

## **Magnetic Resonance Spectroscopy Evaluation of Neuronal Integrity and Astrocytosis in a Phase 2 Study of Laquinimod as a Treatment for Huntington Disease (LEGATO-HD)**

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**Objective:** Evaluate the effect of laquinimod on putaminal and frontal white matter markers of neuronal integrity and astrocytosis using magnetic resonance spectroscopy (MRS) in patients with early Huntington disease (HD).

**Background:** MRS studies in HD indicated decreased putaminal concentrations of the neuronal marker, N-acetyl aspartate (NAA) between controls, premanifest HD, and early HD patients. The concentration of Myo-inositol (ml), a glial cell marker in the putamen, was increased in early HD vs premanifest HD and controls. Laquinimod, which is assumed to modulate inflammatory pathways involved in HD pathology, was evaluated in LEGATO-HD. This Phase 2 study did not meet its primary endpoint of change from baseline in UHDRS-TMS scores, but met its secondary endpoint of benefit in change from baseline in caudate volume loss. The present report describes an ancillary study evaluating the effects of laquinimod on MRS in LEGATO-HD.

**Methods:** MRS scans were performed in 36 patients at baseline and week 52. Spectra were obtained using single-voxel PRESS sequences in left putamen and frontal white matter for: total NAA (neuronal integrity), ml (astrocytosis), total creatine (tCr, brain energy metabolism), total choline (tCho, neuronal membrane turnover), and glutamate (a major CNS excitatory neurotransmitter) + glutamine (Glx).

**Results:** In the putamen, [ml] was nominally significantly decreased in laquinimod-treated patients vs. placebo ( $p < 0.05$ ) at 52 weeks. There were no significant changes in laquinimod-treated groups vs. placebo for [tNAA], [tCr], [tCho], and [Glx] in putamen or for any frontal white matter parameters.

**Conclusions:** The reduction in the glial cell metabolite ml in the putamen of early HD patients taking laquinimod compared to the increased ml levels of HD patients in the placebo group over 52 weeks suggests that laquinimod treatment decreases astrocytosis and gliosis, consistent with its known in vitro and in vivo effects on neuroinflammation.