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# MBP-8298

*Agent for Multiple Sclerosis*

MBP(82-98)

L-Aspartyl-L-glutamyl-L-asparaginyl-L-prolyl-L-valyl-L-valyl-L-histidyl-L-phenylalanyl-L-phenylalanyl-L-lysyl-L-asparaginyl-L-isoleucyl-L-valyl-L-threonyl-L-prolyl-L-arginyl-L-threonine

$C_{92}H_{141}N_{25}O_{26}$
Mol wt: 2013.2568

CAS: 152074-97-0

EN: 306794

**Abstract**

Multiple sclerosis (MS) is a chronic autoimmune inflammatory demyelinating disorder that is estimated to affect about 2.5 million individuals worldwide. The relative risk of MS has been linked to the HLA-DR2 allele and the majority of patients with MS have been shown to have specific autoimmune mechanisms directed against myelin basic protein (MBP). The immunodominant target for both B-cells and T-cells in patients with MS and the HLA-DR2 haplotype has been identified as a region in MBP defined by amino acid residues 85-96, and this epitope is therefore an attractive target for the development of agents to restore immunological tolerance in MS. MBP-8298 is a synthetic peptide with a sequence corresponding to amino acid residues 82-98 of human MBP. MBP-8298 was chosen for further development as a treatment for MS and has been shown to effectively delay disease progression in patients with MS and the HLA-DR2 and/or HLA-DR4 haplotype.

## Synthesis

The title compound is obtained by conventional solid-phase peptide synthesis using an automatic peptide synthesis apparatus (1).

## Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system (CNS) that is estimated to affect between 250,000 and 350,000 individuals in the U.S. alone and about 2.5 million worldwide. The onset of the disorder generally occurs in early adulthood and the disease is characterized by muscle weakness, visual disturbances and neurological impairment. Acute unpredictable attacks of paralysis and visual/sensory disturbances are generally evident during the initial stages of the disease, followed by partial or full recovery. Eventually these episodes are replaced by progressive deterioration, with loss of ambulation, upper body function and autonomic function (*i.e.*, bowel and bladder control) (2-4).

MS is generally thought to be an autoimmune disease involving aberrant activation of T-cells and/or B-cells with epitope specificities that are normally excluded by self-tolerance during early development of the immune system. The disease is triggered by environmental factors (*e.g.*, Epstein-Barr virus or *Chlamydia pneumoniae* infection, smoking) in genetically susceptible individuals. The relative risk of MS has been linked to the incidence of the HLA-DR2 allele, and the majority of patients with MS have been shown to have specific autoimmune mechanisms directed against myelin basic protein (MBP). MBP binds with high affinity to HLA-DR2 and the central region of the MBP molecule in these individuals is immunodominant for MBP-specific T-cells and autoantibodies. This immune response genetic marker has been detected in approximately 50-70% of patients with MS and the HLA-DR2 haplotype, while it is only seen in about 20-30% of the general population (2, 5-9).

In MS, it is thought that MBP-reactive T-cells are responsible for production of the proinflammatory Th1 cytokines TNF-$\alpha$, IL-2 and interferon gamma, which may facilitate the myelin-destructive inflammation in the CNS characteristic of the disease. Studies have suggested that the B- and T-cell epitope of MBP defined by residues 85-96 (Pro85-Val-Val-His-Phe-Phe-Lys-Asn-Ile-Val-Thr-Pro96; $P_{85}$VVHFFKNIVT$P_{96}$) may be involved in the progression of MS in most patients, and this epitope is therefore an attractive target for the development of agents to restore immunological tolerance. Administration of this crucial MBP epitope to MS patients may induce a protective rather than a destructive response toward MBP, and MS flare-ups could be avoided (2, 7, 9, 10).

MBP-8298, or MBP(82-98), is a synthetic peptide that consists of 17 amino acids linked in a sequence identical to a portion of human MBP. The synthetic peptide is a molecular replicate of the site of attack dominant in MS patients with HLA haplotypes DR2 or DR4. The apparent

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mechanism of action of MBP-8298 is the induction or restoration of immunological tolerance with respect to ongoing immune attack at this molecular site. MBP-8298 was chosen for further development as a treatment for MS.

