Safety and efficacy of laquinimod for Huntington's disease (LEGATO-HD) a multicentre, randomised, double-blind, placebo-controlled, phase 2 study

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Safety and efficacy of laquinimod for Huntington's disease (LEGATO-HD): a multicentre, randomised, double-blind, placebo-controlled, phase 2 study

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Summary

Background Laquinimod modulates CNS inflammatory pathways thought to be involved in the pathology of Huntington's disease. Studies with laquinimod in transgenic rodent models of Huntington's disease suggested improvements in motor function, reduction of brain volume loss, and prolonged survival. We aimed to evaluate the safety and efficacy of laquinimod in improving motor function and reducing caudate volume loss in patients with Huntington's disease.

Methods LEGATO-HD was a multicentre, double-blind, placebo-controlled, phase 2 study done at 48 sites across ten countries (Canada, Czech Republic, Germany, Italy, Netherlands, Portugal, Russia, Spain, UK, and USA). Patients aged 21–55 years with a cytosine-adenosine-guanine (CAG) repeat length of between 36 and 49 who had symptomatic Huntington's disease with a Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) of higher than 5 and a Total Functional Capacity score of 8 or higher were randomly assigned (1:1:1:1) by centralised interactive response technology to laquinimod 0·5 mg, 1·0 mg, or 1·5 mg, or to matching placebo, administered orally once daily over 52 weeks; people involved in the randomisation had no other role in the study. Participants, investigators, and study personnel were masked to treatment assignment. The 1·5 mg group was discontinued before recruitment was finished because of cardiovascular safety concerns in multiple sclerosis studies. The primary endpoint was change from baseline in the UHDRS-TMS and the secondary endpoint was percent change in caudate volume, both comparing the 1·0 mg group with the placebo group at week 52. Primary and secondary endpoints were assessed in the full analysis set (ie, all randomised patients who received at least one dose of study drug and had at least one post-baseline UHDRS-TMS assessment). Safety measures included adverse event frequency and severity, and clinical and laboratory examinations, and were assessed in the safety analysis set (ie, all randomised patients who received at least one dose of study drug). This trial is registered with ClinicalTrials.gov, NCT02215616, and EudraCT, 2014–000418–75, and is now complete.

Findings Between Oct 28, 2014, and June 19, 2018, 352 adults with Huntington's disease (179 [51%] men and 173 [49%] women; mean age 43·9 [SD 7·6] years and 340 [97%] White) were randomly assigned: 107 to laquinimod 0·5 mg, 107 to laquinimod 1·0 mg, 30 to laquinimod 1·5 mg, and 108 to matching placebo. Least squares mean change from baseline in UHDRS-TMS at week 52 was 1·98 (SE 0·83) in the laquinimod 1·0 mg group and 1·2 (0·82) in the placebo group (least squares mean difference 0·78 [95% CI –1·42 to 2·98], p=0·4853). Least squares mean change in caudate volume was 3·10% (SE 0·38) in the 1·0 mg group and 4·86% (0·38) in the placebo group (least squares mean difference –1·76% [95% CI –2·67 to –0·85]; p=0·0002). Laquinimod was well tolerated and there were no new safety findings. Serious adverse events were reported by eight (7%) patients on placebo, seven (7%) on laquinimod 0·5 mg, five (5%) on laquinimod 1·0 mg, and one (3%) on laquinimod 1·5 mg. There was one death, which occurred in the placebo group and was unrelated to treatment. The most frequent adverse events in all laquinimod dosed groups (0·5 mg, 1·0 mg, and 1·5 mg) were headache (38 [16%]), diarrhoea (24 [10%]), fall (18 [7%]), nasopharyngitis (20 [8%]), influenza (15 [6%]), vomiting (13 [5%]), arthralgia (11 [5%]), irritability (ten [4%]), fatigue (eight [3%]), and insomnia (eight [3%]).

