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

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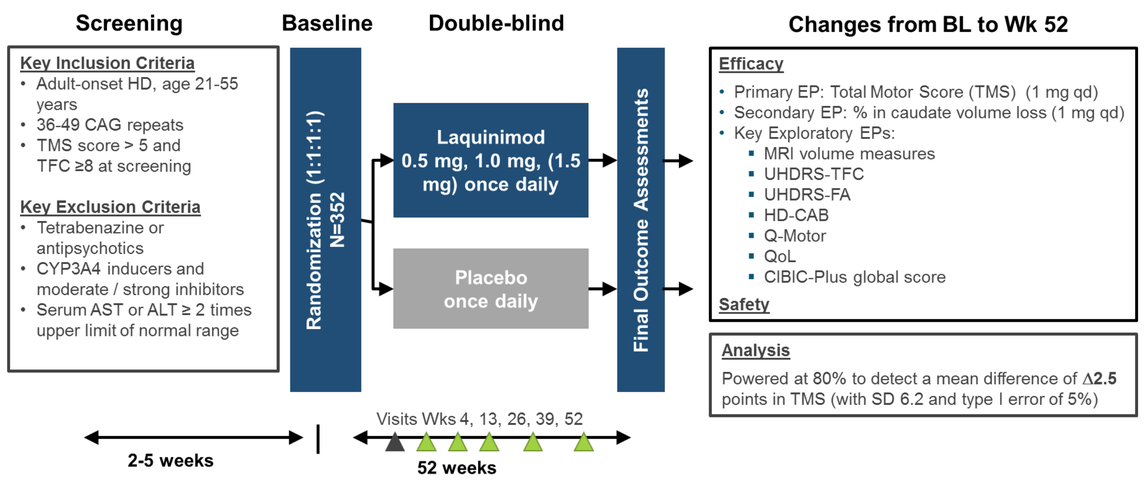
BACKGROUND AND OBJECTIVES

- 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

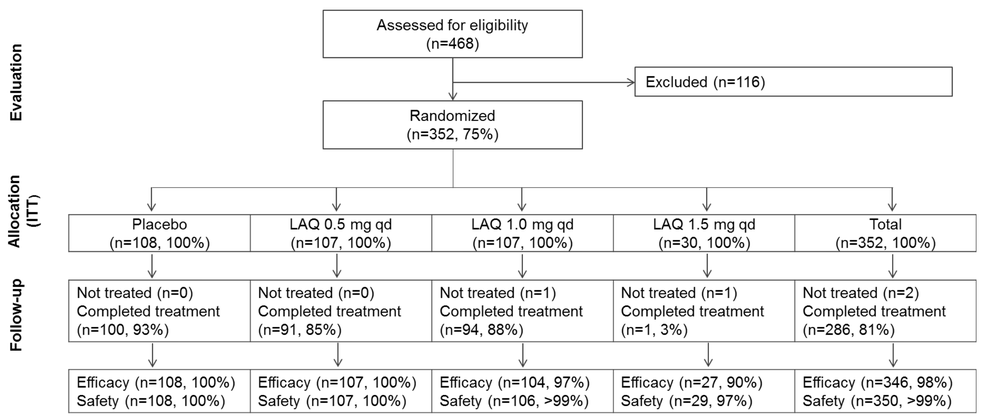
Fig. 1. Patient Screening Criteria and Study Design



RESULTS

Patient Disposition (Fig. 2)

- 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)



Patient Baseline Demographics and Disease Characteristics (Table 1)

- Baseline demographics were well balanced across treatment groups. Patients enrolled were in early stage HD.

