Dirucotide (MBP8298) for the treatment of multiple sclerosis

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Multiple sclerosis (MS) is a chronic and debilitating disease affecting approximately 2.5 million people worldwide, and safe and effective treatment options are sorely lacking. While there are several currently approved drugs that have shown some efficacy at reducing the relapse rate in patients with the relapsing–remitting form of the disease, the impact of this outcome relative to long-term disease progression is unknown. Effective treatment for those with primary or secondary progressive MS is practically nonexistent. Dirucotide (MBP8298) is a synthetic peptide that has shown promise at increasing time to progression with little or no associated toxicity in Phase II studies. The drug is specifically designed to induce tolerance in patients with HLA types DR2 and/or DR4, although patients with other HLA subtypes may also benefit. Dirucotide is now being evaluated in two large Phase III secondary progressive MS trials, as well as a smaller Phase II relapsing–remitting MS trial.

Multiple sclerosis (MS) is a chronic disease of the CNS characterized by increasingly debilitating effects on a wide range of human functions, and enormous prognostic uncertainty. Some estimates indicate that up to 2.5 million people worldwide [101], including approximately 400,000 in the USA [101], 75,000 in Canada [102] and 350,000 in Europe [1], are affected by the disease. The prevalence is highest in locations of extreme latitudes, such as northern Europe and southern Australia, and the middle of North America, although the reason for this variability is not well understood. The onset of the disease is usually in early adult life, with prevalence peaking during the most economically productive middle adult years [2]. In terms of assessing susceptibility to the disease, it is likely that both environmental and genetic factors play a role.

There are four primary categories of MS: relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and progressive relapsing (PRMS). Approximately 85% of patients with MS begin their disease course with a diagnosis of RRMS [2], which is characterized by relapses and subsequent spontaneous remissions. RRMS typically evolves to SPMS with a rate of conversion of 2–3% per annum, and a median time to conversion of 10 years from diagnosis of MS [3,4]. A diagnosis of SPMS indicates a progressive, neurological deterioration with or without clinical relapses superimposed [5]. Most estimates indicate that the number of patients with SPMS is 30–40%, compared with 45–60% with RRMS [103–105], but the numbers may be closer to equal, as patients whose disease is in transition and has features of both forms may sometimes be classified as RRMS in order to continue to use drugs approved for the treatment of RRMS. PPMS is characterized by progressive disease from the onset, with occasional plateaus and temporary improvements, and occurs in approximately 10% of the MS population. The least common form of MS is PRMS. This is a progressive disease from the onset, with acute relapses, with or without full recovery, with periods between relapses of continued progression [6].

MS is believed to consist of two primary clinical phenomena: acute, focal inflammation, and diffuse, chronic and progressive axonal loss. Relapses, associated with focal inflammation, appear to define the clinical picture early in the disease, yet it is still unclear how these relapses might influence the rate of progression of irreversible disability and diffuse neurodegeneration [7,8]. Once the disease reaches the onset of progression, a relatively uniform course is followed [8]. Some data suggest that progression is largely age dependent, and that early in the disease course, neurodegeneration is clinically invisible, but later, the diffuse neurodegeneration dominates and this is expressed as irreversible and progressive disability [7-9]. In this context, treatment aimed at reducing the number of relapses may be beneficial in terms of reducing the frequency of acute symptoms, but effects on the underlying disease progression remain unclear [10].

Current approved treatment options

Corticosteroids have been used for many years to reduce inflammatory activity in MS. These medications can reduce the duration and severity of relapses in some patients; however, there does not appear to be any long-term impact on the disease process [9,11].

Some immunosuppressive agents have also been evaluated, but have shown only modest effect and have associated toxicities. These include cyclophosphamide, azathioprine, cyclosporine, methotrexate and cladribine [11].

More recently, several therapies have been introduced that do improve patient outcomes (Table 1). β -interferon therapy (interferon β -1b, Betaseron/Betaferon® [Bayer Healthcare Pharmaceuticals, NJ, USA], interferon β-1a, Rebif® [EMD-Serono, MA, USA] and interferon β-1a, Avonex[®] [Biogen Idec, MA, USA]), a synthetic polypeptide (glatiramer acetate, Copaxone® [Teva Neuroscience, MO, USA]), and an antineoplastic agent (mitoxantrone, Novantrone® [EMD-Serono]) are currently approved for treatment of RRMS [9-11]. All these products have been shown to reduce the relapse rate in patients with RRMS (for Novantrone, only in 'aggressive transitional' patients) [10]. However, all have significant side effects, and their effectiveness in delaying disability is modest, as are their benefits in patients with other categories of MS, such as SPMS [10,12].

