN-β1a; Merck Serono, Pfizer), both from the phase III REFLEX (REbif FLEXible dosing in early multiple sclerosis) trial, conducted in individuals at risk of developing MS, and from the phase IIIb MOSAIC (Multicenter, Open-label, Single-use AutoInjector Convenience) study, which assessed the agent in patients with the disease (46, 47).

The primary objective of the 2-year, multicenter, randomized, placebo-controlled, parallel-assignment trial was to evaluate the effect of two dosing frequencies of a new formulation of IFN-β1a versus placebo on the time to conversion to McDonald MS (2005) criteria in such individuals. A total of 517 subjects were randomized 1:1:1 to receive IFN-β1a 44 μg 3 times weekly or once weekly (n = 171 and 175, respectively) or placebo (n = 171) as a subcutaneous injection. Multifocal presentation, the presence of Gd-positive lesions and nine or more T2 lesions at baseline predicted a higher risk of McDonald MS (2005) at 2 years. The treatment effect of subcutaneous IFN-β1a for the endpoint of McDonald MS (2005) was greater in the participants receiving treatment three times weekly than in those receiving it once weekly (48). The mean number of combined unique active lesions per patient per scan was reduced significantly with IFN-β1a three times weekly or once weekly (81% and 63%, respectively) versus placebo ($P < 0.001$ for both). The reduction was significantly greater with IFN-β1a dosed three times weekly than with IFN-β1a dosed once weekly ($P = 0.002$) (49). In the double-blind safety population (n = 515), the incidence of ≥ 1 treatment-emergent adverse events occurred in 85.6% of the participants. Most frequently observed adverse events included influenza-like illness, injection-site reaction, cytopenia, depression and suicidal ideation, as well as hepatic disorders. The incidence of these was generally lower with IFN-β1a dosed three times weekly than once weekly (50). Retrospective analysis of data taking into account the revised McDonald MS (2010) criteria indicated a significantly greater treatment effect for IFN-β1a than for placebo on McDonald MS (2005) criteria in subjects meeting the revised criteria (risk reduction of 46% and 34%, respectively, with IFN-β1a dosed three times weekly and once weekly) and in those who did not (respective risk reduction of 51% and 29% with IFN-β1a dosed three times weekly and once weekly). No apparent difference in the treatment effect was reported in participants who tested positive or negative according to the McDonald MS (2010) criteria. Subjects receiving therapy with IFN-β1a three times weekly exhibited significant reductions in the risk of developing clinically definite MS irrespective of whether or not they met the McDonald MS (2010) criteria (risk reductions of 56% and 47%, respectively) (51).

The 12-week, multicenter, open-label, single-arm phase IIIb MOSAIC trial aimed to assess the relationship between elevated levels of C-reactive protein or other inflammatory/autoimmune markers and the incidence of injection-site reactions in patients with relapsing MS treated with subcutaneous IFN-β1a. Participants (N = 109) received treatment with IFN-β1a 44 μg 3 times weekly for 12 weeks using the Rebiject™ II single-use autoinjector. The study's primary endpoint was the proportion of patients rating the single-use autoinjector as "easy to use" or "very easy to use" for self-injection at the end of the 12-week treatment period by completing the User Trial Questionnaire. The autoinjector was described as "easy/very easy to use" by 86% of participants. Injection-site reactions were observed in 43.1% of patients during the trial; 19.1% experienced elevated levels of C-reactive protein that were significantly associated with the incidence of reactions at the site of injection ($P = 0.002$). Only 1.6% of individuals who did not display injection-site reactions had elevated levels of C-reactive protein. No significant correlation was reported between the incidence of injection-site reactions and upregulation of other inflammatory/autoimmune markers (52).

DISCLOSURES

The author states no conflicts of interest.

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