43 Brain MRI Volume Changes after 12 months laquinimod treatment of Huntington disease (LEGATO-HD)

Ralf Reilmann[1], Mark Forrest Gordon[2], Karen E. Anderson[3], Andrew Feigin[4], Sarah J. Tabrizi[5], Blair R. Leavitt[6], Julie C. Stout[7], Paola Piccini[8], Nicola Hobbs,[9] Richard Manber,[9] Beth Borowsky[2], Gail Rynkowski[2], Rita Volkinshtein[2], Juha-Matti Savola[2] and Michael Hayden[2]

[1]George-Huntington-Institute, [2]Teva Pharmaceuticals, [3]MedStar Georgetown University Hospital & Georgetown University Medical Center, [4]NYU Langone Health, [5]UCL Institute of Neurology, [6]University of British Columbia, [7]Monash University, [8]Imperial College, [9]IXICO plc, London

BACKGROUND and OBJECTIVE

- Volume loss in caudate and other brain regions is a hallmark of Huntington disease (HD) pathology and has been shown to correlate with motor and clinical outcomes in HD studies.[1]
- Laquinimod shows improvement in HD animal models including rescue of striatal and callosal atrophy.[2]
- In the phase 2 LEGATO-HD study, the primary endpoint of change from baseline at week 52 of treatment in UHDRS-TMS scores was not met.
- The present report explores the effect of laquinimod on its secondary endpoint (EP) of percent change from baseline in caudate volume (CV), MRI exploratory EPs and subgroup analyses (all preplanned).

METHODS

- Brain MRI was used to assess the change from baseline to week 52 in volume of certain regions, including the caudate, whole brain, white-matter and ventricles using methods described for the TRACK-HD study.
- Patients underwent 3 Tesla MRI at baseline and week 52 following unaccelerated volumetric T1 weighted acquisition protocols developed during the ADNI study (www.adni-info.org).
- Briefly, the change in whole-brain, caudate and ventricular volume were calculated using the Boundary Shift Integral (BSI) technique and MIDAS software. Within-subject scan pairs were registered with 12 degrees of freedom and changes in whole-brain volume, caudate volume and ventricular volume were estimated with Brain BSI, caudate BSI and Ventricular BSI, respectively.
- White-matter volume changes were estimated using a fluid registration approach which generates voxel-compression maps for each participant and is convolved with baseline white-matter segmentation (SPM8) to provide an estimate of white-matter volume change.
- All segmentation and registrations were checked by trained analysts to ensure accuracy.
- Longitudinal change in caudate, whole-brain and white-matter volume were expressed as a percentage of their baseline value. Longitudinal change in ventricular volume was expressed in absolute terms (ml).
- MRI measurements after 6 months on study and out of the window ± 7 days from day 365 were annualized assuming linear change with time.
- For the primary endpoint of TMS and secondary endpoint, statistical analyses were tested using a fallback with loop-back approach to preserve the Type 1 error rate of 5%. As the primary endpoint was not met in the LEGATO-HD study, the secondary endpoint, change in caudate volume from baseline to week 52 for the laquinimod 1.0 mg group was tested with a two sided alpha of 0.005. The remaining statistical tests were conducted at a nominal 0.05 level.
- Subgroup analyses were performed for the secondary endpoint, the change from baseline in caudate volume by sex, median values of TMS, TFC and caudate volume, CAG repeat length and study region (USA vs outside of USA).

RESULTS

Patient Disposition and Demographics

- LEGATO-HD was fully enrolled with 352 patients participating at 48 sites in 10 countries.
- 286 patients completed treatment and 65 terminated early.
- Baseline demographics were well balanced across treatment groups. Patients enrolled were in early stage HD.

