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MEETING REPORT

JOINT 26TH CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS) AND 15TH CONFERENCE OF REHABILITATION IN MULTIPLE SCLEROSIS (RIMS)

AN UPDATE ON CLINICAL FINDINGS TO IMPROVE OUTCOMES IN MULTIPLE SCLEROSIS

S. Vasiliou

Thomson Reuters, Barcelona, Spain

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SUMMARY

Hosted in Gothenburg, Sweden's second largest city, this year's joint 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and 15th Conference of Rehabilitation in Multiple Sclerosis (RIMS), held on October 13-16, 2010, was the largest meeting on multiple sclerosis (MS) to take place in Europe to date. A total of 6,300 participants from 85 different destinations worldwide gathered to discuss recent developments in diagnostic strategies and clinical approaches aiming to develop symptomatic treatments and improve the quality of life for patients with MS. A wide variety of oral sessions and poster presentations addressed topics associated with the challenges of managing MS. Several satellite symposia focused on the disclosure of emerging therapeutic solutions based on results from clinical studies.

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

INTRODUCTION

The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is an independent representative European organization that aims to promote communication and create synergies among clinicians and scientists with a vision to accelerating research and improving clinical outcomes in multiple sclerosis (MS). This year's fourth consecutive joint meeting of ECTRIMS and the European network of MS centers for the Rehabilitation in Multiple Sclerosis (RIMS) was the largest annual international conference dedicated to basic and clinical research in MS. Current advances in the field of MS research have led to improvements in the understanding of the pathophysiology of this condition, resulting in the development of new clinical methods and strategies for diagnosis, treatment and monitoring of disease activity. This report summarizes the latest findings from recently concluded or currently ongoing phase I, II and III clinical studies disclosed at the meeting. Several new agents with encouraging activity in preclinical assessments that are expected to represent promising candidates for clinical evaluation are also discussed.

PHASE I TRIALS

Daily oral doses of **ONO-4641** (Ono Pharmaceutical), a selective agonist of the lysophospholipid $S1P_1$ receptor (sphingosine 1-phosphate receptor 1, S1P receptor Edg-1), were reported to be safe and well tolerated in patients with MS. A total of 32 individuals with a relapsing form of MS and Expanded Disability Status Scale (EDSS) scores of up to 6.5 were included in the study. ONO-4641 was administered to 10 subjects at doses of 0.1-0.4 mg (maintenance dose) in a flexible dose-titration regimen, whereas fixed-dose regi-

mens of 0.05, 0.1 and 0.15 mg were given to 7, 8 and 7 individuals, respectively, for a period of 5 weeks. The agent demonstrated good tolerability in all three fixed-dose cohorts, with no serious adverse events and no clinically significant decreases in heart rate or arrhythmias being observed. Treatment with ONO-4641 at doses of 0.05-0.15 mg correlated with marked reductions from baseline (50-80%) in the average values of peripheral absolute lymphocyte counts, which recovered to > 80% of baseline values within 3 months after the last dose (1). ONO-4641 is currently being evaluated in a randomized, double-blind, parallel-assignment phase II trial in individuals with relapsing–remitting MS. The total number of T_1-weighted gadolinium (Gd)-enhanced lesions obtained by MRI at 4-week intervals for a period of 26 weeks and the total volume of Gd-enhanced lesions, respectively, constitute the primary and secondary outcome measures of the trial. The study is expected to be completed in December 2011 (2).

PHASE II TRIALS

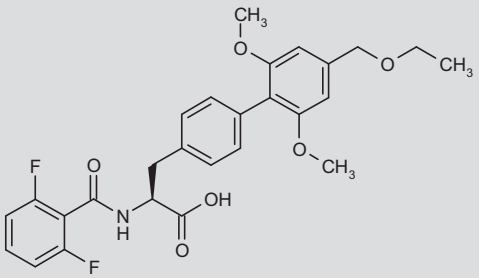
Results were also disclosed from a phase II trial of **ocrelizumab**, a fully humanized CD20-targeted monoclonal antibody (MAb), in subjects with relapsing–remitting MS. A total of 220 patients were randomized 1:1:1:1 to receive ocrelizumab (total doses of 600 or 2000 mg given i.v. on days 1 and 15), placebo or interferon beta-1a (IFN-β-1a) 30 µg/week i.m. The primary outcome measure of the open-label, double-blind study was the comparison of the total number of Gd-enhancing T_1 lesions at weeks 12, 16, 20 and 24 across treatment groups. Annualized relapse rate, the presence of new or persisting Gd-enhancing T_1 lesions, the change from baseline in the volume of T_2 lesions, as well as the tolerability and incidence of adverse events constituted the trial's secondary endpoints (3).

Encouraging 5-year results were recently made available from the CAMMS223 study (4), which evaluated treatment with **alemtuzumab** (CAMPATH-1H, LDP-03; Genzyme, Bayer) in patients with MS. Alemtuzumab is a humanized MAb that targets CAMPATH-1 (CDw52, encoded by the *CD52* gene), a protein present on all lymphocytes and some monocytes. The randomized, open-label, three-arm phase II CAMMS223 trial was conducted in subjects with early active relapsing–remitting MS (N = 334), who were randomized to receive alemtuzumab 12 or 24 mg/day i.v. or IFN-β-1a 44 µg s.c. 3 times/week for 36 weeks. The primary outcome measures were established as sustained accumulation of disability through 6 months, evaluated by the EDSS, and relapse in the time frame of 3 years. A total of 125 and 61 patients, respectively, in the alemtuzumab and IFN-β-1a cohorts displayed highly active relapsing–remitting MS, defined as ≥ 2 relapses occurring in the 24 months prior to the initiation of treatment and ≥ 1 Gd-enhanced lesion at baseline. In this high-risk population, treatment with alemtuzumab (at both doses) correlated with a reduction in the risk of relapse of 81.8% versus IFN-β-1a ($P < 0.0001$) during the 36 months of the study. The annualized relapse rate in patients treated with alemtuzumab and IFN-β-1a was estimated at 0.09 and 0.47, respectively (5). At 36 months, participants receiving alemtuzumab were 72% more likely to experience progression-free disability than those treated with IFN-β-1a. Assessment performed at 48 months revealed that 90.6% of alemtuzumab-treated subjects remained progression-free versus 66.9% of the participants receiving IFN-β-1a (6). Analysis using the Multiple Sclerosis Severity Score (MSSS) algorithm indicated that alemtuzumab (pooled data from both dose groups) resulted in clinically meaningful improvement in the severity of MS (median reduction in MSSS of 2.64 points on a 10-point scale) versus IFN-β-1a at 36 months (7).

