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RESEARCH/CLINICAL UPDATE

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Research Progress Reported at International ECTRIMS Meeting: *Focus on MS Drug Trials, the Immune Attack and Disease Pathology*

Multiple sclerosis research took center stage at the 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held October 10-14, 2007, in Prague. Results were presented from numerous clinical trials, indicating the potential within the MS pipeline. Key findings also were reported on the development of disease.

Here is just a sample of these presentations. The full list of presentations and their summaries (abstracts) are available online at http://www.akm.ch/ectrims2007/.

Notes: 1) Many readers prefer to know the source of funding especially for clinical trials. Funding sources for clinical studies were not consistently disclosed in the meeting program; they are noted below when available. 2) Definitions of types of MS are noted on the final page.

Trials of Experimental Therapies in the Pipeline

►Dr. H. Garren (Bayhill Therapeutics) and colleagues reported preliminary data from a phase II study of **BHT-3009** (one of two doses (.5 mg or 1.5 mg) vs. inactive placebo) in 289 people with relapsing-remitting* (RR) MS. BHT-3009 is a vaccine containing genetic material that instructs cells to produce myelin basic protein (MBP), a component of myelin, an immune target in MS. It is given by periodic injections into the muscle. The primary goal was to determine differences in the rate of new, active brain lesions (areas of inflammation or active damage to nerve fiber insulating myelin) as shown on MRI scans. Dr. Garren focused this presentation on safety data, reporting that BHT-3009 was well tolerated, and also reported that the agent altered immune responses to MBP and several other myelin proteins. Information about the drug's effectiveness is to be presented in the near future. Sponsored by Bayhill Therapeutics. (Abstract # 48) According to a company press release, preparations are underway to conduct a larger-scale, phase III trial.

►A **new formulation of Rebif®** (interferon beta-1a, EMD Serono and Pfizer) proved more tolerable than the original formulation in a two-year study reported by Dr. Gavin Giavannoni and colleagues in a poster presentation (48-week data) and also in a special satellite meeting (96-week data). The new formulation is designed to reduce the development of neutralizing antibodies (Nabs), which are immune system proteins that may reduce effectiveness of interferon treatments. In this open-label study, 260 people with relapsing forms of MS‡ injected 44 mcg of Rebif under the skin three times weekly, and the results were compared with historical data from the previously completed EVIDENCE study (in which the original Rebif was compared to Avonex® -- interferon beta 1a, Biogen Idec). At 96 weeks, 17.4% of patients treated with the new formulation were Nab positive compared with 21.4% of patients in the EVIDENCE study at 48 weeks. Injection site reactions occurred in much fewer of those on the new formulation: 30.8%, compared with 85.8% in the EVIDENCE study. Funded by Merck Serono International S.A. (Abstract #P193) The new formulation of Rebif was approved for release in Europe, and according to company press releases, it has also applied to the U.S. FDA for approval.

►Dr. I. Catz and colleagues (University of Alberta) reviewed the safety of **MBP8298** (BioMS), a synthetic fragment of myelin basic protein (MBP, a component of myelin), which reduces the production of spinal fluid antibodies that react against MBP. Over 11 years of its use as an IV injection in clinical trials, 27 patients have received a total of 492 injections, with 152 adverse events, mostly facial flushing, burning sensation, and nausea/headache. Of the 39 cases of facial flushing, 35 occurred before the manufacturing process was improved in 2003. Fourteen adverse events were serious, including one death, but none were attributed to the medication. MBP8298 is currently under study in two studies in secondary-progressive*** (SP) MS (510 people in the U.S., and 611 people in Europe) and one study in 218 people with RR MS. Funded by BioMS Medical Corp. (Abstract # P571) Dr. L. Arfors and colleagues reported on an interim safety analysis of the European study, showing no significant safety concerns and no signs of worsening disease on MRI. All studies are ongoing and are fully enrolled. Funded by BioMS Medical Corp. (Abstract # P573)