## Clinical Studies

The effect of intrathecal (i.t.) administration of the $P_{85}$VVHFFKNIVT$P_{96}$-containing peptides MBP(86-95) and MBP(82-98) was examined in a phase I trial in 40 patients with monosymptomatic or polysymptomatic relapses. No adverse events were reported. Those patients with monosymptomatic relapses required a dose of 50 mg daily for 4-5 days to reduce MBP-specific autoantibodies (anti-MBP) in the cerebrospinal fluid (CSF). Although doses of 50 mg daily for 4 days and 100 mg b.i.d. for 2 days effectively neutralized CSF anti-MBP antibodies in polysymptomatic patients, tolerance could not be sustained. Intravenous administration of the agents did not prevent future relapses, which were previously shown to correlate with increases in CSF anti-MBP antibody titers (11).

A phase I trial in 53 patients with chronic progressive MS examined the efficacy of peptides containing the $P_{85}$VVHFFKNIVT$P_{96}$ epitope, including MBP(82-98), MBP(75-95) and MBP(86-95), compared to an inactive control peptide, MBP(35-58), in inducing tolerance to MBP. Initial studies conducted in 8 patients revealed that only the i.v. route of administration induced tolerance to MBP, as quantified by anti-MBP autoantibodies in CSF; i.t. and s.c. injections were ineffective. No neurological or systemic adverse events were reported with any route of administration. Single i.v. injections (about 5-6 mg/kg in 50 ml saline) of the peptides containing the crucial epitope resulted in the absence of CSF anti-MBP autoantibodies for 3-4 months; a second injection prolonged tolerance to 1 year in the majority of patients. The duration of tolerance was found to be dependent on MHC class II haplotype, such that all patients with the disease-associated HLA-DR2 haplotype displayed prolonged tolerance (12).

An open-label phase I trial conducted in 56 patients with chronic progressive MS compared the kinetics of CSF anti-MBP autoantibodies for 2 years following i.v. administration of MBP-8298 (n=41) at study onset and infrequently subsequent to rises in CSF anti-MBP autoantibodies or saline (n=15; every 6 months). CSF anti-MBP autoantibodies were persistently increased throughout the 2-year period in the control group. The kinetics of CSF anti-MBP autoantibodies in patients receiving MBP-8298 fit one of four profiles: prolonged suppression to normal titers after 4 peptide injections (n=15); significant suppression to normal titers for shorter durations after 3 and 5 peptide injections (n=9 and 1, respectively); significant suppression after the initial injection followed by increases unaffected by 3 subsequent MBP-8298 injections (n=8); and no significant suppression of titers after 3 peptide injections (n=8). Results show that B-cell tolerance observed with i.v. MBP-8298 is variable among patients. This variability was speculated to be due to the absence or presence of co-existing T-cell tolerance (13).

The efficacy of MBP-8298 (50 mg i.v. every 6 months for 24 months) was examined in a double-blind, placebo-controlled phase II trial in 32 patients with progressive MS. No serious adverse events were reported and no significant differences were observed in laboratory parameters or magnetic resonance imaging (MRI) studies between treatment and placebo groups. After 24 months of treatment, no significant difference was detected in Expanded Disability Status Scale (EDSS) scores between treatment and placebo groups. However, analysis of a subgroup of 20 patients with HLA haplotype DR2 and/or DR4 revealed significant benefits for MBP-8298 over placebo (response rate = 62.5% of all patients). In addition, a significantly longer time to progression of 78 months was observed in the MBP-8298 group during the 5-year follow-up period compared to 18 months for placebo. The majority of MBP-8298-treated patients had significant reductions in CSF anti-MBP autoantibodies, although these levels did not correlate with clinical benefit (14-16).

MBP-8298 continues to undergo phase II/III development for the treatment of MS. A multicenter, randomized, double-blind, placebo-controlled phase II/III study plans to enroll 553 patients with secondary progressive MS and HLA-DR2 and/or HLA-DR4 haplotypes to examine the efficacy and safety of MBP-8298 (500 mg i.v. every 6 months for 2 years). The primary endpoint is a significant increase in time to progression according to EDSS scores. The study expects to include 453 patients in the primary study group, with 408 evaluable for efficacy (17).

## Sources

BioMS Medical Corp. (CA); licensed from the University of Alberta (CA).

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