In the open-label extension phase of CAMMS223, participants remained on treatment for > 5 years after randomization. Evaluable data during years 4 or 5 were obtained from 149 and 46 patients, respectively, treated with alemtuzumab and IFN-β-1a. At 5 years following randomization, 87% and 62% of individuals, respectively, receiving alemtuzumab (pooled data from both dose levels) and IFN-β-1a did not exhibit sustained accumulation of disability. This effect was also seen in 85% of subjects who were given only two cycles of treatment with alemtuzumab. Infections, autoimmunity involving thyroid abnormalities and malignancies were observed in 72%, 30% and 2% of alemtuzumab-treated subjects, respectively, and in 51%, 4% and 1% of patients receiving IFN-β-1a, respectively (8). One participant in the study's extension phase who had received two annual treatment cycles of alemtuzumab at 12 mg/day exhibited anti-glomerular basement membrane disease, confirmed by renal biopsy. The relationship between the antibody's mechanism of action and the onset of secondary autoimmunity requires additional investigation (9). The Markov transition model for repeated ordinal data was used to evaluate EDSS measurements obtained in CAMMS223 in order to calculate the time to disability accrual. The analysis revealed that alemtuzumab-treated individuals displayed a lower risk of progression to a confirmed EDSS score ≥ 3 than subjects receiving IFN-β-1a (10).

A phase III trial (CARE-MS I) aiming to assess the efficacy of alemtuzumab versus IFN-β-1a is currently ongoing but not open to recruitment (11). CARE-MS I has been designed as a global, randomized, rater-blind, active-controlled, 24-month study to investigate the effects of treatment with 2 annual cycles of alemtuzumab 12 mg/day or IFN-β-1a 44 µg 3 times weekly in 581 treatment-naive subjects with relapsing–remitting MS. Rate of relapse and the accumulation of disability are its primary endpoints. Topline efficacy outcomes from CARE-MS are expected to be disclosed in 2011 (12). Long-term freedom from relapse was associated with prolonged suppression of $CD3^+/CD4^+$ T cells in 48 patients with relapsing–remitting MS following treatment with alemtuzumab in a separate study (13).

Firategrast (GlaxoSmithKline), an orally bioavailable antagonist of integrin α4β1 and α4β7, was well tolerated and reduced the number of new Gd-enhanced lesions in a phase II study performed in subjects with relapsing forms of MS. The randomized, double-blind, placebo-controlled, dose-finding, multicenter trial included patients with relapsing–remitting MS (N = 343) who had experienced at least 2 relapses in the previous 24 months, exhibited at least 1 relapse or Gd-enhanced lesion by MRI and displayed at least 5 T_2 lesions by MRI scan of the brain. The participants were randomized to receive placebo (n = 99) or firategrast 150 mg (n = 48), 600 mg (n = 95) or 900/1200 mg (for females/males; n = 100) twice daily for 24 weeks followed by a 12-week core follow-up phase. A statistically significant difference was noted between subjects treated with firategrast 900/1200 mg and those receiving placebo at the primary outcome measure, established as the cumulative number of new Gd-enhanced lesions in the brain during treatment (respective adjusted



Firategrast

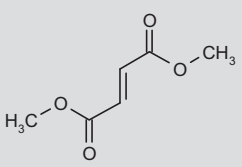
cumulative mean rates of Gd-enhanced lesions of 2.69 vs. 5.31; P = 0.0026). A 49% reduction in new Gd-enhanced lesions was observed in the cohort treated with firategrast 900/1200 mg versus values in the group receiving placebo. Patients treated with 900/1200 mg firategrast also displayed a statistically significant decrease in the number of new T_2 lesions versus those receiving placebo (P = 0.009) (14).

The effect of firategrast on leukocyte counts, including subsets of lymphocytes, in the cerebrospinal fluid (CSF) of patients with relapsing–remitting MS, as well as the evaluation of the $CD4^+/CD8^+$ cell ratio in the blood and CSF during and after treatment, constituted the primary objective of an open-label, nonrandomized, single-group assignment phase II study of the compound (15). Participants (N = 46) received open-label treatment with firategrast at 900 mg (females) or 1200 mg (males) b.i.d. for up to 24 weeks. The agent was associated with a reduction in the median total lymphocyte counts, as well as $CD4^+$, $CD8^+$ and $CD19^+$ lymphocyte subsets in the CSF. The mean and median ratios of $CD4^+/CD8^+$ lymphocytes remained > 2 in the blood and CSF during the study period and following discontinuation of the treatment through to week 36. No safety concerns were reported in the study (16).