Interpretation Laquinimod did not show a significant effect on motor symptoms assessed by the UHDRS-TMS, but significantly reduced caudate volume loss compared with placebo at week 52. Huntington's disease has a chronic and slowly progressive course, and this study does not address whether a longer duration of laquinimod treatment could have produced detectable and meaningful changes in the clinical assessments.

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See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE from Jan 1, 1970, to Aug 30, 2023, for Articles published in English, using the terms "laquinimod" and "Huntington's disease". We identified no published randomised controlled trials of laquinimod in patients with Huntington's disease. Neuroinflammatory pathways contribute to the disease pathology in rodent models of Huntington's disease and laquinimod can attenuate cytokine release, prolong survival, reduce brain volume loss, and convey motor benefits in the YAC128 Huntington's disease mouse model. To date, no treatments for Huntington's disease have improved motor symptoms other than chorea, and none has shown a joint effect on a clinical endpoint and brain volume. Therefore, we decided to explore the efficacy and safety of a range of doses of laquinimod for individuals with early symptomatic Huntington's disease over 52 weeks.

Added value of this study

Laquinimod compared with placebo did not reduce motor impairment, as assessed by the the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) in the 52 weeks studied. However, caudate volume loss was reduced in the secondary analysis. Laquinimod was safe and well tolerated. The preservation of brain volume and exploratory supportive clinical evidence in some measures of the novel objective Quantitative Motor Battery (Q-Motor) might might suggest a possible central effect of laquinimod of unknown clinical significance.

Implications of all the available evidence

This study did not show level 1b evidence that laquinimod conveys motor benefit on the UHDRS-TMS after 52 weeks, but did provide evidence of preservation of caudate volume. To date, no study of this size including participants with Huntington's disease has reported a benefit in caudate volume in two dose groups, accompanied by exploratory beneficial signals in the rater-independent clinical Q-Motor measures. To our knowledge, these results represent the first clinical observations supporting a possible role of neuroinflammation in the pathology of Huntington's disease that could be modulated by therapeutic intervention. Considering the favourable safety profile and acknowledging the unmet therapeutic needs in Huntington's disease, further investigation of laquinimod or other immune-modulating therapeutics might be warranted.

Introduction

In Huntington's disease, several features of immune-mediated CNS inflammation, including microglial and astrocytic activation, elevated inflammatory cytokines, increased NF-κB activity, and low *BDNF* transcription, are associated with progressive neuronal dysfunction and striatal degeneration.[1,2] Laquinimod is an orally active CNS immunomodulator that downregulates inflammatory monocytic, microglial, and astrocytic activation, suppresses NF-κB activation, and upregulates *BDNF*.[3] Thus, laquinimod might counteract these pathological processes in Huntington's disease. Clinical data from patients with relapsing-remitting multiple sclerosis show a benefit of laquinimod on brain atrophy and mixed effects on clinical endpoints after more than 1 year of treatment.[4–7] The results suggest that, in addition to peripheral inflammation-modulating effects, laquinimod might also have neuroprotective effects, and affect CNS inflammatory processes beyond T-cell-driven lesions. These effects could be important in Huntington's disease, for which intrinsic CNS inflammatory phenotypes have been shown to correlate with disease progression.[8] Therefore, we did a phase 2 study to identify a laquinimod dose that might be safe and effective in people with early Huntington's disease.

For more on the **European Huntington's Disease Network** see www.ehdn.org
For more on the **Huntington Study Group** see www.huntingtonstudygroup.org

Methods

Study design and participants

In this multicentre, multinational, randomised, double-blind, placebo-controlled, phase 2 study, we compared the efficacy and safety of laquinimod (0·5 mg, 1·0 mg, and 1·5 mg) with placebo, given orally once daily for 52 weeks. The study was done at 48 sites in ten countries (Canada, Czech Republic, Germany, Italy, Netherlands, Portugal, Russia, Spain, UK, and USA), and was sponsored by Teva Pharmaceutical Industries in collaboration with the European Huntington's Disease Network and the Huntington Study Group. An independent data safety monitoring board oversaw the study and reviewed unmasked safety data to ensure the safety of the participants, and reviewed study conduct issues. The study was conducted in accordance with the principles of Good Clinical Practice and with the US Food and Drug Administration (FDA) guidelines for safety monitoring. All patients provided written informed consent before enrolment and the protocol was approved by the institutional review boards for each site.