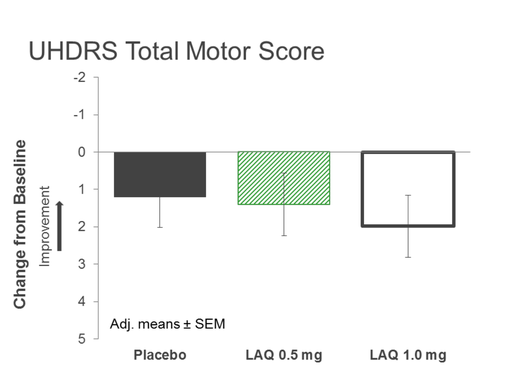
	Placebo (N=108)	LAQ 0.5 mg (N=107)	LAQ 1.0 mg (N=107)	LAQ 1.5 mg (N=30)	Total (N=352)
Age*	43.8 (7.8)	43.3 (7.8)	44 (7.8)	45.5 (6.0)	43.9 (7.6)
Sex, Male, n (%)	52 (48)	55 (51)	53 (50)	19 (63)	179 (51)
Race, White, n (%)	104 (96)	103 (96)	105 (98)	28 (93)	340 (97)
Ethnicity, Not Hispanic or Latino, n (%)	96 (89)	95 (89)	96 (90)	28 (93)	315 (89)
Weight kg*	73.7 (18.7)	72.1 (16.1)	72.2 (15.5)	75.9 (15.8)	72.9 (16.7)
Height cm*	169.6 (10.6)	169.9 (8.9)	171.2 (9.1)	171.7 (10.4)	170.3 (9.6)
BMI kg/m^2*	25.4 (5.3)	24.9 (5.0)	24.5 (4.3)	25.7 (4.3)	25 (4.8)
Number of CAG repeats*	44.2 (2.4)	44.4 (2.5)	44 (2.2)	44.2 (2.2)	44.2 (2.4)
Months from HD diagnosis*	32.3 (31.9)	45.8 (42.0)	41.5 (50.3)	38.7 (34.7)	39.8 (41.7)
UHDRS-TMS*	26.4 (14.6)	24 (13.2)	22.1 (10.7)	26.7 (14.4)	24.4 (13.2)
UHDRS-Total Functional Capacity*	11 (1.8)	11.1 (1.7)	11.2 (1.5)	11.4 (1.6)	11.1 (1.7)
Normalized Caudate volume (ml)*	6.06 (1.86)	5.78 (1.82)	6.03 (1.79)	5.43 (1.28)	N/A

*mean (SD)

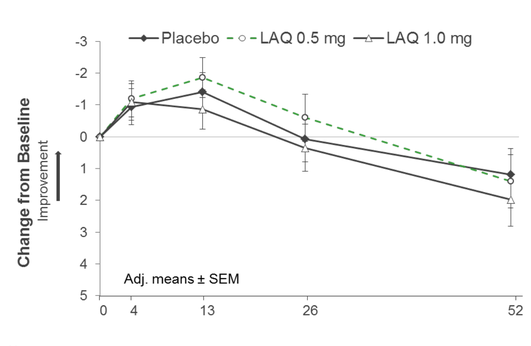
RESULTS

Primary Endpoint UHDRS Total Motor Score was not met (Fig. 3)

- 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



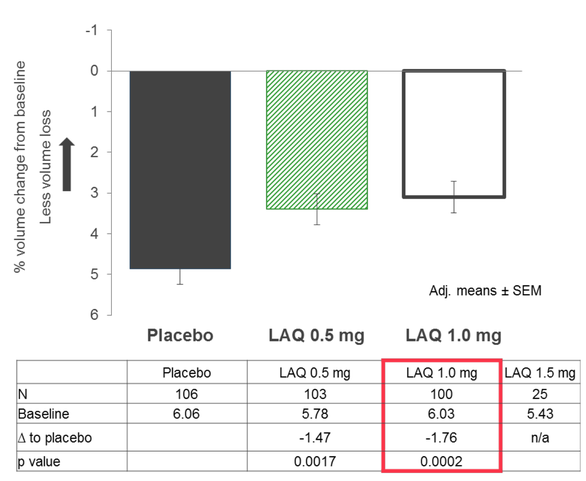
	Placebo	LAQ 0.5 mg	LAQ 1.0 mg	LAQ 1.5 mg
N	108	107	104	27
Baseline	26.4	24	22.1	26.7
Δ to placebo		0.2	0.78	n/a
p value		0.8543	0.4853	