Betaseron was approved in Europe and Canada for use in SPMS [13], but in a US trial it failed to slow progression over 3 years compared with placebo [14], and the US FDA limited its extended approval to SPMS patients who continue to experience relapses. A combined analysis of these two trials indicated that baseline differences and differences in disease activity in the two study populations contributed the most to the disparity [15]. Novantrone has been approved in the USA for use in SPMS, but cardiotoxicity limits its use to 2–3 years.

Natalizumab (Tysabri[®], Elan, Biogen Idec, MA, USA) a monoclonal antibody for intravenous administration, has been approved by the FDA for the treatment of MS, but was withdrawn from the market in February 2005 to allow assessment of risk of progressive multifocal leukothe encephalopathy (PML). On 5 June, 2006, the FDA approved an application for resumed marketing of Tysabri with a special restricted distribution program for patients with relapsing forms of MS. Tysabri is indicated for use as monotherapy for patients who have not responded adequately to, or cannot tolerate, other treatments for MS. The risk of PML associated with natalizumab is estimated to be 1 out of 1000 over a mean treatment period of approximately 18 months [16].

There are no currently approved therapies for PPMS or PRMS (Table 1).

Current clinical trials

The National MS Society website [101] and the US NIH website [106] list over 130 and 350 trials, respectively, with only a small percentage of these being Phase III. The vast majority of ongoing

Table 1. Current	t approved di	sease-modifying treatme	nts for RRMS	and SPMS.	
On the market	Approved indication	Product characteristics	Efficacy	Side effects	Administration/dosing
Interferon β-1a (Avonex [®]), interferon β-1a (Rebif [®]), glatiramer acetate (Copaxone [®])	RRMS	 β-interferon, slows inflammation Polypeptide, myelin decoy 	Relapses reduced 29–37%	Flu-like symptoms, redness at site, depression	Intramuscular or subcutaneous daily, several times per week or weekly
Interferon β-1b (Betaseron [®] / Betaferon [®])	RRMS and SPMS [*]	 β-interferon, slows inflammation 	Relapses reduced 31%	Flu-like symptoms, depression	Subcutaneous every other day
Natalizumab (Tysabri®)	RRMS	 Monoclonal antibody 	Relapses reduced 66%	PML has been reported	iv. infusion every 4 weeks
Mitoxantrone (Novantrone [®])	SPMS	 Cytotoxic drug, immunosuppressant 	Slows progression	Cardiotoxicity, hair loss	iv. once very 3 months (maximum use 2–3 years)

*Restricted to SPMS with relapses.

iv.: Intravenous; PML: Progressive multifocal leukoencephalopathy; RRMS: Relapsing–remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis.

clinical studies in MS are being conducted in patients with relapsing-remitting disease, with some of these including SPMS patients who continue to have relapses.

For patients with RRMS, 12 Phase III trials are listed as enrolling subjects, or having recently completed enrollment. Some of the more novel trial designs include the evaluation of laquinimod (Teva Neuroscience), glatiramer acetate (Copaxone) plus estriol, FTY720 (fingolimod, Novartis [Basel, Switzerland]), cladribine (EMD Serono), omega-3 fatty acids, and interferon β -1a (Avonex) plus simvastatin (Zocor[®]) (Merck & Co., NJ, USA) in an effort to decrease the rate of relapse.

Only two Phase III clinical trials are currently enrolling patients with SPMS with an end point of reducing the rate of disease progression, both with a randomized, double-blind design. Cyclophosphamide is being evaluated versus methylprednisolone in a 360 patient study, and dirucotide (MBP8298 [BioMS Medical, Alberta, Canada]) is being evaluated versus placebo in a 510 patient study. A double-blind, placebo-controlled Phase II–III study with dirucotide in Canadian and European patients with SPMS recently completed enrollment of 611 patients. Additionally, a study with mitoxantrone in 336 patients in a randomized, double-blind, three-dose study recently ended.

Unfortunately, both mitoxantrone and cyclophosphamide are unlikely to have a significant impact for the average SPMS patient. While mitoxantrone is already approved for the treatment of MS, its use is limited by toxicity. Similarly, the use of cyclophosphamide is limited by its depletion of lymphocytes.