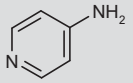
Biogen Idec's **BG-12** (BG-00012, dimethyl fumarate), which acts as an activator of nuclear factor erythroid 2-related factor 2 (NFE2-related factor 2, encoded by the *NFE2L2,* or *NRF2,* gene) and suppresses the activation of nuclear factor NF-κB, is currently undergoing clinical development for the treatment of relapsing–remitting MS. Recent preclinical studies suggest that the agent's mechanism of action may involve a dual antiinflammatory and neuroprotective role. The pharmacokinetics, safety and tolerability of BG-12 coadministered with IFN-β-1a or glatiramer acetate were evaluated in two open-label, randomized, crossover trials conducted in healthy subjects. The participants received BG-12 (240 mg t.i.d. for 2 or 3 days) alone or in combination with a single dose of either IFN-β-1a (30 µg i.m.) or glatiramer acetate (20 mg s.c.) administered on day 2. In 24 and 25 participants, respectively, who completed the BG-12/IFN-β-1a and BG-12/glatiramer acetate trials, comparable concentrations of monomethyl fumarate were recorded, suggesting no clinically significant effect of either adjunct therapeutic on the metabolism of BG-12. The most common adverse events (AEs) included flushing and flu-like symptoms in individuals receiving BG-12 in combination with glatiramer acetate and IFN-β-1a, respectively. An open-label phase II study has been designed to assess the safety, efficacy and pharmacodynamics of the combination regimens in patients with relapsing–remitting MS. A total of 100 participants receive treatment with IFN-β-1a or glatiramer acetate monotherapy for 2 months, followed by a 6-month period of administration of BG-12 240 mg t.i.d. as add-on therapy. The trial is currently ongoing and is expected to be completed in early 2012 (17, 18).

PHASE II/III TRIALS

Prolonged-release (PR) oral tablets (10 mg b.i.d.) of the selective blocker of neuronal potassium channels **fampridine** (4-aminopyridine, dalfampridine, Ampyra®; Biogen Idec, Acorda Therapeutics) were reported to improve the speed of walking in subjects with MS according to pooled data from two phase III trials (MS-F203 [19] and MS-F204 [20]) and a phase II study (MS-F202 [21]). Participants were randomized to receive treatment with fampridine PR tablets or placebo for a period of 9, 14 and 15 weeks, respectively, in MS-F204, MS-F202 and MS-F203. The primary outcome measures were the percentage of responders, defined as subjects exhibiting a walking speed in at least 3 of 4 on-treatment visits that is faster than the maximum speed recorded in any of 5 off-treatment visits on the timed 25-foot walk (T25FW), and the percentage of change from baseline in average walking speed measured using the T25FW. Significantly more responders were observed in the fampridine-treated groups than in the cohort receiving placebo (37.3% vs. 8.9%; P < 0.001) in pooled analyses involving 631 participants from all three trials. Increases in walking speed of ≤ 10%, 20%, 30% and 40%, respectively, relative to baseline were reported in 87.8%, 59.3%, 29.9% and 14% of individuals receiving fampridine versus 32.5%, 13.1%, 3.8% and 2.5% of the subjects in the placebo group, respectively (22). The response to treatment with fampridine was not influenced by demographic characteristics such as age, race and gender in the intent-to-treat population. The differences seen in the



BG-12



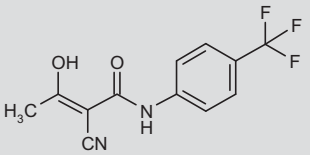
Fampridine

rate of response to treatment between the fampridine and placebo cohorts were independent of clinical characteristics (including the type of MS, duration of disease, EDSS score, lower extremity manual muscle test [LEMMT] and Ashworth scores) and they were not affected by the patient-reported status at baseline (23).

The safety and efficacy of fampridine were also assessed in a subpopulation of the MS-F204, MS-F202 and MS-F203 trials (n = 394) who received concomitant treatment with a disease-modifying therapy, such as glatiramer acetate, natalizumab or IFN-β. No significant difference was observed in the percentage of responders to fampridine in the presence or absence of any disease-modifying therapy (36% and 39.8%, respectively) and the type of disease-modifying therapy did not appear to affect the response to fampridine (37.1%, 36.8% and 27.3% of responders, respectively, received glatiramer acetate, IFN-β and natalizumab). The combination regimens were described as well tolerated, with the overall incidence of treatment-related adverse events being similar in subjects treated with or without a disease-modifying therapy (24).

The long-term safety and efficacy of fampridine are currently being investigated in subjects who completed the MS-F203 and MS-F204 phase III trials, regardless of responder status, in two open-label extension studies (MS-F203EXT [25] and MS-F204EXT [26]). In both MS-F203EXT and MS-F204EXT, patients receiving chronic treatment with fampridine PR tablets were assessed for performance in T25FW at 2, 14 and 26 weeks and every 6 months thereafter (primary outcome measure). Interim analyses indicated sustained improvements in the speed of walking compared with baseline for a period of up to 2.5 years during the open-label phase. Serious treatment-related adverse events were reported in 27.4% and 11.9%, respectively, of subjects receiving fampridine in MS-F203EXT and MS-F204EXT (27).

