MIS416 in Patients with Multiple Sclerosis: A novel immunomodulator

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Background: Multiple sclerosis (MS) has both autoimmune and inflammatory components that disease may reflect a shift towards innate inflammation being a significant cause of continuing neurodegeneration. Activation of innate pattern recognition receptors (PRR) has been implicated in both the pathogenesis as well as the regulation of multiple sclerosis (MS). MIS416 is a myeloid targeted therapy, consisting of a micro-particulate formulation of gram positive Propionibacterium acnes bacteria, which have been biochemically modified to retain the bacterial DNA within the bacterial cell wall skeleton as a source of naturally occurring toll-like receptor-9 (TLR-9) and nucleotide oligomerization domain-2 (NOD-2) immune stimulatory ligands. MIS416 activate a series of signal transduction pathways follow which lead to activation of inflammatory pathways involving macrophages, Natural Killer (NK) and NKT cells, dendritic cells and monocytes. However, it has a modulatory effect on these pathways and induces activation of a wide range of tumoricidal pathways like those involving members of the Tumor Necrosis Factor (TNF) family, such as Fas, TRAIL (TNF-Related Apoptosis Inducing Ligand) and TNF-alpha. These pathways correlate with the production of NFkB-dependant inflammatory cytokines which act locally and modulate a range of different immune responses. So MIS416 can target both the regulatory functions and the defensive (pathogenic) functions of the innate immune system. The studies have investigated the effect MIS415 in SPMS and PPMS. MIS416 administration at 500 mg/week is generally well tolerated in this patient group. The nature of the most common adverse effect (i.e., pyrexia, headache, fatigue, weakness, transaminase elevations, myalgia and muscle stiffness) is consistent with the known mechanism of action of MIS416, indicating likely uptake by the reticuloendothelial system and subsequent activation of signal transduction pathways. The severity and frequency of side effects diminish

with repeat dosing, indicating a potential development of tolerance to exposure.

Conclusion: Although studies were not demonstrated efficacy of MIS416 in patients but no progression or exacerbations of disease state were observed over the course of the studies. It is recommended that efficacy of MIS416 is investigated further in a larger studies.

Key words: Multiple Sclerosis, MIS416, immunomodulator