Primary progressive MS has even fewer latestage trials than SPMS, with only one Phase II–III trial listed. This double-blind, placebo-controlled study in 439 patients was designed to evaluate time to progression during a 96-week treatment period. Patients were randomized 2:1 to rituximab (Genentech [CA, USA] and Biogen Idec) or placebo. Results of the study were recently released and indicated that the primary end point was not met.

Dirucotide (MBP8298) overview

Dirucotide is an antigen-based therapy. Antigenbased approaches for the treatment of autoimmune diseases are particularly attractive because modifications of essential immunological activities unrelated to the disease can be avoided. Dirucotide is an investigational drug that has been specifically designed to selectively suppress autoimmune cells that target the region of myelin basic protein (MBP) comprising amino acids 82-98, which represents a dominant molecular site of inappropriate immune attack by B cells in the spinal fluid of MS patients [17]. It is also the target of T cells in MS patients with HLA haplotype DR2 [18], who make up the largest fraction of all MS patients [19]. HLA type genetically determines the range of molecular sites that may be attacked in any individual, and it is known that a number of HLA-DR haplotypes, in addition to DR2, can enable immune attack at this same site [20]. These include HLA-DR4, which makes up the second largest contingent of MS patients, and several less common HLA haplotypes. The frequency of HLA-DR2 plus HLA-DR4 in MS populations is in the range of twothirds to three-quarters, depending on the ethnic makeup of the study group.

It has been known for decades that high-dose intravenous injection of a soluble foreign protein induces antigen-specific tolerance in animals [21]. Although molecular and cellular mechanisms have not been elucidated, a rapid effect of soluble protein or peptide on effector T cells in the spleen has recently been visualized *in vivo*, in an animal model of MS [22]. Movement of T cells with specificity for the administered antigen was arrested and the cells formed clusters, became nonresponsive to antigen and seemed to undergo antigen-related cell death. Disease symptoms were ameliorated by the treatment, as had been reported previously in a number of other animal disease models of MS [23–27].

Dirucotide is an exact synthetic copy of an amino acid sequence found in endogenously expressed human MBP, and it is administered according to the 'classic' method of high dose tolerance induction by the intravenous route. This is distinct from the altered peptide ligand approach, which has not been successful in clinical trials [28,29]. The altered peptide ligand is a strategically modified MBP sequence, and it is therefore immunologically 'foreign' in humans. It was administered by an immunogenic route (subcutaneously) at a dose (relatively low) that was expected to elicit a potentially beneficial novel immune response. Novel immune responses were detectable, but did not prove to be beneficial in clinical trials.

In Phase I studies, intravenous injections of dirucotide 500 mg in a single dose or as repeat injections induced long-lasting immunological tolerance to MBP in a significant fraction of patients with progressive MS, as indicated by suppression of anti-MBP antibody in the cerebrospinal fluid (CSF) to low or undetectable levels for periods of 6–18 months after dosing [30,31]. Patients with progressive, rather than relapsing disease, were chosen because CSF autoantibody levels were elevated and stable, and could therefore serve as a surrogate indicator of drug effect.

A double-blind, placebo-controlled Phase II study in 32 progressive MS patients showed a statistically significant (p = 0.01) effect of dirucotide treatment on disease progression versus placebo in a subset of 20 patients with HLA haplotypes HLA-DR2 or HLA-DR4 [32]. The effect in the group of 32 patients overall was not significant (p = 0.31). Long-term follow-up treatment showed an unprecedented 5-year delay (from 18 months for patients receiving placebo to 78 months for patients receiving dirucotide) in the median time to disease progression in the identified subset of patients (p = 0.004; Figure 1) [32].

The observation that clinical response to treatment with dirucotide was related to HLA-DR haplotype in the Phase II study implies that T-cell activity must be addressed to achieve the clinical effect. This can be implied because T cells only recognize peptides when they are presented by HLA molecules on the surface of other cells, whereas B cell or antibody interactions with antigen do not involve HLA molecules. Autoantibody levels in the CSF of most of the dirucotide-treated patients were suppressed in this study, as had been reported previously [31], and this effect may be necessary, but it was not sufficient to ensure a clinical response. Possible effects of the treatment on T cells, T-cell subsets or the production of cytokines were not assessed in this study, but are being evaluated in ongoing studies.

1.0 Dirucotide 0.8 Probability 0.6 0.4 0.2 0 0 20 40 60 80 100 Months Each treatment arm represents ten patients. Data from 0 to 24 months are from

Figure 1. Time to first confirmed disease progression in a subset

of patients (20 out of 32) with HLA haplotypes DR2 or DR4.