Patients eligible for screening included adults (aged 21–55 years) with onset of Huntington's disease (ie, equivalent to a diagnostic confidence level of 4) from age 18 years. After signing the informed consent, including consent to provide a blood sample for cytosine-adenine-guanine (CAG) repeat length genetic analysis, patients were screened to determine whether they were eligible to participate. Key inclusion criteria included having a CAG repeat length of 36–49, and motor symptoms of Huntington's disease, as assessed by a Unified Huntington's Disease Rating Scale (UHDRS)-Total Motor Score (UHDRS-TMS) of more than 5, and a UHDRS-Total Functional Capacity (UHDRS-TFC) score of 8 or higher. Based on their UHDRS-TFC scores at

baseline, the participants enrolled had early-stage Huntington's disease, designated either stage 1 (score of 11–13) or stage 2 (score of 7–10, although the minimum score in this study was 8).[9] Key exclusion criteria included use of immunosuppressive or cytotoxic agents within 12 months, use of tetrabenazine and antipsychotic agents within 30 days, use of moderate or strong inhibitors or inducers of cytochrome P450 3A4 within 2 weeks, unsuitability for MRI, abnormally elevated concentrations of liver enzymes (≥2 times upper limit of normal) and bilirubin (≥1·5 times upper limit of normal), or having a medical condition or laboratory result that, based on the investigator's opinion, made the patient unsuitable to participate. Full eligibility criteria are in the appendix (pp 3–5).

Randomisation and masking

Participants were randomly assigned to treatment through a qualified randomisation service provider using interactive response technology. The randomisation code was generated by the Teva Clinical Supply Chain department according to specifications from the Teva Biostatistics department. All clinical personnel involved in the study and patients were masked to treatment allocation. Initially, we planned to randomly assign 400 patients (1:1:1:1 ratio, 100 patients within each group) to receive once-daily laquinimod 0·5 mg, 1·0 mg, or 1·5 mg, or matching placebo, for 52 weeks. In December 2015, the Teva Corporate Safety Board adopted the recommendation of the data safety monitoring boards of two studies evaluating laquinimod as a treatment for multiple sclerosis to discontinue the dose groups of laquinimod 1·2 mg per day and 1·5 mg per day, owing to an imbalance in cardiovascular events between the study groups.[6,7] On Jan 10, 2016, as recommended by the data safety monitoring board of the LEGATO-HD study, the laquinimod 1·5 mg dose group was discontinued as a proactive safety measure. The LEGATO-HD study continued with the laquinimod 0·5 mg and 1·0 mg groups with enhanced monitoring and safety precautions, such as exclusion of participants with a history of ischaemic heart disease or myocardial infarction. Thus, approximately 300 patients (100 patients in the laquinimod 0·5 mg, laquinimod 1·0 mg, and matching placebo study groups), plus the 30 patients who were already randomly assigned to laquinimod 1·5 mg, were enrolled in the study. The only change to the original randomisation list was that the patient numbers for laquinimod 1·5 mg per day were removed by the interactive response technology vendor. All patients who discontinued the 1·5 mg per day dose were unmasked and not re-randomised.

Participants were instructed to take three capsules once daily, at the same time of day during the entire study. Each capsule contained either 0·5 mg laquinimod or placebo, depending on treatment allocation (ie, the laquinimod 1·5 mg group received three 0·5 mg laquinimod capsules, the laquinimod 1·0 mg group received two 0·5 mg laquinimod capsules and one placebo capsule, the laquinimod 0·5 mg group received one 0·5 mg laquinimod capsule and two placebo capsules and the placebo group received three placebo capsules). An external non-Teva statistician provided unmasked data to the data safety monitoring board.