Table 1. Patient baseline characteristics*

	Placebo (n = 108)	LAQ 0.5 mg (n = 107)	LAQ 1.0 mg (n = 107)
Age, years	43.8 (7.8)	43.3 (7.8)	44.0 (7.8)
Sex, n (%) males	52 (48%)	55 (51%)	53 (50%)
CAG repeats	44.2 (2.4)	44.4 (2.5)	44.0 (2.2)
Months from HD diagnosis	32.3 (31.9)	45.8 (42.0)	41.5 (50.3)
Months from onset of HD symptoms	52.7 (43.6)	60.9 (43.0)	57.8 (51.1)
Caudate volume (mL)**	6.1 (1.8)	5.8 (1.8)	6.0 (1.8)
Whole-brain volume (mL)**	1352.7 (135.7)	1356.6 (162.8)	1354.9 (134.9)
White-matter volume (mL)**	569.9 (59.2)	564.1 (68.3)	561.7 (57.6)
Ventricular volume (mL)**	35.1 (22.9)	34.6 (16.9)	31.6 (15.4)

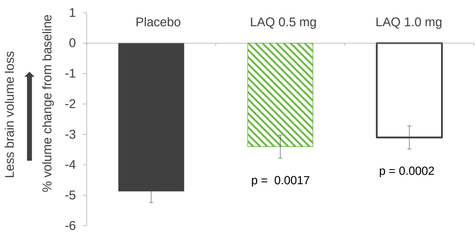
*ITT cohort, values are mean (SD) unless otherwise specified
**Brain regional volumes are normalized by dividing the volume region by the Pseudo Total Intracranial volume (pTIV) factor.

RESULTS

Secondary Endpoint : Change in Caudate Volume

- For the secondary endpoint, patients treated with laquinimod 1.0 mg showed reduced CV loss from baseline to week 52 compared to placebo-treated patients (p = 0.0002, **Fig 1**).

Fig 1 vMRI % Caudate volume loss (annualized)

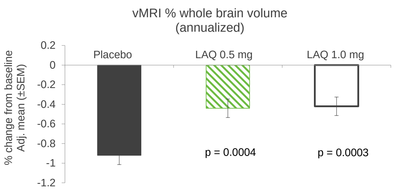


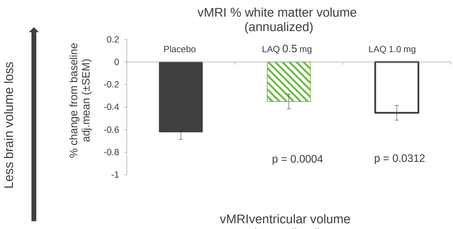
	Placebo	LAQ 0.5 mg	LAQ 1.0 mg
N	106	103	100
Baseline*	6.06	5.78	6.03
Δ to placebo		-1.47	-1.76
p value		0.0017	0.0002

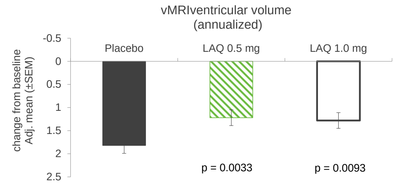
All efficacy analyses were performed on the FAS set and a Fallback with Loop-back approach to control Type 1 error was applied. As the primary endpoint failed to reach significance, the secondary endpoint, change in caudate volume was tested at a 2-sided alpha level of 0.005. *Normalized baseline volume (in milliliters) is calculated by dividing the caudate volume by Pseudo Total Intracranial Volume (pTIV) factor.

Exploratory Endpoints

- All exploratory volumetric data showed consistent treatment effects on brain volume loss at week 52 for laquinimod 0.5 mg and 1.0 mg doses.







Subgroup analyses

- Preplanned subgroup analysis of caudate volume revealed that all subgroups showed a positive response to laquinimod doses 0.5 mg and 1.0 mg compared to placebo treatment (all p < 0.0514).

CONCLUSIONS

- The secondary endpoint of LEGATO-HD, the change in caudate volume for 1 mg laquinimod group, was met.
- Consistency was seen in lessening of volume loss across other brain structures assessed in both the 0.5 and 1.0 mg laquinimod treated arms compared to placebo, and across all preplanned subgroups.
- Based on the TRACK-HD observational study, approximately 3% of caudate volume loss was expected in 52 weeks, however, we observed 4.9% loss of caudate volume in the placebo arm.
- The reduction of brain volume loss in the laquinimod groups did not correlate with improvements in the primary endpoint, UHDRS-Total Motor Score (UHDRS-TMS) and other clinical outcomes.
- However, improvements in some quantitative motor (Q-Motor) assessments of speeded hand tapping (digitomotography) were observed – see MDS Poster 44.

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