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Legato-HD Study: A Phase 2 Study Assessing the Efficacy and Safety of Laquinimod as a Treatment for Huntington Disease

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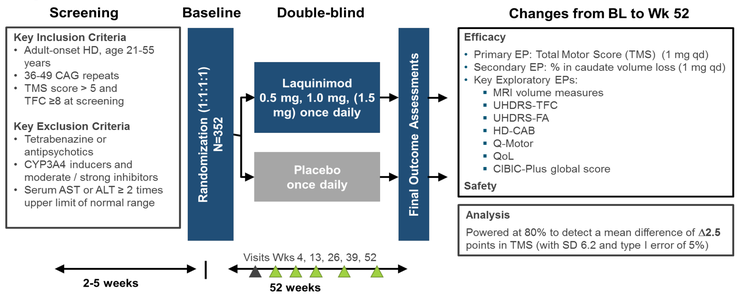
BACKGROUND AND OBJECTIVES

- In Huntington disease (HD), immune-mediated CNS inflammation involving microglial and astrocytic activation, elevated inflammatory cytokines, increased NF_KB activity and low levels of BDNF gene transcription are associated with progressive neuronal dysfunction and striatal degeneration.[1]
- Laquinimod is an orally active, CNS immunomodulator that downregulates inflammatory monocytic, microglial and astrocytic activation, suppresses NF_KB activation and upregulates BDNF,[2] all implicated in the pathological processes in HD.
- The LEGATO-HD study originally included three dose arms, 0.5 mg, 1.0 mg and 1.5 mg versus placebo in a 12-month multicenter double blind phase 2 study in patients with HD. Cardiovascular safety concerns were observed in multiple sclerosis studies with laquinimod doses of 1.2 mg and 1.5 mg. Although no similar concern was identified in LEGATO-HD, Teva discontinued the 1.5 mg arm in January 2016 as a precautionary safety measure and continued to evaluate the efficacy and safety of the 0.5 mg and 1.0 mg doses.

METHODS

Patient Screening Criteria and Study Design

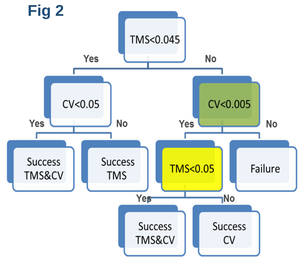
Fig 1



Statistical Method

- Fallback method with the loop-back feature[3] was selected to test the primary and secondary endpoints while preserving the experiment-wise type I error rate of 5%
  - Alpha is split between the endpoints of interest:
    0.9*0.05=0.045 for TMS
    0.1*0.05=0.005 for Caudate volume (CV)
  - Hypothesis testing starts with the TMS tested at alpha of 0.045 and if successful, the CV hypothesis will be tested at the level of 0.05 ("full alpha")
  - If the TMS is not successful, CV hypothesis has chance of being successfully tested at alpha of 0.005
  - If the TMS hypothesis fails at alpha of 0.045, and the CV hypothesis is successful at alpha of 0.005, the TMS hypothesis can be retested at alpha 0.05 ("loop-back ").
  - Fig 2 depicts hypotheses testing, where the green and the yellow boxes represent the fallback and the "looped back" alpha paths.
  - No multiplicity control was applied for the exploratory endpoints

Fig 2



RESULTS

Patient Disposition and Demographics

- LEGATO-HD was fully enrolled with 352 patients participating at 48 sites in 10 countries
- 286 patients completed and 65 terminated early (including 30 who discontinued from the 1.5 mg dose arm)
- Baseline demographics were well balanced across treatment groups
- Patients enrolled were in early stage HD.