Procedures

The study consisted of nine clinic visits: visit 1 occurred during the screening period (2–5 weeks before baseline, visit 2 was the baseline visit, visits 3–8 occurred during the 52 week double-blind treatment period, and visit 9 occurred 1 month after treatment ended. The study procedures and assessments performed at each clinic visit can be found in the protocol. Briefly, safety evaluations, physical examinations, and laboratory tests were done at each visit. As part of the safety evaluations, the Columbia Suicide Severity Rating Scale was assessed at baseline and at weeks 4, 13, 26, 39, 52, and 56. MRI scans were done at baseline and at week 52, and the efficacy assessments were done at baseline and at weeks 4, 13, 26, and 52 during the treatment period.

For the **protocol** see https://www.ghi-muenster.de/protocols/legato-hd

Outcomes

Full details of the LEGATO-HD study endpoints are in the statistical analysis plan. The primary endpoint was the change from baseline in UHDRS-TMS for the laquinimod 1·0 mg group, compared with placebo, at week 52. UHDRS is a clinical research tool developed to provide a uniform rater assessment of the severity of clinical symptoms including motor, cognitive, behavioural, and functional domains; UHDRS-TMS comprises 31 motor assessments, covering eye movements, speech, hand movements, dystonia, chorea, gait, and balance. All raters in the LEGATO-HD study were UHDRS-TMS certified.[10]

For the **statistical analysis plan** see https://www.ghi-muenster.de/protocols/legato-hd-sap

The secondary endpoint was percent change in caudate volume for the 1·0 mg group, compared with placebo, at week 52. Given that laquinimod has shown evidence of reducing brain volume loss in multiple sclerosis clinical studies,[4–6] another neuroinflammatory disease, we wanted to assess the effects of laquinimod on brain volume loss that occurs in patients with Huntington's disease. We used brain MRI to assess the change in volume of certain predefined regions, including the caudate, whole brain, white matter, and ventricles, from baseline to week 52. Changes in the predefined regions of brain volume were calculated by a medical image service provider, IXICO (London, UK). All sites used 3-Tesla (3T) MRI machines that were specified by IXICO, and phantoms were scanned to standardise assessments and qualify site MRI scans. 3T MRI scans at baseline and week 52 were done according to unaccelerated volumetric T1-weighted acquisition protocols developed during the Alzheimer's Disease Neuroimaging Initiative study. Change in caudate volume, whole brain volume, and ventricular volume were calculated using

For more on the **Alzheimer's Disease Neuroimaging Initiative study** see www.adni-info.org

the Boundary Shift Integral (BSI) technique.[11–13] The BSI is an intensity-driven technique within the MIDAS software,[11] which measures change over time in the brain directly from within individual-registered (aligned) MR scan pairs. This technique has been optimised to provide robust measures of brain volume change from multisite data[13] and detect Huntington's disease-related pathology over 12 months.[14] White matter volume change was estimated using a non-linear registration approach. Voxel volume change derived from within-individual non-linear registration was summed over an automated baseline white matter mask, to estimate within-individual volume change.

A priori-defined MRI exploratory endpoints were percent change in caudate volume for laquinimod 0·5 mg, and percent whole brain volume change, percent white matter volume change, and absolute change in ventricular volume for the laquinimod 0·5 mg and 1·0 mg groups.