Teriflunomide (sanofi-aventis), an oral immunomodulator that acts by reversibly inhibiting the activity of dihydroorotate dehydrogenase (DHOdehase, encoded by the *DHODH* gene), administered at doses of 7 and 14 mg/day p.o. was found to reduce disease activity, as assessed by magnetic resonance imaging (MRI) in a 36-week, placebo-controlled phase II study conducted in 179 patients with relapsing MS (28). Following the trial's completion, 147 participants entered an extension study aiming to assess the immunomodulator's long-term safety and efficacy. Subjects who had received placebo in the controlled phase of the trial were randomized to receive teriflunomide (7 or 14 mg), whereas individuals who were initially included in the active treatment groups continued on their assigned dose. Teriflunomide-treated patients exhibited minimal progression of disability, measured as mean change from baseline in the EDSS scores at 372 weeks. During the extension phase, the annualized relapse rates were estimated at 0.269 and 0.193, respectively, in the cohorts receiving 7 and 14 mg teriflunomide (29). Subjects who completed the EDSS assessment at week 372 of the open-label extension phase of the study (n = 84) were assessed for the impact of teriflunomide on fatigue using the Fatigue Impact Scale and on the quality of life (QoL) according to the MSQoL-54 questionnaire. Long-term (7-year) teriflunomide therapy correlated with a moderate decline in physical health-related QoL (HRQoL), although patient-assessed fatigue and mental HRQoL remained stable throughout the extension trial (30). A total of 85 of the 147 participants in the long-term extension phase of the study continued treatment with teriflunomide for at least 8 years. Evaluation of the incidence of treatment-emergent adverse events (TEAEs), as well as assessment of laboratory parameters and vital signs, revealed that the treatment was well tolerated, with a favorable safety profile, similar to that seen during the 36-week controlled phase of the trial. The most frequently reported TEAEs included nasopharyngitis, upper respiratory tract infections, diarrhea, alopecia and nausea (31).



Teriflunomide

The pharmacokinetics and tolerability of teriflunomide were also assessed in individuals (N = 24) with mild to moderate hepatic impairment, given the role that the liver plays in the metabolic clearance of the agent. Administration of a single 14-mg oral dose of the compound in an open-label, parallel-group study was associated with systemic exposure that was similar between healthy volunteers and subjects with hepatic impairment. The therapy did not affect vital signs or ECG measurements and no serious AEs occurred in this study (32).

Teriflunomide was also evaluated in the randomized, double-blind, placebo-controlled, parallel-group, stratified, multicenter, multinational phase III TEMSO trial (TEriflunomide Multiple Sclerosis Oral [33]). The study was designed to investigate the effects of the agent on the frequency of relapses (primary endpoint), the burden of disease (as evaluated by the total volume of lesions assessed by MRI) and the number of Gd-enhanced T_1 lesions, number of unique lesions, as well as the volume of hypointense T_1 lesions and brain atrophy. The participants (N = 1,088) were stratified according to EDSS score at baseline (≤ 3.5 and > 3.5) and were randomized to receive once-daily teriflunomide (7 or 14 mg p.o.) or placebo for 108 weeks, followed by either a 16-week washout period or entry into an optional extension study. Evaluations by MRI were performed at baseline and at weeks 24, 48, 72 and 108. Treatment with teriflunomide at either dose level significantly decreased the burden of disease compared with placebo (relative reduction of disease burden versus placebo of 39.4% and 67.4%, respectively, in the 7- and 14-mg teriflunomide groups; respective P values = 0.03 and 0.0003). The active treatment was also associated with significantly fewer Gd-enhanced T_1 lesions and unique active lesions per scan than placebo. Reductions in the relative risk ratio versus placebo of 47.7% and 69.4%, respectively, were calculated for the 7- and 14-mg doses of teriflunomide ($P < 0.001$ for both doses) (34).

Patients who completed the TEMSO trial were given the option to participate in an extension study that aimed to evaluate the long-term safety and efficacy of teriflunomide (35). Subjects treated with

placebo during TEMSO were randomized to receive teriflunomide (7 or 14 mg) and individuals who had previously received active treatment were maintained on their assigned dose. This phase III trial is estimated to be completed in March 2011. TOWER, a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial designed to investigate the safety and efficacy of teriflunomide in patients with relapsing MS is currently open for recruitment (36). It is expected to enroll 1,110 subjects and is estimated to be completed in October 2011.

Natalizumab (Tysabri®; Elan, Biogen Idec), a humanized MAb that targets CD49d (VLA-4), was evaluated for efficacy and tolerability in subjects with relapsing forms of MS in a large number of presentations. The effects of the compound on cognitive performance and quality of life, as well as its safety profile in pediatric patients and during pregnancy, were also addressed. Treatment with natalizumab has previously been reported to correlate with a decrease in the rate of clinical relapse and reduced the risk of sustained disability progression in patients with relapsing–remitting MS, according to results obtained from the AFFIRM trial. In AFFIRM, natalizumab was found to decrease the cumulative probability of progression of sustained disability by 42-54% compared with placebo over a 2-year period, as measured on the EDSS (37). Evaluation of the visual function of patients during AFFIRM revealed that natalizumab was associated with a higher cumulative probability of visual improvement, defined as an increase of ≥ 7 letters from baseline and sustained for 12 weeks (57% and 39% increase, respectively, vs. placebo with low contrast acuity [LCA] of 2.5% and 1.25%; *P* = 0.012 and 0.014, respectively) (38).

Patients who participated in AFFIRM, SENTINEL or GLANCE feeder trials (39-41) were included in a multinational, 48-week, open-label, single-arm study (STRATA) designed to assess the long-term safety and efficacy of natalizumab. The annualized relapse rate in STRATA was lower in patients who had received natalizumab compared with placebo during the feeder studies (0.17 vs. 0.22). The mean scores on the EDSS either remained stable or exhibited an improvement during STRATA and were consistently lower in natalizumab-treated subjects than in patients receiving placebo in the feeder trials (42).

Post hoc analysis of data from two studies of natalizumab conducted in patients with relapsing–remitting MS (AFFIRM and SENTINEL), as well as from two clinical studies performed in subjects with secondary progressive MS, revealed that the agent led to improvements in ambulation in both populations independent of its effects on relapses (43).

The impact of natalizumab on various motor skills of patients with MS was addressed in a study involving 28 subjects with a mean duration of disease of 8 years. Treatment with the compound for 6 months was associated with significant improvements in measures of handgrip dynamometry and nine-hole peg test performed in the right hand. No changes were seen in other outcome measures, including the timed 10-meter maximum walking speed and the Berg balance test. A marked improvement, which did not reach statistical significance, was observed in the functional ambulation category (44).