Safety: Laquinimod was safe and well-tolerated in this early HD population

- No new safety signal was identified related to laquinimod
- There was no reported event of ischemic heart disease (Tables 1 and 2)
- There were no consistent shifts from baseline in suicidal behavior or suicidal ideation related to treatment

Table 1. Summary of adverse events*

	Placebo N=108 PY=103	LAQ 0.5 mg N=107 PY=95	LAQ 1.0 mg N=106 PY=98	LAQ 1.5 mg N=29 PY=10
All AEs	83 (77) 309.4	89 (83) 374.6	75 (71) 362.4	22 (76) 959.5
AEs leading to discontinuations	6 (6) 6.8	6 (6) 6.3	9 (8) 14.3	3 (10) 56.4
Serious AEs	8 (7) 9.7	7 (7) 12.6	5 (5) 7.1	1 (3) 9.4
Related (by investigator) AEs	24 (22) 43.5	46 (43) 107.0	36 (34) 75.3	12 (41) 225.8

*n (%) Event rate per 100 patient-years (PY)

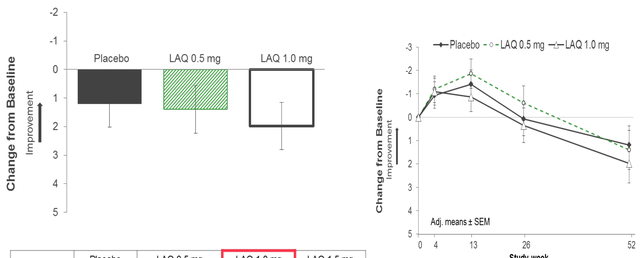
Table 2. Cardiovascular adverse events

Preferred Term	Placebo N=108 PY=103	LAQ 0.5 mg N=107 PY=95	LAQ 1.0 mg N=106 PY=98	LAQ 1.5 mg N=29 PY=10
Atrioventricular block first degree	0	0	0	1 (3) 9.4
Defect conduction intraventricular	0	0	0	1 (3) 9.4
Left ventricular hypertrophy	0	0	1 (1) 1.0	
Sinus tachycardia	0	0	1 (1) 1.0	0
Tachycardia	0	0	3 (3) 3.1	0

n (%) Event rate per 100 patient-years (PY)

Efficacy: Primary endpoint UHDRS-TMS was not met but secondary endpoint % change in caudate volume loss was met

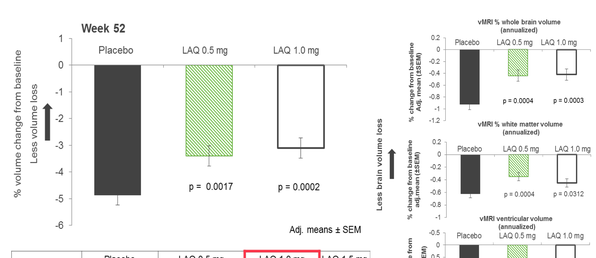
Fig 3. Primary endpoint UHDRS-Total Motor Score



	Placebo	LAQ 0.5 mg	LAQ 1.0 mg	LAQ 1.5 mg
N	108	107	104	27
Baseline	26.4	24	22.1	26.7
Δ to placebo		0.2	0.78	n/a
p value		0.8543	0.4853	

	0	4	13	26	52
Placebo	108	107	106	104	98
LAQ 0.5 mg	107	107	99	97	92
LAQ 1.0 mg	104	104	100	99	95

Fig 4. Secondary endpoint % Caudate volume loss and Exploratory MRI endpoints



	Placebo	LAQ 0.5 mg	LAQ 1.0 mg	LAQ 1.5 mg
N	106	103	100	25
Baseline	6.06	5.78	6.03	5.43
Δ to placebo		-1.47	-1.76	n/a
p value		0.0017	0.0002	

UHDRS-Total Motor Score

- Scale assesses eye movements, speech, alternating hand movements, dystonia, chorea, and gait
- Based on the mechanisms of action of laquinimod, we expected less decline in motor or other features compared to placebo, but no improvement of symptoms.
- Based on a historical observational study, we expected TMS worsening by ~3 units in 52 weeks
- In LEGATO-HD, TMS in placebo arm worsened only 1.2 units in 52 weeks
- Preplanned subgroup analysis of TMS did not reveal a particular subgroup that showed a response to laquinimod