►Dr. G. Mancardi (University of Genoa) provided an update on the status of **hematopoietic stem cell transplantation** (in which blood or bone marrow stem cells, usually the patient's own, are used to reconstitute the immune system in hopes of stopping immune attacks in MS). From 1995 to 2007, more than 300 people have been treated. According to a survey of patients in the database of the Europe Blood and Transplantation Group, 63% of people have improved or stabilized. From 1995 to 2000, 8% of patients died, but mortality has been substantially reduced since then. The results were best in rapidly evolving, severe MS. Among 58 cases in Italy, 63% of people with SP MS improved or stabilized, versus 95% of those with RR MS. Dr. Mancardi pointed out that this therapy has not yet been proven to be clinically effective. (Abstract #72)

►Dr. M. Freedman and the Canadian Bone Marrow Transplantation Study Group reported on 25 patients enrolled in this study who have active, relapsing MS with high risk of disease progression; 15 have received full treatment (**hematopoietic stem cell transplantation,** described above). No patient has experienced relapses or has any new disease activity on MRI. Mild disease progression has been observed in four people with high EDSS scores (indicating greater disability) upon entering the study. Three patients with lower disability at entry showed improvement in their disability scores after treatment. One person died due to complications in administering busulfan, one drug involved in the protocol, but the protocol has since been changed to make administration more tolerable. This study is ongoing. Sponsored by the Multiple Sclerosis Foundation of Canada. (Abstract #73)

►Dr. X. Montalban (University of Barcelona) and colleagues reported on preliminary results of the phase II "CHOICE" study of **daclizumab** (PDL Biopharma and Biogen Idec) in 230 people with relapsing forms of MS who were taking an interferon beta. In this study, while continuing on their interferon treatment, 78 people received 1 mg daclizumab injection under the skin every 4 weeks, 75 received 2 mg every 2 weeks, and 77 received placebo, for 24 weeks and were observed for 48 weeks afterward. Ninety percent of people completed the study and the investigators found the addition of daclizumab to interferon beta generally well tolerated. The primary endpoint of the study – number of new or enlarged areas of active damage on MRI – was significantly reduced by 72% in the high-dose group compared with placebo. The low-dose grouped showed a 25% reduction compared with placebo – not a statistically significant finding. Funded by PDL Biopharma. (Abstract #50) A company press release indicated that they are initiating a further study by the end of 2007.

►Dr. H. Ehrenreich (Max Planck Institute of Experimental Medicine, Gottingen, Germany) and colleagues reported results from a small, uncontrolled study of a laboratory-produced version of **erythropoietin**, a naturally-occurring hormone used to treat anemia, in 8 patients with chronic, progressive (secondary-progressive) MS. The rationale was that erythropoietin has potential as a nervous system-protecting agent. Five people took a high dose of the intravenous drug, along with two control patients who had Parkinson's disease, and three received a low dose. The group was followed for 48 weeks. Although this was primarily a safety study, with no adverse events reported, the investigators also reported that motor and cognitive function improved and improvements persisted for three to six months after treatment. The low-dose and control groups did not improve. Funding source not published. (Abstract #118)

►Dr. J. Drulovic (University of Belgrade) and colleagues reported on a study of **MN-166** (MediciNova), an experimental oral drug, in 292 people with RR MS (93%) or SP MS (7%). People were randomly assigned to receive MN-166 at low or high dose (30 or 60 mg) or placebo. There was no significant difference seen between the groups in the study's primary endpoint -- the accumulation of disease activity observed on MRI. However, MN-166 was associated with a significant reduction in loss of brain tissue volume over one year, and also

with a significant increase in time to first relapse. Gastrointestinal events – mostly mild – occurred in 22% of the high-dose group, 15% of the low-dose group, and in 8% of those on placebo. Additional early studies, including studies investigating higher doses, are planned. Funded by MediciNova Inc. (Abstract #52)