The primary objective of a prospective, open-label, single-arm, noninterventional, multicenter monitoring program (TYSABRI 24 PLUS observational program) is to assess the long-term safety of natalizumab in patients with relapsing–remitting MS receiving continuous treatment with the agent for at least 24 months. The study is expected to include 1,000 participants in ≤ 400 centers in Germany. Initiation of interim analysis has been planned for September 2011 (45).

The long-term efficacy and tolerability of natalizumab were also addressed in a cohort of 46 patients with relapsing–remitting MS who had received treatment with the compound for at least 36 months. The annualized relapse rate was estimated at 0.2 and 0.08, respectively, after 1 and 2 years of treatment, and no relapses were observed in the third year. In assessments performed at 12, 24 and 36 months, no signs of activity on MRI were reported in 84%, 96% and 96% of individuals, respectively (46).

In a cohort of 48 patients with severe, active relapsing–remitting MS lasting for an average of 9.8 years, long-term (36 months) treatment with natalizumab was described as well tolerated, with no severe side effects being reported, and appeared to exhibit beneficial effects on the annualized relapse rate, which was reduced from 2.8 before natalizumab to 0.6 following treatment with the agent (47).

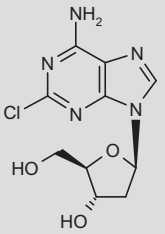
Patients with relapsing forms of MS (N = 112) who had displayed an inadequate response to previous treatment with disease-modifying drugs (95%) were evaluated for their response to treatment with natalizumab for 12 months based on measures of clinical disease activity and radiological parameters. Following 1 year of therapy with natalizumab, the annualized relapse rate was decreased by 89% compared with the previous year. The vast majority of patients were reported to be free from relapses or were described as free from a 3-month confirmed progression of disability (80% and 91%, respectively) (48).

Administration of natalizumab 300 mg i.v. every 28 days to pediatric patients with relapsing–remitting MS (N = 34), who displayed a mean of 2.9 relapses in the year prior to the initiation of therapy and exhibited activity on MRI scans, resulted in a marked decrease in the rate of relapse and correlated with reductions in EDSS scores after a mean follow-up period of 16 months. Natalizumab was well tolerated, the most common AEs being headache, vertigo, diarrhea, nausea and increased levels of white blood cells (n = 8, 3, 2, 2 and 7, respectively) (49).

Results from a case study support the potential use of natalizumab for the treatment of the Marburg variant of MS, a rare form of the disease that is characterized by a rapid progression of neurological deterioration despite therapy with standard agents. Administration of natalizumab to a 36-year-old woman with Marburg MS resulted in complete resolution of all enhancing lesions in the brain and spinal cord (> 10) within 2 weeks of the initiation of treatment (50).

PHASE III TRIALS

Several presentations were held on subanalyses of CLARITY, a study of **cladribine** (Centocor Ortho Biotech, Merck Serono, EMD Serono, Ivax) conducted in patients with relapsing–remitting MS. The intent-to-treat population of the randomized, double-blind phase III CLARITY (CLAdRIbine tablets treating mulTiple sclerosis orallY [51]) trial (N = 1,326) was stratified by baseline criteria, which are known predictors of clinical activity and disease progression,

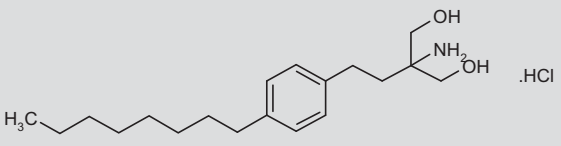


Cladribine

and was included in the assessment of the efficacy of cladribine tablets (3.5 mg, n = 433; 5.25 mg, n = 456) versus placebo (n = 437). The analysis showed that cladribine treatment at either dose correlated with highly significant decreases in the annualized relapse rate versus placebo in subjects stratified by a history of previous treatment with a disease-modifying drug or by relapse history (one relapse plus baseline T_2 lesion volume of > 5 mL or EDSS score of < 2 or ≥ 2) (52). In patients with ≤ 1, 2 or ≥ 3 relapes in the 12 months prior to the initiation of the study who had disease of varying duration (< 3, 3-10 and > 10 years) and received either cumulative dose of cladribine, consistent decreases were reported in MRI outcomes (reductions in T_1 Gd-positive lesions, active T_2 lesions and combined unique lesions) at 96 weeks, regardless of the burden of T_2 lesions (lesion number or volume) at baseline (53). Nonlinear mixed-effect analysis revealed a significant correlation between the EDSS score at baseline and the rate of disease progression ($r = 0.69$; $P < 0.001$). Nonlinear mixed-effect modeling predicted a 40% reduction in the progression of disease according to EDSS score in cladribine-treated patients (regardless of dose level) compared with those receiving placebo (54). Post hoc analysis of the disease activity-free status of participants in CLARITY indicated that significantly more subjects treated with cladribine over 24, 48 and 96 weeks achieved disease activity-free status compared with those receiving placebo ($P < 0.001$). Sustained disease activity-free status at 96 weeks was reported in approximately 66% and > 80%, respectively, of cladribine-treated subjects who were disease activity-free at 24 and 48 weeks following the initiation of treatment (55). Treatment discontinuation due to a perceived lack of efficacy or as a result of disease progression was lower in participants treated with cladri-bine (1.2% and 1.1%, respectively, with 3.5 and 5.25 mg/kg) than in those receiving placebo (5.5%). During the 96-week study, rescue therapy with steroids was administered to 2.5%, 2% and 6.2% of participants, respectively, in the cohorts receiving cladribine 3.5 mg, 5.25 mg and placebo, indicating a satisfactory perception of cladribine therapy (56). In patients receiving cladribine at either dose (n = 884), a higher incidence of AEs was observed during weeks 0-48 (treatment period 1; TP1) than during weeks 48-96 (TP2; 73.6% vs. 63.5%, respectively) although the severity of AEs was similar during the two treatment periods. Some less common AEs (e.g., vertigo, alopecia and rash) occurred with higher frequency in the cladribine-treated group than in the placebo cohort during TP1, but not TP2, which suggested that their onset was not linked to cumulative dose-related effects. Analyses of the 96-week CLARITY Extension trial data will provide results regarding safety and efficacy of the treatment for up to 192 weeks (57).