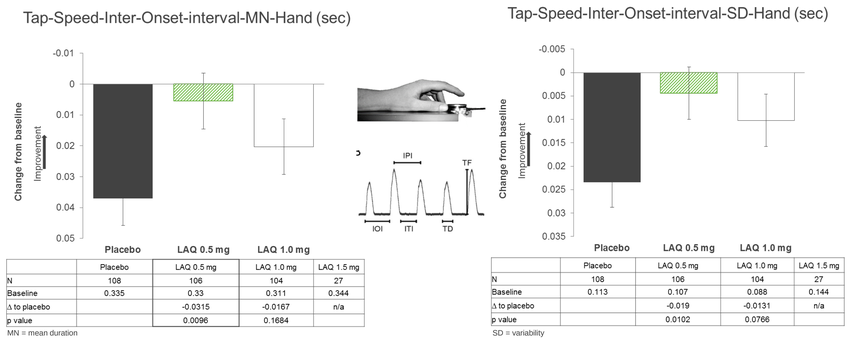
Percent change in caudate volume loss

- Volume loss in caudate and other brain regions (white matter, grey matter and whole brain) is hallmark of HD pathology
- Caudate volume is a sensitive biomarker in very early HD
- Caudate volume loss correlates with disease progression
- Caudate volume loss correlates strongly with motor and other clinical outcomes in long-term observational studies
- Based on a historical observational study, ~3 % caudate volume loss was expected in 52 weeks. In LEGATO-HD, caudate volume loss of 4.9% was observed in the placebo arm
- The other volumetric MRI data (white matter and whole brain; ventricular volume) showed consistent and strong treatment effect (both doses) in reduction of brain volume loss in 52 weeks

Efficacy: Exploratory Endpoints: no treatment effects in rater-dependent outcome measures, effects shown for Q-Motor

- There were no treatment effects seen in rater-dependent outcomes for functional capacity (UHDRS-TFC, UHDRS-FA, mPPT), clinical global impression (CIBIC-Plus), psychiatric (PBA-S, HADs), cognitive (HD-CAB, CDR-SB), and quality of life (HD-QoL, EQ-5D-5L, WLQ) assessments.
- Q-Motor measures are sensitive, standardized, rater-independent, unbiased, and correlated with caudate volume loss in HD biomarker studies (TRACK-HD, TRACK-ON-HD).[4]
- As illustrated in Fig. 5, Q-Motor revealed nominally significant improvements in tapping measures in the 0.5 mg group and positive trends for 1 mg group, compared to placebo.
- As in previous studies, all Q-Motor measures worsened in the placebo group and no placebo effects were seen in Q-Motor measures.

Fig 5. Quantitative Motor (Q-Motor) Assessment



	Placebo	LAQ 0.5 mg	LAQ 1.0 mg	LAQ 1.5 mg
N	108	106	104	27
Baseline	0.335	0.33	0.311	0.344
Δ to placebo		-0.0315	-0.0167	n/a
p value		0.0096	0.1684	

MN = mean duration

	Placebo	LAQ 0.5 mg	LAQ 1.0 mg	LAQ 1.5 mg
N	108	106	104	27
Baseline	0.113	0.107	0.088	0.144
Δ to placebo		-0.019	-0.0131	n/a
p value		0.0102	0.0766	

SD = variability

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CONCLUSIONS

- In this placebo-controlled study of patients with early HD, laquinimod treatment showed no evidence of improved rater-dependent clinical outcomes, whereas laquinimod treatment demonstrated a statistically significant reduction in volume loss in caudate for the 1 mg dose, and nominally significant reduction in volume loss in caudate for the 0.5 mg dose and in whole brain and white matter for both doses.
- Q-Motor measures suggest a nominal effect of laquinimod on motor coordination congruent with less decline in motor signs based on progression signals known from studies such as TRACK-HD [4] and PRIDE-HD.[5]
- Jointly, the treatment effects on MRI brain volume and Q-Motor measures suggest a central effect of laquinimod in LEGATO-HD of unknown clinical significance.
- The lack of clinical effect could be due to possible confounders such as the relatively short treatment period of 52 weeks and rater biases in clinical scales.
- Analysis of MRS regarding neuronal integrity and astrocytosis and PET regarding neuroinflammation could further elucidate the nature of changes observed in the brain.

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