NEUROASPIS® Plp10 The Novel Nutraceutical Intervention as an Adjuvant Treatment for Multiple Sclerosis

“The polyunsaturated fatty acid (PUFA) composition of membrane phospholipids plays an important role in immune-related and non-immune-related inflammation. PUFA and antioxidant deficiencies, along with decreased cellular antioxidant defense mechanisms, have been reported in MS patients. Increased or uncontrolled inflammation contributes to several different acute and chronic diseases, and it is characterized by the production of inflammatory cytokines, arachidonic acid (AA)-derived eicosanoids (prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs) and other oxidized derivatives), and other inflammatory agents such as reactive oxygen species (ROS), nitric oxide (NO) and adhesion molecules. During inflammation, glutamate homeostasis is altered by the release of increased quantities of glutamate by activated immune cells, which can result in the over activation of glutamate receptors and, in turn, excitotoxic oligodendroglial death[1]. In vitro and in vivo studies have demonstrated that dietary eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), linoleic acid (LA) and γ-linolenic acid (GLA) can be implicated and modulate almost all known complex networks of events and pathways in MS pathophysiology. The brain membrane fatty acid composition can be modified with dietary supplementation, but the process has been shown to be age dependent (taking much longer in adults’ vs developing brains) and possibly dependent on the quantity of the dietary/supplemented PUFAs[2].

The anti-inflammatory properties of Ω-3 PUFAs include the production of PGs and TXs of the 3-series and of LTs of the 5-series. Resolvins and protectins are biosynthesized from Ω-3 fatty acids via cyclooxygenase-2/lipoxygenase (COX-2/LOX) pathways, and they promote the control of inflammation in neural tissues. T-cell proliferation in acute and chronic inflammation can also be reduced by supplementation with either Ω-6 or Ω-3 PUFAs[1]. Furthermore, vitamin E is an important antioxidant that can interrupt the propagation of free radical chain reactions. Specifically, vitamin E (α-tocopherol, an isoform of vitamin E) efficiently detoxifies hydroxyl, perhydroxyl and superoxide free radicals, whereas γ-tocopherol (another isoform of vitamin E) appears to be more efficiently implicated in trapping NO radicals[3]. In addition, α-tocopherol exerts non-antioxidant properties, including the modulation of cell signaling and immune functions, regulation of transcription and induction of apoptosis. Moreover, Ω-3 fatty acid electrophilic derivatives formed by COX-2 in activated macrophages can stimulate the nuclear respiratory factor (Nrf), which induces the transcription of neuroprotective and antioxidant-related genes and can activate the peroxisome proliferator-activated receptor γ (PPARγ) for an anti-inflammatory response. In animal studies, EPA and DHA have proved to be endogenous ligands of the retinoid X receptor (RXR), with

positive effects on neurogenesis[1]. Additionally, in 2008, Salvati, et al. reported evidence of accelerated myelination in DHA-treated and EPA-treated animals[4]. Moreover, DHA and EPA have been reported to significantly decrease the levels of metalloproteinases (MMP)-2, MMP-3, MMP-9 and MMP-13, which have a significant role in the migration of lymphocytes into the central nervous system by inducing the disruption of the blood brain barrier, an important step in the formation of MS lesions.

Based on the aforementioned observations, specific PU-FAs and antioxidant vitamins fulfil the criterion of biological plausibility and have the potential to diminish the severity and activity of MS symptoms, potentially even promoting recovery (remyelination).

Neuroaspis® PLP10 represents a formulation consisting of EPA/DHA Ω-3, LA/GLA Ω-6 PUFA, other structured molecules as MUFA and reactive oxygen/nitrogen species (ROS/RNS) antioxidants; tested on relapsing remitting MS patients (Phase II and an ongoing Phase III).

We contacted a 30-month randomized, double-blind, placebo-controlled, proof-of-concept clinical study at the Cyprus Institute of Neurology and Genetics with 20 patients randomly assigned to receive PLP10 and 20 placebo. PLP10 treatment significantly reduced the ARR by 72%, and the risk of sustained disability progression by 86% compared to placebo when patients on natalizumab were excluded; and without any adverse or significant side effects[5]. The red blood cell lipid profile was supportive to the reported PLP10 efficacy by the statistically significant increased quantitative content of the supplemented PUFA as well as by the increased significant release of arachidonic acid (inflammation initiator molecule) when γ-tocopherol was present; supporting the synergistic theory of all PLP10 ingredients for activity.

This is the first nutrient formula that holds strong promise as an effective adjuvant treatment for RRMS.

**BIBLIOGRAPHY**