Rater-dependent exploratory measures included the UHDRS-TFC and UHDRS-Functional Assessment scores, Clinician's Interview-Based Impression of Change (CIBIC-Plus), modified physical performance test (mPPT), Huntington's disease health-related quality-of-life, 5 Level EuroQoL-5 Dimensions Questionnaire (EQ-5D-5L), Work Limitations Questionnaire (WLQ), Clinical Dementia Rating Sum of Boxes (CDR-SB), Hospital Anxiety and Depression Scale (HADS), and Problem Behaviors Assessment-Short form (PBA-s); prespecified exploratory endpoints were the change from baseline to week 52 for both laquinimod groups, compared with placebo, for each assessment. As rater-independent exploratory measures, the Huntington's Disease-Cognitive Assessment Battery (HD-CAB) and the Quantitative Motor Battery (Q-Motor) were assessed at screening, baseline, and weeks 4, 13, 26, and 52 at all sites. All Q-Motor assessments are based on the application of precalibrated and temperature-controlled force transducers and three-dimensional position sensors with very high sensitivity and test–retest reliability across sessions and sites in a multicentre clinical study.[10]

Safety measures included adverse event reporting, electrocardiography (ECG) and clinical laboratory parameters, vital signs, physical examinations, and premature discontinuations from the study.

Statistical analysis

All changes in the statistical analysis plan, compared with the protocol, were approved on June 19, 2018, before database lock on July 17, 2018, and performed by the sponsor while fully masked to treatment allocations. Changes in the statistical analysis plan from the protocol included that primary and secondary endpoint analyses should be for laquinimod 1·0 mg compared with placebo, because the 1·5 mg group had been discontinued, we needed to reconsider the approach to multiplicity, and higher efficacy was expected with the higher dose considering results from studies in multiple sclerosis.[4–6] The endpoints functional capacity using the UHDRS-TFC scale, change from baseline in HD-CAB total score, and clinical global impression using the CIBIC-Plus were listed as secondary objectives in the protocol and were defined as exploratory endpoints in the final statistical analysis plan since they were considered less likely to show clinically meaningful changes in early Huntington's disease after just 1 year based on observational data from Huntington's disease.[14,15] The HD-CAB total score was revised to HD-CAB composite score to comply with new standards. The exploratory endpoints in the final statistical analysis plan also included analyses comparing laquinimod 0·5 mg with placebo for the primary and secondary endpoints. Refinement of the statistical methods included use of the fallback method[16] to analyse the primary and secondary endpoints, change to country instead of site as a covariate in the analyses, and removal of the use of the last observation carried forward method for participants terminating the study early.

We estimated that approximately 100 patients per group would provide a power of 80% to detect a significant effect of an active laquinimod group compared with placebo, assuming a true mean difference of 2·5 points or more in the change from baseline in UHDRS-TMS, an SD of 6·2, and a type I error of 5%. We estimated that approximately 100 patients per group would provide a power of 80% to detect a beneficial effect of 0·95 (30% of the estimated decline in placebo) or more in the percent change from baseline in caudate brain atrophy of an active laquinimod group compared with placebo, assuming an SD of 2·36 and a type I error of 5%.

Briefly, for all efficacy measures, the analyses included all patients in the intention-to-treat population (all randomised patients), who received at least one dose of study drug and had at least one post-baseline UHDRS-TMS assessment (ie, the full analysis set). For the primary endpoint, the change from baseline to week 52 or early termination visit in the UHDRS-TMS was compared between the laquinimod 1·0 mg and placebo groups using a mixed-model-repeated measures model (SAS mixed procedure) with repeated sub-command. The model included the following fixed effects: treatment group with 3 levels (placebo, laquinimod 0·5 mg, and laquinimod 1 mg), categorical week in trial with 4 levels (week 4, week 13, week 26, and week 52), treatment by week interaction; country, UHDRS-TMS at baseline, and week by UHDRS-TMS at baseline interaction. The least squares mean and SE for the laquinimod 0·5 mg, laquinimod 1·0 mg, and placebo groups, and the least squares mean difference, 95% CIs, and p values for each laquinimod dose versus placebo comparison (laquinimod 0·5 mg *vs* placebo, and laquinimod 1·0 mg *vs* placebo) were presented at all visits. The inferential p value for the primary endpoint was for the comparison of laquinimod 1·0 mg versus placebo at week 52. Preplanned subgroup analyses for the primary efficacy endpoint were for sex (self reported), median

baseline UHDRS-TMS, UHDRS-TFC, and caudate volume, CAG repeat length, and whether the clinical site was within or outside the USA (details are in the statistical analysis plan).