Studies of Approved Therapies

►In a head-to-head comparison trial, Dr. D. Mikol and researchers from the REGARD Study Group compared **Rebif®** (interferon beta-1a, EMD Serono and Pfizer) against **Copaxone®** (glatiramer acetate, Teva Pharmaceutical Industries) in RR MS. In this study, 386 participants were randomly assigned to receive the current formula of Rebif and 378 received Copaxone for 96 weeks. The primary goal was to determine differences in the time to first relapse, but these findings were not statistically different between the two drugs. Overall the investigators noted that the study population had much less active disease compared with previous trials in relapsing-remitting MS. Funding source not published. (Abstract #119)

►In a special satellite meeting and in a poster presentation, Dr. M. Panzara (Biogen Idec) and colleagues presented updates on its TOUCH™ prescribing program in the U.S. and TYGRIS global observation program for **Tysabri®** (natalizumab, Biogen Idec and Elan Pharmaceuticals), a treatment approved for relapsing forms of MS given by IV infusion every four weeks. The TOUCH program is designed to track opportunistic infections and to understand their risk factors. As of September 2007, approximately 17,000 people are currently being prescribed Tysabri or are involved in clinical trials, 10,500 of those in the U.S. No new cases have been confirmed of PML (progressive multifocal leukoencephalopathy), a brain disease that occurred in three people (two of whom died) who had been in earlier clinical trials of Tysabri. Funded by Biogen Idec, Inc and Elan Pharmaceuticals. All told, about 26,200 people in the world have been exposed to Tysabri in clinical trials and post-marketing settings. (Abstract #P565)

►In a small, ongoing study in 12 people taking **Tysabri**, Dr. B. Khatri (Aurora St. Luke's Medical Center, Milwaukee) and colleagues are exploring whether plasma exchange (a blood-cleansing process that involves removing and replacing the liquid portion of blood) could reduce the concentration of Tysabri in the blood and possibly serve as an intervention in case a patient develops PML. Preliminary data from this PLEX study suggest that the three courses of plasma exchange used in this study achieved a significant reduction in Tysabri concentration. So far none of those treated has experienced an increase in MS disease activity following plasma exchange. Further study is needed to determine whether plasma exchange is an effective intervention for PML. Funded by Biogen Idec, Inc and Elan Pharmaceuticals. (Abstract #P576)

►In recent years, continued research on **Copaxone** (glatiramer acetate, Teva Pharmaceutical Industries) has uncovered more information about how it fights MS inflammation and more recently, researchers have suggested that it may influence brain repair mechanisms. Along these lines, Dr. C. Silva and colleagues presented work showing that Copaxone generates immune T cells that are anti-inflammatory. In lab culture dishes, these T cells produce growth factors that can promote the generation of myelin-making cells (oligodendrocytes). To test their capacity to promote myelin repair, they gave daily injections of Copaxone to mice whose myelin had been injured in the spinal cord (lysolecithin-induced demyelination). Treatment doubled the amount of immature oligodendrocyte repair cells (oligodendrocyte precursor cells) normally stimulated in this situation. Future studies will focus on whether the elevation of repair cells results in increased myelin repair. Supported by Teva Pharmaceuticals and the Multiple Sclerosis Society of Canada. (Abstract #P240)

►Dr. D. Langdon and colleagues in the **Betaseron®** (interferon beta-1b, Bayer Healthcare Pharmaceuticals Inc) 16-Year Long-term Follow-up Study Group administered cognitive tests to 179 people who had originally participated in the pivotal North American clinical trial of Betaseron that led to its approval. The investigators attempted to correlate the cognitive test results with the MRI and EDSS (a disability measure) data obtained for the clinical trial 16 years earlier. They found that people with higher EDSS scores (worse disability) and greater amounts of disease evidence on MRI scans had significantly lower cognitive test scores 16 years later. The 16-year followup study is funded by Bayer Schering Pharma AG. (Abstract #P749)

