24 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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BACKGROUND

- Previous magnetic resonance spectroscopy (MRS) studies in Huntington disease (HD) indicate decreased putaminal concentrations of the neuronal marker, N-acetyl aspartate (NAA), between controls, premanifest HD, and early HD patients.[1-3]
- 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 the LEGATO-HD study.
- While the LEGATO-HD study did not meet its primary endpoint of change from baseline in UHDRS-TMS scores, it met its secondary endpoint of a change from baseline in caudate volume loss.
- The present report describes a sub-study of the LEGATO-HD study evaluating the effects of laquinimod on MRS.

OBJECTIVE

- Evaluate the effect of laquinimod on putaminal and frontal white matter markers of neuronal integrity and astrocytosis using MRS in patients with early HD.

METHODS

- Eligible participants from selected LEGATO-HD sites included men and women (aged 21-55 years) with adult onset HD.
- MRS scans were performed on 3T scanners in patients at baseline and week 52.
- Two voxels of interest in the putamen (5.25mL) and a frontal white matter region (2.25mL) using a PRESS sequence (TE=35ms, TR=2000ms and NSA=128) using the same protocol that was used in the MRS study for the TRACK-HD study and its extension[1-3] (see **Fig 1a and 1b**).
- The MRS results were analyzed at the UBC site using LCModel (Version 6.3-0L)[4] and poor quality spectra were rejected.
- Metabolite concentrations were derived for N-acetyl aspartate (NAA, a marker of neuronal integrity), tNAA (NAA & N-acetyl aspartyl glutamate); Creatine (Cr, a marker of brain energy metabolism), total Choline (tCho, a marker for neuronal membrane turnover), Glutamate (Glu, an CNS excitatory neurotransmitter), Glx (pooled Glutamate and Glutamine) and Myo-inositol (mI, an astrocyte marker) using an internal water standard (NSA=16) and assumed tissue water content.
- Mean metabolite concentrations were compared between placebo and each laquinimod dose group using an ANCOVA with treatment, site continent (North America or Europe), and baseline value as fixed effects.
- As no adjustment for multiplicity was defined for this ancillary study, the analysis results are presented with nominal p-values and cannot be interpreted inferentially.

RESULTS

Table 1. Patient Demographics

Characteristics**	Placebo (n = 18)	LAQ 0.5 mg (n = 19)	LAQ 1.0 mg (n = 15)
Age	45.6 (6.8)	45.7 (6.3)	47.1 (6.1)
Sex, Male, n (%)	9.0 (50.0)	11.0 (58.0)	9.0 (60.0)
Weight kg	76.2 (18.4)	73.5 (15.1)	70.0 (13.8)
Height cm	170.5 (12.6)	171.4 (9.7)	172.8 (9.7)
BMI kg/m^2	26.1 (5.1)	24.9 (4.0)	23.3 (3.0)
Number of CAG repeats	43.8 (2.9)	43.9 (1.5)	43.6 (1.6)
Months from HD diagnosis	33.8 (25.1)	60.5 (49.5)	67.6 (72.9)
Months from first HD symptoms	53.6 (33.7)	58.1 (44.3)	83.5 (60.1)
UHDRS-TMS	22.2 (11.6)	24.5 (12.9)	25.6 (12.8)
UHDRS-Total Functional Capacity (TFC)	11.8 (1.5)	11.2 (1.6)	11.0 (1.5)
TFC subgroups, n (%)			
TFC ≤ 10	2 (11)	8 (42)	4 (27)
TFC 11-13	16 (89)	11 (58)	11 (73)