For the secondary endpoint, percent change in caudate volume from baseline to week 52 or early termination visit was compared between the laquinimod 1·0 mg and placebo groups using an analysis of covariance model (SAS mixed procedure). The model included the following fixed effects: treatment group (3 levels: placebo, laquinimod 0·5 mg, and laquinimod 1·0 mg), country, and caudate volume at baseline.

To maintain the experiment-wise type I error rate of 5%, the fallback method with the loop-back feature was used to test the primary and secondary endpoints.[16] The fallback method permits interpretation of an endpoint with a robust treatment effect using a modest amount of alpha retained as a fallback, even if the preceding endpoint is unsuccessful, without inflating the Type I error rate. In this method, the alpha is split between the endpoints of interest using weights reflecting their clinical importance; the sum of weights always equals 1. In our setting, we used weights of 0·9 for the UHDRS-TMS and 0·1 for caudate volume, yielding an alpha of $0·9\times0·05=0·045$ for UHDRS-TMS, and an alpha of $0·1\times0·05=0·005$ for caudate volume.

The exploratory MRI endpoints were analysed using procedures similar to those used for the secondary endpoint analysis except that their baseline values were used as the covariate instead of caudate volume and both doses of laquinimod were compared with placebo. The exploratory endpoints from the rater-independent Q-Motor assessments were analysed using procedures similar to the primary endpoint, except that the baseline score for each of the measures was used in the interaction terms instead of the UHDRS-TMS score and both doses of laquinimod were compared with placebo.