►Dr. K. Hawker (University of Texas Southwestern Medical Center, Dallas) and colleagues reported on an ongoing study of **Rituxan®** (rituximab, Genentech and Biogen Idec) in 439 people with PP MS***. The primary goal of the study is to determine the treatment's effect on time to disease progression as measured by the EDSS disability scale. The trial required that all participants had signs of specific antibodies (oligoclonal bands) in their spinal fluid, which the investigators believe may account for the fact that 25% of participants have MRI signs of active inflammation. The investigators believe these demographics increase the possibility of detecting a therapeutic effect for Rituxan, a treatment that acts on immune system activity, specifically B cells. The trial is slated to go for 96 weeks. Funded by Genentech, Inc. (Abstract #P553)

Findings on MS Development

►In late-breaking news, Dr. F. Martinelli Boneschi (Ospedale Maggiore, Milan) and colleagues reported having completed a scan of the genome (all genetic material) in a group of 197 people with primary-progressive MS, a course experienced by about 10% of those diagnosed with the disease. They selected 20 genetic variations for further study, and compared them with genetic material from 234 controls. One variation in the HLA region (immune system genes associated with MS) was more than twice as common in PP MS as in

controls. They are now comparing the results with scans of RR and SP MS, and doing other analyses of their findings. (Abstract #114)

►Dr. R. Zivadinov (SUNY Buffalo) and colleagues reported on a study of 759 people with MS, of whom 198 had a family history of MS. Evaluating MRI scans, the group found more severe disease activity in those with a family history of MS, particularly those with first-degree relatives with the disease. Further study is necessary to determine exactly how genetics affect MS severity. (Abstract #P281)

►Dr. Zivadinov also reported on cigarette smoking and MRI findings in 368 people with MS, of whom 96 were active smokers and 32 were former smokers. Measures of brain tissue volume indicate significantly lower volumes in smokers, and a significant relationship between lower volume and higher average use of packs per day. (Abstract #P607) Recent studies have debated the association between smoking and MS progression: A 2005 Harvard University study showed an association between smoking and risk of MS progression, but a recent report from the Netherlands found no such connection.

►Dr. R. Magliozzi and colleagues in London and Rome recently identified B-cell follicles, sack-like structures, in the membrane that surrounds the outer layer of the brain (cerebral meninges) of people with SP MS, providing further insights into the role of B cells in the immune attack. They found that these abnormal structures were associated with a younger age of diagnosis and onset of disability, and a more aggressive disease course. In a follow-up study, the team analyzed areas of disease activity from 10 people with SPMS and ectopic B cell follicles, 10 people with SP MS and no B cell follicles, and three controls. They found increased damage to the cerebral cortex, the outer layer of the brain, in people who had SP MS and follicles -- including decreases in nerve cells and myelin-producing cells, in association with a marked increase in immune activity of cells called microglia. Identifying these follicles in people with SP MS may help predict a more aggressive course of MS. (Abstract #45).

►During a special session, Dr. F. Aloisi (Rome) described further work exploring B cell follicles and the possibility that their formation could be linked to an infection of B cells with Epstein-Barr virus (EBV, the virus linked to infectious mononucleosis and other disorders). Using techniques to unravel the presence of EBV in brain tissue samples from people with MS, they showed possible signs of accumulation of EBV-infected B cells and plasma cells in the follicles and in MS lesions. They also showed evidence of an immune attack toward EBV-infected cells in the MS brain. Although previous studies have suggested that exposure to EBV increases the risk of developing MS, possible evidence of the virus's presence in brain lesions was lacking. This study by an international team is bound to stimulate other investigators to attempt to replicate their findings and to seek further evidence of a direct link between EBV and MS. (Presentation #60, no abstract)

*RR MS – Relapsing-remitting MS, a course of MS in which clearly defined flare-ups are followed by partial or complete recovery periods.
**PP MS – Primary-progressive MS, a slow but nearly continuous worsening of disease from onset.
***SP MS – Secondary-progressive MS, an initial period of relapsing-remitting MS, followed by a steadily worsening disease course with or without occasional flare-ups or minor recoveries.
‡Relapsing forms of MS – Usually includes individuals with relapsing-remitting MS and also those with secondary-progressive disease who still experience flare-ups.

-- Research and Clinical Programs Department

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