**mean (SD) unless otherwise specified

Fig 1a. Sample Voxel Placement in Left Putamen

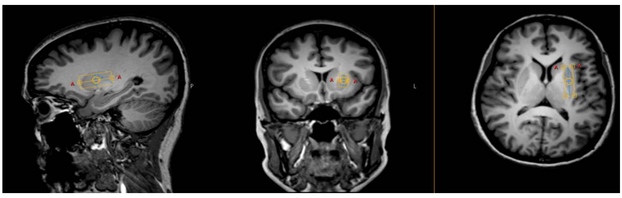
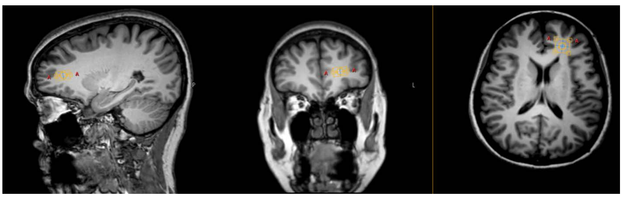


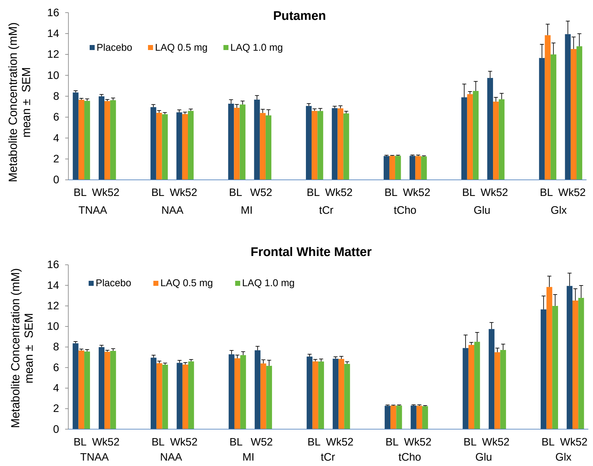
Fig 1b. Sample Voxel Placement in Left Frontal White Matter

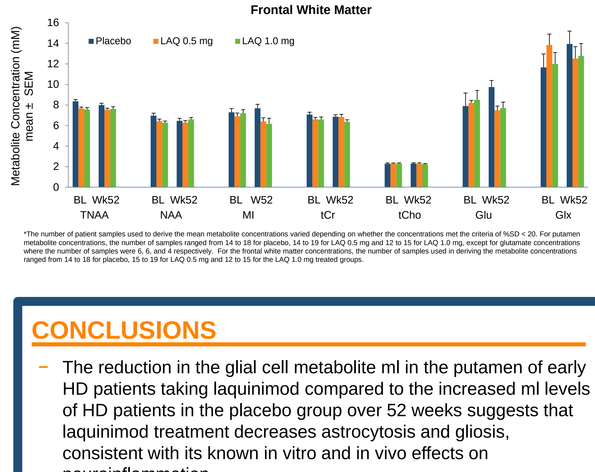


Metabolite Concentrations

- In the putamen, [ml] was nominally significantly decreased from baseline in patients treated with laquinimod 0.5 mg and 1.0 mg (LS mean difference = -1.01 p = 0.0464 and -1.43, p = 0.0117, respectively) at 52 weeks, compared to placebo-treated patients.
- 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.

Fig 2. Metabolite Concentrations





*The number of patient samples used to derive the mean metabolite concentrations varied depending on whether the concentrations met the criteria of %SD < 20. For putamen metabolite concentrations, the number of samples ranged from 14 to 18 for placebo, 14 to 19 for LAQ 0.5 mg and 12 to 15 for LAQ 1.0 mg, except for glutamate concentrations where the number of samples were 6, 6, and 4 respectively. For the frontal white matter concentrations, the number of samples used in deriving the metabolite concentrations ranged from 14 to 18 for placebo, 15 to 19 for LAQ 0.5 mg and 12 to 15 for the LAQ 1.0 mg treated groups.

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.

References

1. Sturrock A, et al. Neurology 2010; 75; 1702-1710.
2. Tabrizi SJ, et al. Lancet Neurology 2013;12: 637-649.
3. Sturrock A, et al. Movement Disorder 2015; 30: 393-401.
4. Provencher SW. MRM. 1993; 30: 672-679.

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