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

Ralf Reilmann1, Mark Forrest Gordon2, Karen E. Anderson3, Andrew Feigin4, Sarah Tabrizi5, Blair R. Leavitt6, Julie C. Stout7, Paola Legato-HD Study: A Phase 2 Study Assessing the Efficacy and Safety of Laquinimod as a Treatment for Huntington Disease

BACKGROUND AND OBJECTIVES

— In Huntington disease (HD), immune-mediated CNS inflammation involving microglial and astroglial activation, elevated inflammatory cytokines, increased NF-κB 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 astroglial activation, suppresses NF-κB activation and upregulates BDNF, all implicated in the pathological processes in HD.2
— 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 0.5 mg and 1.0 mg doses.

METHODS

RESULTS

Primary Endpoint UHDRS Total Motor Score was not met (Fig. 3)
— Scale assesses eye movements, speech, alternating hand movements, dyskinesia, 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

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 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

CONCLUSIONS

— Laquinimod was safe and well-tolerated in this early HD population
— There was no reported event of ischemic heart disease
— There was no reported event of atrial fibrillation
— 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

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REFERENCES