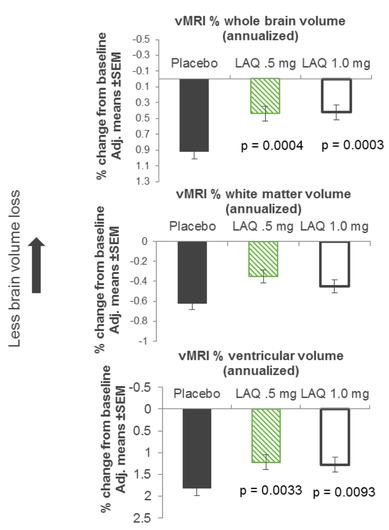
N					
Placebo	108	107	106	104	98
LAQ 0.5 mg	107	107	99	97	92
LAQ 1.0 mg	104	104	100	99	95

Secondary Endpoint vMRI % Caudate volume loss was met (Fig. 4)

- 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



	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	



Safety (Tables 2 and 3, Fig. 5)

- Laquinimod was safe and well-tolerated in this early HD population
- No new safety signal was identified related to laquinimod
- There were no consistent shifts from baseline in suicidal behavior or suicidal ideation related to treatment
- There was no reported event of ischemic heart disease

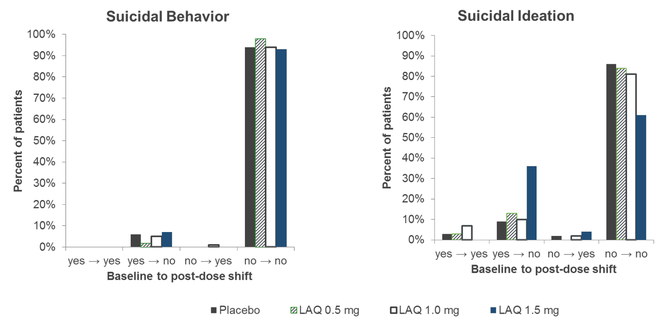
Table 2. Summary of adverse events and tolerability findings

	Placebo N=108 PY =103.4	LAQ 0.5 mg N=107 PY=95.3	LAQ 1.0 mg N=106 PY=98.2	LAQ 1.5 mg N=29 PY=10.6
All AEs	83 (77) 309.38	89 (83) 374.59	75 (71%) 362.39	22 (76%) 959.45
AEs leading to discontinuations	6 (6) 6.77	6 (6) 6.30	9 (8) 14.25	3 (10) 56.44
Serious AEs	8 (7) 9.67	7 (7) 12.59	5 (5) 7.13	1 (3) 9.41
Related (by investigator) AEs	24 (22) 43.51	46 (43) 107.03	36 (34) 75.33	12 (41) 225.75

Table 3. Cardiovascular adverse events

Preferred Term	Placebo N=108 PY=103.4	LAQ 0.5 mg N=107 PY=95.3	LAQ 1.0 mg N=106 PY=98.2	LAQ 1.5 mg N=29 PY=10.6
Atrioventricular block first degree	0	0	0	1 (3) 9.41
Defect conduction intraventricular	0	0	0	1 (3) 9.41
Left ventricular hypertrophy	0	0	1 (1) 1.02	
Sinus tachycardia	0	0	1 (1) 1.02	0
Tachycardia	0	0	3 (3) 3.05	0

Fig 5. Shifts in C-SSRS Ratings from Baseline to Post-Dose



CONCLUSIONS

- The Phase 2 LEGATO-HD trial evaluated the safety and efficacy of laquinimod as a treatment in HD.
- The study did not meet its primary endpoint of change in UHDRS-TMS after 12 months of treatment compared to baseline.
- The study met its secondary endpoint of percent reduction in caudate volume loss.
- The safety results were similar to the expected event profile in this patient population.

ACKNOWLEGMENTS

- The authors greatly appreciate the commitment of the patients, investigators, and coordinators who participated in this study.
- LEGATO-HD was sponsored by Teva Pharmaceuticals Ltd. Netanya Israel.

Presented at EHDN 14-16 September 2018
Vienna, Austria

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