The safety, efficacy and tolerability of oral **fingolimod hydrochloride** (FTY-720, Gilenya™; Novartis) at doses of 0.5 and 1.25 mg once daily versus placebo were evaluated in 1,272 subjects with relapsing–remitting MS during the phase III FREEDOMS study (58). The annualized relapse rate at 24 months was the primary outcome measure of the 24-month, randomized, double-blind, placebo-controlled, parallel-group trial. Secondary outcome measures included the time to 3- and 6-month confirmed disability progression as measured in the EDSS and the time to relapse, as well as the proportion of relapse-free patients at 24 months. In the overall intent-to-treat population, the primary endpoint was met by subjects in both fingolimod-treated cohorts, with significant reductions in annualized relapse rate of 54% and 60%, respectively, seen in the groups receiving 0.5 and 1.25 mg versus the cohort receiving placebo. Subgroup analysis of annualized relapse rate by demographics, as well as disease activity and disease severity at baseline, revealed that fingolimod therapy consistently reduced annualized relapse rate over 24 months versus placebo, irrespectively of these parameters. The agent was also effective in treatment-naive patients, as well as in individuals who had previously received one or more disease-modifying therapies (59).

In a 12-month, randomized, double-blind, active-controlled, parallel-assignment phase III study (TRANSFORMS [60]), fingolimod displayed superior efficacy at reducing the frequency of relapses in patients with relapsing–remitting MS versus IFN-β-1a. A total of 1,027 individuals who completed the core trial entered the double-blind extension phase of TRANSFORMS. Subjects who had received fingolimod in the core study continued with their initially assigned daily dose of the agent (0.5 mg, n = 356; 1.25 mg, n = 330), whereas patients originally treated with IFN-β-1a (n = 341) were switched to either dose of fingolimod. The 24-month extension phase was completed by 882 individuals. The annualized relapse rate over 24 months was lower in participants receiving continuous fingolimod therapy (annualized relapse rate = 0.18 and 0.20, respectively, at doses of 0.5 and 1.25 mg) than in subjects who switched from IFN-β-1a to fingolimod (annualized relapse rate = 0.33; $P < 0.001$ for both comparisons). Similar incidences of AEs were reported for continuous treatment at either dose of fingolimod, with serious AEs seen in 11.4% and 14.3%, respectively, of those treated with fin-



Fingolimod hydrochloride

golimod 0.5 and 1.25 mg. The most common AEs included respiratory and cardiac disorders, as well as infections. A small number of cases of skin cancer and macular edema were also noted (61).

In 341 patients who switched from IFN-β-1a to fingolimod (0.5 mg, n = 167; 1.25 mg, n = 174) in the extension phase of TRANSFORMS, significant reductions in annualized relapse rate were observed following treatment with fingolimod for 12 months (reductions of 30% and 36%, respectively, seen in subjects switching to 0.5 and 1.25 mg fingolimod; $P < 0.05$ for both). Switching to fingolimod at either dose level also correlated with a significant decrease (62-63%) in the mean number of cumulative T_2 lesions (62).

The effect of initial treatment with fingolimod on cardiovascular parameters was assessed using pooled data from the FREEDOMS and TRANSFORMS trials. A transient decrease in heart rate, which was greater in the group receiving 1.25 mg than in the cohort receiving 0.5 mg, was reported following administration of the first dose of the agent. All symptoms associated with this reduction, which was attenuated with continued treatment, were described as infrequent, transient or had limited clinical significance (63). Treatment with fingolimod significantly reduced the annualized relapse rate (by ≥ 50%) versus placebo and IFN-β-1a, according to results from the pooled intent-to-treat population from FREEDOMS and TRANSFORMS (64). A linear mixed-effect pharmacokinetic model that adequately described pooled data from these phase III trials revealed that the exposure to the active metabolite of fingolimod (fingolimod phosphate) in the blood is slightly decreased in males and heavier subjects, although this reduction is not clinically relevant. The exposure to fingolimod phosphate was not affected by concomitant administration of other medications, including baclofen, fluoxetine, paroxetine and oral contraceptives (65). Fingolimod therapy results in a rapid decrease in lymphocyte counts immediately after initiation of the treatment. Steady-state levels are attained within 2 weeks and chronic treatment with the agent correlates with stable lymphocyte counts according to analysis of pooled data obtained from a total of 2,615 patients from FREEDOMS and TRANSFORMS, as well as a 6-month phase II trial and its 60-month extension in subjects with relapsing MS. Following discontinuation of fingolimod, recovery of the mean lymphocyte counts was seen within 45 days (66).

Long-term safety analyses from all three core trials and their extension phases revealed a similar incidence of AEs in subjects treated with fingolimod 0.5 or 1.25 mg (89.6% and 92.4%, respectively) and placebo (92.6%). Elevation in liver enzymes, lower respiratory tract infections, macular edema and transient bradycardia upon initiation of therapy were more commonly associated with fingolimod. The 0.5-mg dose of fingolimod exhibited a more favorable benefit-to-risk profile than the 1.25-mg dose based on similar efficacy benefits observed with the two doses versus placebo or IFN-β-1a (67).

