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

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BACKGROUND and OBJECTIVE

− Volume loss in caudate and other brain regions is a hallmark of Huntington disease (HD) pathophysiology and has been shown to correlate with motor and clinical outcomes in HD studies.

− Laquinimod shows improvement in HD animal models including rescue of striatal and cortical atrophy.3

− 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.4

The present report explores the effects of laquinimod on its secondary endpoint (EP) of percent change from baseline in caudate volume (CV). MRI exploratory EPs and subgroup analyses (44) performed.

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.5

− Patients entered in a 5-arm trial LAQ at baseline and week 52 following a randomized, unblinded, placebo-controlled design.6

− Briefly, the change in whole-brain, caudate and ventricular volume were calculated using the BrainVoyager QX (BVQ) technique and SPM8 software.7

− 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 BrainVox, BrainSIS and Ventricles SIS, respectively.

− White-matter volume changes were estimated using a fluid registration approach which generates warping and 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 changes 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 of the effects of treatment on study and out of the window 7 days from drug day 352 were analyzed assuming linear change over the time.

− For the primary endpoint of TMS and secondary analysis, statistical tests were used in a false discovery rate approach to preserve the Type 1 error rate of 0.05. 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 1.0 mg group was tested with a two-sided alpha level of 0.005. The remaining statistical tests were conducted at a nominal 0.05 level.

− Subgroup analyses were performed for the secondary endpoint, with the change in caudate volume by sex, median values of TMS, TFC and caudate volume, C24D 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 45 sites in 10 countries. 268 patients completed treatment and 65 terminated early. Baseline demographics were well balanced across treatment groups. Patients enrolled were in early stage HD.

Subgroup analyses

− Preplanned subgroup analyses of caudate volume revealed that all subgroups showed a positive response to laquinimod doses 0.5 mg and 1 mg compared to placebo treatment (p < 0.014).

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 all brain structures assayed in both the 0.5 mg 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 4.5% loss of caudate volume in the placebo arm.

− The reduction of brain volume loss in the laquinimod group did not correlate with improvements in the primary endpoint, UHDRS-TMS Score (UHDRS-TMS) and other clinical outcomes.

− However, improvements in some quantitative motor (Q-Motor) assessments of speech and hand tapping (digiometry) were observed – see MDS Poster 44.

Table 1. Patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LAQ 0.5 mg</th>
<th>LAQ 1.0 mg</th>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>43.8 (8)</td>
<td>43.7 (8)</td>
<td>44.0 (8)</td>
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<tr>
<td>Sex, % males</td>
<td>52 (48)</td>
<td>56 (51)</td>
<td>53 (56)</td>
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<tr>
<td>CAG repeats</td>
<td>42 (3)</td>
<td>42 (3)</td>
<td>42 (3)</td>
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<td>Years HD diagnosis</td>
<td>5 (3)</td>
<td>5 (3)</td>
<td>5 (3)</td>
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<tr>
<td>History of HD symptoms</td>
<td>57 (47)</td>
<td>60 (49)</td>
<td>57 (48)</td>
</tr>
<tr>
<td>CV at baseline (mL)</td>
<td>20.8 (7)</td>
<td>21.0 (7)</td>
<td>20.7 (7)</td>
</tr>
<tr>
<td>Percentage change from baseline</td>
<td>-0.6 (0.2)</td>
<td>-0.6 (0.2)</td>
<td>-0.6 (0.2)</td>
</tr>
<tr>
<td>White-matter volume (mL)*</td>
<td>35.1 (22.9)</td>
<td>34.6 (16.9)</td>
<td>31.6 (15.4)</td>
</tr>
<tr>
<td>Percentage change from baseline</td>
<td>-0.3 (0.2)</td>
<td>-0.3 (0.2)</td>
<td>-0.3 (0.2)</td>
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*normalized baseline volume (in milliliters) is calculated by dividing the caudate volume by Pseudo Total Intracranial Volume (pTIV) factor.

Group differences were tested using a two-sided alpha level of 0.005. p = 0.0033, p = 0.0093, p = 0.0004, p = 0.0003, p = 0.0001, p = 0.0016.

Adj. mean (±SEM) for all preplanned subgroups.

Subgroup analyses

− Preplanned subgroup analyses of caudate volume revealed that all subgroups showed a positive response to laquinimod doses 0.5 mg and 1 mg compared to placebo treatment (p < 0.014).

REFERENCES


Report no disclosures.

Research sponsored by Teva Pharmaceutical Industries Ltd.

Neutype Israel

Presented at Movement Disorder Society September 22-26 2019 in Nice France