Each treatment arm represents ten patients. Data from 0 to 24 months are from a Phase II double-blind clinical trial, and data from 24 to 84 months are from the open-label, follow-up treatment of the patients from the original dirucotide treatment group.

While examining the Phase I, Phase II and compassionate use follow-on study data with dirucotide, carried out over a period of more than 12 years, none of the observed disease exacerbations were deemed to be peptide induced. A total of 19 out of 32 patients from the Phase II study (including some originally assigned to placebo) who derived clinical benefit from dirucotide treatment have been dosed with dirucotide 500 mg intravenous every 6 months for more than 7 years. Most of these patients have HLA haplotypes DR2 or DR4, both of which enable presentation of the dirucotide peptide to T cells. Thus, no peptideinduced disease exacerbation has been seen to date in what should be the most susceptible subgroup of MS patients (HLA-DR2 and/or HLA-DR4), nor in patients with other randomly occurring HLA-DR haplotypes. No safety issues have been identified in any of these studies.

Anecdotal evidence from these studies suggests that the dirucotide epitope may sometimes be dominant in the less frequent HLA haplotypes DR5, DR6, DR7 and DR8, but the sample size has been too small to justify conclusions. The Phase II study results also suggest that the dirucotide epitope is active, but subdominant, in some patients with other HLA-DR haplotypes, and the peptide may therefore provide some clinical benefit in a wider population.

Based on the encouraging results obtained in the early clinical studies, the decision was made to move on to a pivotal Phase III program targeting patients with SPMS. Additionally, a Phase II RRMS trial is also ongoing to explore the potential of dirucotide in this patient population. Table 2 outlines the current status of the ongoing clinical trials with dirucotide.

The results of the HLA distribution of all screened patients (n = 788) in MAESTRO-01 were shown in a poster presentation at the 23rd Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS) [33]. Overall, 70.38% of the screened patients were DR2 and/or DR4 positive (52.26% were DR2 positive, 21.69% were DR4 positive and 7.56% were both DR2 and DR4 positive). More female than male patients were DR2 and/or DR4 positive (71.72 vs 67.92%, respectively).

As of April 2008, safety data from the ongoing MAESTRO-01 clinical trial have been subject to multiple consecutive reviews by an independent data safety monitoring board (DSMB). No safety issues have been identified, and at each meeting, the DSMB has recommended that the trial continue.

Table 2. Curre	ent clinical tr	ials with dirucotide.			
Study name	Indication	General design	End points	Enrolment	Timelines
MAESTRO-01 (Phase II–III)	SPMS	 Double blind, placebo controlled Four doses, 6 months apart iv. injection over 3–5 min HLA DR2/4 negative allowed, but capped at 100 subjects Stratified by EDSS score and HLA status Powered for DR2 and/or DR4 positive 47 sites in ten countries (Canada and EU) 	 Primary: time to progression by EDSS with 6-month confirmation Secondary: safety, relapse rate, MRI, quality of life 	Fully enrolled with 611 subjects (100 HLA DR2/4 negative)	 Formal safety analysis on first 100 subjects in April 2007 Formal unblinded interim analysis on first 200 subjects in summer 2008 Final analysis in 2009
MAESTRO-02 (extension)	SPMS	 Open label Only subjects who completed MAESTRO-01 are eligible Same schedule as parent study 	 Primary: safety Secondary: time to progression, relapse rate, quality of life, MRI 	Over 95% of eligible subjects rolling into extension study	No pre-set end
MAESTRO-03 (Phase III)	SPMS	 Double blind, placebo-controlled Four doses, 6 months apart HLA DR2 or DR4 positive only Stratified by EDSS score Over 60 US sites 	 Primary: time to progression by EDSS with 6-month confirmation Secondary: safety, relapse rate, MRI, quality of life 	510 to be enrolled by first half of 2008	 Formal interim analysis after 133 subjects complete study Final analysis in early 2011
MINDSET-01 (Phase II)	RRMS	 Double blind, placebo controlled Three doses over 15 months, then two open-label doses of dirucotide 24 sites in six central and eastern European countries 	 Annualized relapse rate 	Fully enrolled with 218 subjects	 Double-blind portion analysis in early 2009 Final study analysis in 2010

EDSS: Expanded Disability Status Scale; iv: Intravenous; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progessive multiple sclerosis.