INFORMS, an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel-assignment phase III study has been designed to investigate the ability of fingolimod to delay the progression of sustained disability in patients with primary progressive MS for a period of ≥ 36 months (68). The trial will evaluate the effects of daily oral treatment with fingolimod (0.5 or 1.25 mg) on the number, size and inflammatory activity of lesions in the gray matter of the cortex. A potential association between these findings and measures of disease progression and disability will also be addressed (69). INFORMS is estimated to enroll 654 participants and is expected to be completed in December of 2013. Administration of fingolimod to 72 healthy volunteers resulted in a mild to moderate and dose-dependent attenuation of the immune response. The majority of subjects treated with 0.5 mg fingolimod retained the capacity to exhibit clinically relevant increases in the levels of T-cell-dependent and -independent antibodies according to data from a 4-week, exploratory, randomized, double-blind, placebo-controlled, parallel-group trial (70).

Treatment of 88 healthy volunteers with fingolimod (0.5 or 1.25 mg) for a period of 4 weeks at steady state during a randomized, double-blind, placebo-controlled, parallel-group trial had no effect on platelet counts and did not correlate with alterations in platelet function versus placebo. Both doses of fingolimod were described as well tolerated (71).

Clinical data on the safety and efficacy of **glatiramer acetate** (Copaxone®; Teva) were disclosed in a number of presentations. Previous findings from PreCISe, a randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational phase III trial (72) suggested that treatment of patients exhibiting early symptoms of MS with glatiramer acetate 20 mg s.c. once daily for 36 months may delay or reduce the risk of conversion of the condition to clinically definite MS (CDMS) compared with placebo. A total of 481 subjects were randomized in PreCISe. The double-blind phase of the trial was completed by 423 subjects and 409 patients entered the 5-year prospectively planned open-label extension phase of PreCISe, in which subjects who had been given placebo in the double-blind part of the study were switched to active treatment (delayed glatiramer acetate-treated group), whereas individuals who had received initial therapy with glatiramer acetate continued on the preassigned treatment schedule (early glatiramer acetate-treated cohort). During the 5-year extension study, CDMS was observed in 33% and 49.5% of participants, respectively, in the early and delayed glatiramer acetate-treated groups. Early administration of glatiramer acetate correlated with a significant decrease (41.1%) in the risk for development of CDMS ($P = 0.0005$ vs. delayed treatment) (73). MRI analysis showed that early exposure to glatiramer acetate resulted in significant reductions in the cumulative number of new T_2 lesions and decreased the volume of T_2 lesions at the last observation compared with delayed treatment with the agent over the 5-year period of the study. Treatment with glatiramer acetate was well tolerated, with 33% of participants withdrawing their consent over 5 years (74).

The ability of glatiramer acetate to sustain the effects of treatment with natalizumab for 12-18 months in subjects with relapsing–remitting MS was addressed in an open-label, progressive, multicenter trial. At 4 weeks after administration of the last dose of natalizumab, subjects with relapsing–remitting MS (N = 40) received treatment with glatiramer acetate 20 mg/day s.c. for up to 12 months. Interim data obtained from 31 individuals who received glatiramer acetate for at least 3 months indicated the presence of a clinical relapse in 9 patients. In 23 subjects who completed at least 6 months of treatment, 11 exhibited evidence of reactivation of disease in MRI scans; however, no evidence of rebound was seen. A decrease in the annualized relapse rate was noted during treatment with glatiramer acetate compared with the period prior to initiation of treatment with natalizumab (0.42 vs. 2.3) (75).

The safety and tolerability of a new reduced-volume formulation of glatiramer acetate (20 mg/0.5 mL) compared to the marketed formulation of the agent (20 mg/1.0 mL) were assessed in patients with relapsing–remitting MS (N = 148) in an open-label, randomized, two-arm, single crossover, multicenter trial (76). Compliance to the reduced-volume and marketed formulations of glatiramer acetate was estimated to be 99.5% and 99.6%, respectively. The daily mean intermediate pain score was lower in patients receiving the new formulation than in those treated with the marketed preparation throughout the 14-day treatment period. The incidence of adverse events was < 20% for both formulations of the agent. Urinary tract infection, upper respiratory tract viral infection, arthralgia and headache were most frequently seen with the 20 mg/0.5 mL preparation of glatiramer acetate, whereas contusion, muscular weakness and ataxia were most commonly associated with the 20 mg/1.0 mL formulation (77).

In a retrospective, cross-sectional, single-center trial, a total of 1,062 participants with relapsing–remitting MS who had received treatment with interferons or glatiramer acetate were included in an analysis that aimed to identify demographic, clinical and MRI predictors of response to treatment. Higher age at the time of disease onset, lower annualized relapse rate before the initiation of treatment and fewer MRI active lesions at baseline were identified as predictors of a complete response to either treatment ($P < 0.0001$, $P = 0.02$ and $P = 0.01$, respectively) (78).

Treatment of 36 subjects with relapsing–remitting MS with glatiramer acetate correlated with a response to therapy in 80% of subjects, as observed by a reduction in the relapse rate. Analysis of the profiles of gene expression in treatment responders using Affymetrix U133A2 revealed that a three-gene classifier could predict the response to glatiramer acetate with accuracy, sensitivity and specificity of 98.2%, 100% and 87.5%, respectively (79).

The objective of a prospective 2-year trial was to establish whether the human leukocyte antigen (HLA) background and changes in cytokine production as a result of early treatment with glatiramer acetate could predict the clinical response to the agent at the end of 2 years in 62 patients with relapsing–remitting MS. The annualized relapse rate and EDSS scores of responders (n = 42) and nonresponders (n = 20) to glatiramer acetate exhibited comparable values at baseline but were significantly different at the end of the 2-year study period. HLA-DQ6 displayed a positive predictive value of response to glatiramer acetate of 89%. Significant increases in the levels of interleukins IL-4 and IL-10 and reductions in the levels of IL-18, caspase-1 and TNF-α detected in responders at 6 months relative to baseline were described as predictors of a favorable clinical response to glatiramer acetate at 2 years (positive predictive values of 0.79, 0.80, 0.82, 0.89 and 0.86, respectively) (80).

