The Efficacy and Safety Results of Laquinimod as a Treatment for Huntington Disease (LEGATO-HD)

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Objective: Evaluate the efficacy and safety of laquinimod in patients with Huntington disease (HD).

Background:
Laquinimod has been shown to modulate CNS-resident inflammatory pathways involved in the pathology of HD.

Design/Methods:
LEGATO-HD compared three dose arms (0.5, 1.0, and 1.5 mg once daily) versus placebo in a 52 week phase 2 study in patients with early HD. Cardiovascular safety concerns were observed in multiple sclerosis studies with laquinimod 1.2mg and 1.5mg doses. Although no similar concern was identified in LEGATO-HD, Teva discontinued the 1.5mg arm in 2016 as a precautionary safety measure and continued to evaluate 0.5 and 1.0mg doses. Primary endpoint was change from baseline in Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and secondary endpoint was percent change in caudate volume (CV), both for 1.0mg dose group vs placebo at week 52. Exploratory endpoints included changes in MRI volume measures and Quantitative (Q) Motor, CIBIC-Plus, UHDRS-Total Functional Capacity (TFC) and UHDRS-Functional Assessment (FA) scores. Primary and secondary endpoints were under Type I error control, whereas exploratory endpoints were not. Safety measures included adverse event reporting, clinical and laboratory examinations.

Results:
The study did not meet its primary endpoint of change from baseline in UHDRS-TMS ($p=0.4853$), but met its secondary endpoint of percent change in CV loss ($p=0.0002$). There were treatment effect differences between the laquinimod-treated and placebo-treated patients for all MRI exploratory measures. There were no treatment effects seen in rater-dependent clinical outcome measures. Certain Q-Motor rater-independent assessments (such as tap speed inter-onset-interval of the hands) provided evidence for treatment effect. Laquinimod was well tolerated and there were no new safety findings.

Conclusions:
While laquinimod treatment resulted in reduced volume losses in caudate and other brain regions for early HD patients, there was no evidence of improved rater-dependent clinical outcomes in the LEGATO-HD study.