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Blinded safety data from all randomized patients in MAESTRO-01 were also presented in poster format at ECTRIMS [34], and included an evaluation of MRI results of the first 100 patients who completed 1 year on the study. By protocol design, this cohort underwent more frequent visits to the study sites, and had more MRIs than the remaining study population. No changes in the median count of lesions were observed. Overall, self-limiting injection-site reactions were seen in a small percentage of patients. A total of 66 serious adverse events were reported, 12 of which were considered to be possibly related to the study drug by the investigator (the study blind was not broken for any of these events). No anaphylactic reactions were reported. In the summer of 2008, an unblinded review will be conducted by the DSMB as a formal interim analysis.

Periodic DSMB reviews of data from both MAESTRO-03 and MINDSET-01 have consistently resulted in recommendations for study continuation, with no safety concerns.

To date, and including data from all studies, dirucotide is associated with a relatively benign safety profile. Assuming a dose regimen interval of 6 months equates to 'exposure', the accumulated exposure to intravenous dirucotide is over 1000 patient-years through April 2008. No safety concerns have been identified.

Conclusion

MS is a serious disease of enormous prognostic uncertainty. Approved treatment that will safely increase the time to progression for patients with MS, whether it be relapsing–remitting or progressive MS, remains lacking.

Based on clinical results to date, dirucotide may represent a first-in-class drug to delay the progression of MS over a relatively long period of time, without showing treatment-limiting adverse side effects. It has a favorable administration schedule and safety profile, induces peptide-specific immunologic tolerance and has induced significantly delayed disease progression in an HLA Class II-defined cohort of MS patients. An HLA Class II-defined responder group making up approximately 70% of the MS population has been identified (HLA-DR2 and/or -DR4), and further studies to evaluate clinical benefit in patients with other HLA-DR haplotypes are ongoing.

Future perspective

Dirucotide holds great potential for patients suffering from MS, a disease with few effective treatment options. The drug is particularly convenient, in that it is administered only once every 6 months, and to date it has shown a remarkably benign side-effect profile. In Phase II, the drug showed a 5-year delay in median time to

Executive summary

Mechanism of action of dirucotide (MBP8298)

- Dirucotide (MBP8298) is a first-in-class, antigen-based therapy.
- Dirucotide induces peptide-specific immunologic tolerance.
- A, HLA Class II-defined responder group, making up approximately 70% of the multiple sclerosis (MS) population, has been identified (HLA-DR2 and/or -DR4).

Clinical efficacy of dirucotide

- Phase I: dirucotide (MBP8298) induced long-lasting immunological tolerance to myelin basic protein (MBP), as indicated by suppression of anti-MBP antibody in the cerebrospinal fluid to low or undetectable levels in patients with progressive MS.
- Phase II: dirucotide-treated patients experienced a statistically significant 5-year delay in disease progression compared with placebo-treated patients.
- Two double-blind, placebo-controlled Phase III secondary progressive MS (SPMS) trials and one Phase II relapsing–remitting MS (RRMS) trial are ongoing.
- An unblinded interim analysis for the MAESTRO-01 SPMS Phase II–III study is to take place in summer 2008 with final analysis in 2009.
- Final analysis results for primary end point in the MINDSET-01 RRMS study are expected to be available in the first quarter of 2009.
- Final analysis for the MAESTRO-03 study is due in early 2011.

Safety & tolerability of dirucotide

- Dirucotide is administered by intravenous injection over 3–5 min, once every 6 months.
- Occasional mild injection-site reactions have been observed.
- No anaphylactic reactions have been reported to date.
- Frequent safety reviews by independent data safety monitoring boards indicate no safety concerns.

progression, relative to placebo, in patients with progressive MS who were HLA-DR2 and/or -DR4 positive. It is currently being evaluated in two large, pivotal trials designed to determine whether or not this outcome can be replicated. The future of dirucotide is, of course, dependent on the results of these trials. If the findings in Phase III can demonstrate similar results to that seen in Phase II, MS sufferers may have a new therapeutic option with a favorable side-effect profile that might halt or significantly slow the progression of their disease. For many, the unpredictability inherent with a diagnosis of MS is the most difficult aspect of the disease. So, while the dream continues for the day when treatment will be available to reverse the damage caused by MS, a drug that can safely halt progression would be a

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huge step forward. Final analysis for the first of the two pivotal trials will take place in 2009, and for the second trial, in early 2011.

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