PRECLINICAL STUDIES – NEW MOLECULES IN PRECLINICAL DEVELOPMENT

Researchers at Almirall disclosed preclinical data that support the development of **LAS-189913**, a novel agonist of the lysophospholipid $S1P_1$ receptor for the treatment of immune-mediated inflammatory conditions such as MS. In vitro, LAS-189913 exhibited potent agonist activity at the $S1P_1$ receptor (EC_{50} = 18 nM), with selectivity over $S1P_3$ (> 750-fold), $S1P_4$ and $S1P_5$ receptors, while showing no effect on the $S1P_2$ receptor in [^{35}S]-GTPγS binding assays performed using membranes from CHO cells expressing one of the five lysophospholipid receptor subtypes. Oral administration of the compound to rats resulted in a significant decrease in the levels of circulating lymphocytes at doses of ≥ 0.3 mg/kg, with sustained lymphopenia (> 70% for 24 hours) seen at a dose of 3 mg/kg. In Lewis rats with experimentally induced encephalomyelitis, treatment with LAS-189913 at 3 mg/kg correlated with inhibition of the progression of neurological disability, similar to the effects of fingolimod (81).

The pharmacokinetics and pharmacodynamics of LAS-189913 were investigated in Wistar rats, cynomolgus monkeys and beagle dogs in an attempt to estimate the clinically effective dose of the compound in humans. Following i.v. administration of the agent at 1 mg/kg in rats, 0.5 mg/kg in monkeys and 0.1 mg/kg in dogs, the respective half-life values were estimated at 8.2, 22.2 and 23.1 hours. The predicted half-life in humans was 35 hours, which supported the suitability of LAS-189913 for once-daily administration. Using an inhibitory E_{max} model to evaluate the relationship between the concentration of LAS-189913 in the plasma and circulating lymphocyte counts, the concentration of the agent in plasma that was able to induce sustained optimal lymphopenia for 24 hours in all three animal species was calculated at approximately 200 ng/mL at trough. A decrease from baseline of 70-80% in total lymphocyte counts was seen in all species at doses of 1-3 mg/kg. It is estimated that doses of 10-20 mg/day may be clinically effective in humans with MS based on predictions from allometric scaling and using data obtained from pharmacokinetic/pharmacodynamic modeling. The agent is also expected to exhibit a rapid rate of absorption and good oral bioavailability (70%) in humans (82).

Two new small-molecule dual inhibitors of proto-oncogene serine/threonine-protein kinases pim-1 and pim-3, designated **AR-452530** and **AR-460770**, were described as potentially useful for the treatment of lymphocyte-mediated autoimmune conditions by scientists at Array BioPharma. The team used mice with experimental autoimmune encephalomyelitis (EAE) induced by injection of a peptide derived from myelin-oligodendrocyte glycoprotein (MOG; amino acid residues 35-55). Treatment of the animals with AR-452530 200 mg/kg p.o. b.i.d. for 14 days, starting at a time point when the disease had reached 20% of development, correlated with a significant reduction in the severity of the condition (52% decrease of AUC; $P < 0.001$). Similar results were observed in animals receiving AR-460770 100 mg/kg p.o. b.i.d. In an adoptive transfer model of MOG-induced EAE, treatment of restimulated lymphocytes with AR-452530 1 μM resulted in a reduction in the AUC of clinical score by 40%, compared with values in animals transplanted with control cells. In the acute phase of myelin proteolipid protein (PLP)-induced EAE in mice, subtherapeutic oral administration of AR-460770 100 mg/kg b.i.d. for 7 days was associated with a significant 64% reduction in the AUC of clinical score, whereas in a relapsing–remitting model of PLP-induced EAE, animals receiving AR-460770 100 mg/kg b.i.d. p.o. from the time of disease onset experienced a significant reduction in the incidence of relapse episodes compared with those in the control group ($P < 0.001$) (83).

Vaccinex has developed **VX15/2503** (VX15/Anti-SEMA4D), a human monoclonal IgG_4 antibody that targets semaphorin-4D in both mice

and humans. Semaphorin-4D is known to play a role in the activation and survival of lymphocytes, microglia, neural precursors and oligodendrocytes, and is considered a potential target to decrease the severity of demyelinating conditions such as MS. VX15/2503 was shown to block the interaction between semaphorin-4D and its receptor plexin-B1 in several in vitro functional assays and exhibited favorable safety and pharmacokinetic profiles in a recent preclinical study. In an immunofluorescence-based receptor-blocking assay, VX15/2503 at 10 and 40 μg/mL blocked the binding of semaphorin-4D to plexin-B1 and B-cell differentiation antigen CD72, and inhibited the association of semaphorin-4D with oligodendrocyte precursor cells isolated from rats. Pharmacokinetic analysis of the antibody given as a single i.v. dose (0.01, 0.1, 1, 10 and 100 mg) to Sprague-Dawley rats and cynomolgus monkeys revealed similar half-life values (ranging from 6 hours to 10 days) in the elimination phase in the two species. Following repeated i.v. administration to rats and monkeys at 10, 30 and 100 mg/kg, the agent did not display toxicity and demonstrated similar dose-dependent saturation in the two species. VX15/2503 is currently undergoing IND-enabling toxicological testing and is expected to enter clinical development for the treatment of secondary progressive MS in early 2011 (84).

DISCLOSURES

The author states no conflicts of interest.

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