1.0 Background on Multiple Sclerosis

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a disease characterized by multifocal areas of inflammation, demyelination, and axonal damage within the central nervous system (CNS). In the U.S., it is estimated that about 350,000 individuals suffer from MS. The cause of MS has not been established, but it is twice as common in women as in men, and more common in Caucasians than in African-Americans or Asian-Americans, suggesting that genetic susceptibility plays an important role.

The pathogenesis of MS includes autoreactivity against myelin components through activation of CD4+ T cells, with loss of normal Th1/Th2 regulatory mechanisms, production of antimyelin antibodies by B cells, and possibly inhibition of CD8+ cytotoxic/suppressor T cells.

The most common clinical symptoms of MS are paresis; paresthesia; visual impairment; sexual, bowel, and urinary dysfunction; spasticity; and incoordination. The extent of neurological deficit, the rate of progression, and the frequency of relapses (also known as exacerbations or attacks) are variable from one individual to the next. Cognitive functions are impaired in 40% to 50% of patients.

The first clinical signs of MS typically begin in young adulthood and MS rarely presents outside the age range of 20 to 50 years. About 90% of patients experience relapses and remissions. Relapses appear suddenly over a period of hours to days, and resolve over a period of days or weeks. Remissions after relapse are often incomplete. Accumulation of neurologic disability usually occurs in the context of progressive MS; therefore, conversion from relapsing-remitting to secondary progressive MS is an important event in the natural history of this disease. About 50% of patients with relapsing-remitting MS convert to a progressive course of the disease within 10 years after diagnosis.

Most patients live a normal life span marked by many years of severe progressive disability. The cause of death in patients with MS is rarely the disease itself, but may be related to respiratory or urinary tract infections.

Although all neurological deficits contribute to overall disability, ambulatory impairment is often the key factor that determines functional status. Therefore, the rating scales most commonly used in clinical trials to evaluate new treatments depend largely on ambulatory deficits to characterize overall disease severity. In 1983, Dr. Kurtzke proposed the Expanded Disability Status Scale (EDSS) to describe degrees of MS neurologic impairment. It is an ordinal scale ranging from 0.0 to 10.0, with 0.5 point increments (see Appendix A), and based largely on ambulatory impairment in its middle range (EDSS 4.5 to 7.5 points). Since the majority of patients with progressive forms of MS fall in the middle range, this scale has been widely used in clinical trials. Other scales have been developed, but the EDSS scale remains the most commonly used in clinical trials.

Overall response to treatment in clinical trials has been assessed using various endpoints, including the effect on one or more disability scales, relapse rate and time to relapse, and proportion of patients free of relapse. Composite indices using multiple efficacy endpoints have been proposed but have not been uniformly adopted.

Prior to 1996, numerous terms were used to describe the clinical forms of MS, which led to difficulty in comparing the results from different clinical trials. In 1996, a consensus classification of MS recognized four disease categories, as shown in the table that follows.

Clinical Disease Categories in Multiple Sclerosis*

Disease category	Definition
Relapsing-remitting	Episodes of acute relapse followed by complete or incomplete recovery and a stable course between relapses.
Secondary progressive	Gradual neurologic deterioration with or without relapses in a patient who previously had relapsing-remitting MS.
Primary progressive	Gradual, nearly continuous neurologic deterioration from the onset of symptoms.
Progressive relapsing	Gradual neurologic deterioration from the onset of symptoms but with subsequent superimposed relapses.

* Adapted from Lublin FD, Reingold SC. Neurology 1996;46:907-911.

This classification is now widely used in designing clinical trials. However, in cases in which patients were diagnosed prior to 1996, it is sometimes difficult to retrospectively assign a patient to a specific category.

1.2 Current Therapies in Multiple Sclerosis

Current therapies are based on the hypothesis that MS is an organ-specific autoimmune disease. Most agents act as immunosuppressors and/or immunomodulators. Specific therapies aimed at repairing myelin and axonal damage are under investigation.

1.2.1 Corticosteroids

Corticosteroids are the mainstay treatment for acute relapses. Corticosteroids have immunomodulatory and anti-inflammatory effects that decrease the blood-brain barrier permeability, reduce edema, and possibly improve axonal conduction. Corticosteroids shorten the duration of a relapse but do not generally affect the degree of recovery. Methylprednisolone is usually given intravenously (IV) at a daily dose of 500 to 1000 mg for 3 to 5 days.

1.2.2 Interferon Beta

Two forms of recombinant interferon beta, beta-1a and beta-1b, have been approved in the U.S. for the treatment of patients with relapsing-remitting MS. The mechanism of action of interferon beta in MS is not well understood, but may include its antiproliferative effects on T cells, decreased expression of major histocompatibility complex (MHC) class II antigens, and other immunoregulatory properties. The interferons beta were shown to reduce the relapse rate of about 30% of patients with relapsing-remitting MS with mild to moderate disability. Interferon beta-1b was shown to induce a major reduction in gadolinium (Gd)-enhancing lesions on magnetic resonance imaging (MRI) scans. Interferon beta1a was also shown to reduce the rate of EDSS progression by about 30% in relapsing-remitting MS.

Depending on its type, interferon beta is given by subcutaneous or intramuscular administration once or three times a week. Interferon beta is associated with various adverse events, including influenza-like symptoms, injection site reactions, serum aminotransferase elevation, and depression. Neutralizing antibodies have been reported in 5% to 40% of patients by the third year of treatment and may lead to decreased efficacy.

1.2.3 Glatiramer Acetate

Glatiramer acetate is also approved in the U.S. for the treatment of patients with relapsing-remitting MS. Glatiramer acetate, a complex of synthetic peptides resembling myelin basic proteins, was shown to reduce the annualized rate of relapse by about 30% in patients with relapsing-remitting MS. Glatiramer acetate is given daily by SC injection. The most common side effect associated with glatiramer acetate is injection site reaction, which has been reported in up to 90% of patients. Other uncommon adverse events include flushing, chest tightness, shortness of breath, palpitations, and anxiety.

1.2.4 Immunosuppressive Chemotherapy

Clinical trials with methotrexate, azathioprine, cyclophosphamide, and cladribine have been reported in patients with severe relapsing-remitting or progressive MS. These antiproliferative immunosuppressive agents are usually reserved for patients who have failed interferon beta or glatiramer acetate treatment. The benefit/risk ratio of these agents remains unclear since few well-controlled, adequately powered, long-term studies have been done and the results of these studies have been conflicting.

1.2.5 Summary of Current Therapies in MS

Currently there are no approved therapies in the U.S. for the treatment of patients with secondary progressive MS. Furthermore, some patients with relapsing-remitting disease either do not respond to approved therapies or progress after initial response. The current