

The *in vitro* and clinical effects of RT001 in progressive supranuclear palsy (PSP) were reported at the Rare Diseases and Orphan Products Breakthrough Summit 2020 based on research led at the University College London and the California Movement Disorders Center.

Lipid peroxidation (LPO) is a chemical reaction that liberates reactive oxygen species (ROS). These compounds are known to be elevated in PSP, and are considered to be important in the pathophysiology of the disease. PSP is associated with accumulations of intracellular tau protein. Excess ROS may modify tau, reducing its solubility and clearance in PSP. RT001 is deuterium-stabilized linoleic acid in drug form, that prevents ROS and LPO. In the current series of studies, researchers derived mesenchymal stem cells from 3 patients with PSP, treated them with RT001, and compared these effects to cells derived from normal subjects with PSP. The effects of this treatment on LPO, ROS, glutathione, mitochondrial number, structure and membrane potential (MMP) were measured before and after RT001 incubation. In parallel with the *in vitro* studies, the 3 PSP patients were treated with RT001 2.88g BID for up to 18 months and they were assessed with serial clinical evaluations.

Increased LPO and ROS with lower baseline glutathione levels were seen in the PSP MSCs compared to controls. These levels were restored to control levels after a 72-hr incubation with RT001. Similar restorative effects were seen in the MMP, the number of mitochondria, and their structure.

During the 18-month patient treatment period, scores in the widely accepted PSP Rating Scale (PSP-RS) and the Unified Parkinson's Disease Rating Scale (UPDRS) were determined every 3 months. The slopes of these scores were compared to those obtained from disease progression predicted by large natural history studies of PSP. The slope of the PSP-RS changed from the historical decline of 0.91 points/month to a mean of decline of 0.05 points/month (+/- 0.51) indicating a halting of progression. The UPDRS slope changed from an expected decline of 0.95 points/month to an average increase in score of 0.33 points/month (+/- 0.48), indicating a potential reversal of progression. Mean plasma and RBC membrane levels of drug were 21% and 19% of total linoleic acid. Importantly, levels of di-deuterated arachidonic acid (D2-AA) in both plasma and RBC also increased, indicating normal enzymatic processing of the stabilized LA into stabilized AA.

The researchers concluded that incubation of MSCs derived from PSP patients with RT001 reduces baseline elevations in LPO and improves mitochondrial function. These findings are correlated with a reduction in long-term clinical progression of disease when PSP patients are treated with RT001 as measured by 2 different validated scales. The beneficial clinical effects observed in PSP patients treated with RT001 and predicted by *in vitro* testing of PSP-MSCs will be evaluated in a Phase 2 clinical trial of PSP patients in Europe which has been initiated, and thereafter, an already FDA approved Phase 3 clinical trial in the US.