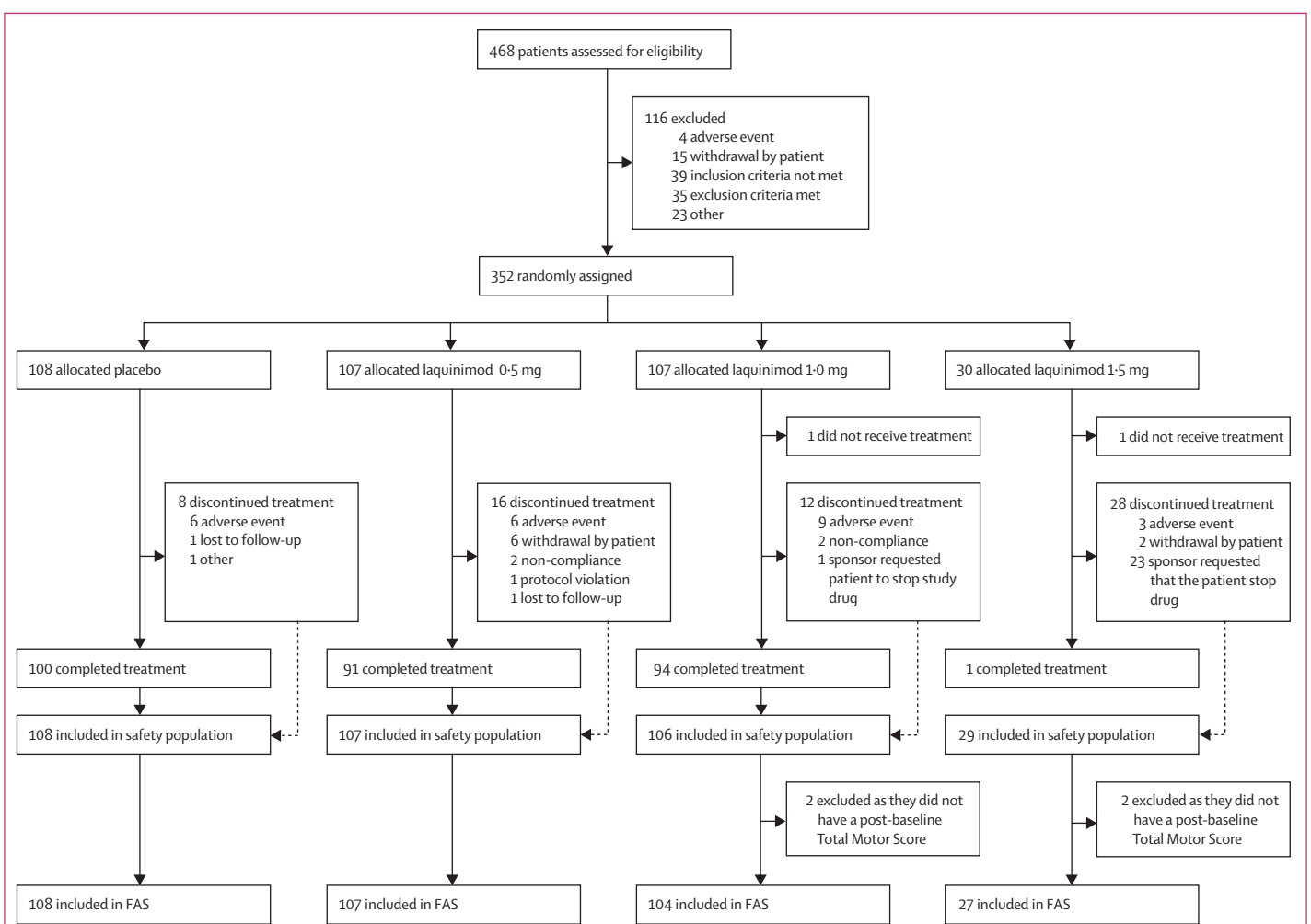

Figure 1: **Trial profile**
The safety population included all randomised patients who received at least one dose of study drug. The FAS included all randomly assigned participants who received at least one dose of study drug and had at least one post-baseline Unified Huntington's Disease Rating Scale-Total Motor Score assessment. FAS=full analysis set.

The safety population included all randomised patients who received at least one dose of study drug. All data were processed and summarised by the use of SAS version 9.3 or later.

The trial is registered with ClinicalTrials.gov, NCT02215616, and EudraCT, 2014–000418–75.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Oct 28, 2014, and June 19, 2018, 468 patients were screened and 352 randomly assigned to a treatment group: 108 to placebo, 107 to laquinimod 0·5 mg, 107 to laquinimod 1·0 mg, and 30 to laquinimod 1·5 mg. Of the 116 patients who were not enrolled, 74 were excluded on the basis of eligibility criteria, 15 patients withdrew consent, four patients had an adverse event, and 23 patients withdrew for other reasons. 286 (81%) patients completed the study, 64 discontinued treatment, and two did not receive treatment (including 28 who discontinued from the 1·5 mg group; figure 1).

Demographic and clinical characteristics were similar in the treatment groups (table 1).

Change from baseline to week 52 in the UHDRS-TMS did not differ significantly between the laquinimod 1·0 mg group (least squares mean 1·98 [SE 0·83]) and placebo group (1·20 [0·82]; least squares mean difference 0·78 [95% CI –1·42 to 2·98]; p=0·4853; figure 2). Preplanned subgroup analysis of the UHDRS-TMS results indicated that there was no particular subgroup (on the basis of sex, CAG repeat length, site location median, and baseline values of UHDRS-TMS, UHDRS-TFC, and caudate volume) that showed a response to laquinimod (data not shown).

Change in caudate volume differed significantly between the laquinimod 1·0 mg group (least squares mean 3·10 [SE 0·38]) and the placebo group (4·86 [0·38]) (least squares mean difference –1·76 [95% CI –2·67 to –0·85]; p=0·0002; figure 3). The exploratory MRI volumetric measures of caudate volume loss for the laquinimod 0·5 mg group, and whole brain volume loss,

	Placebo (n=108)	Laquinimod 0·5 mg (n=107)	Laquinimod 1·0 mg (n=107)	Laquinimod 1·5 mg (n=30)	Total (N=352)
Age, years	43·8 (7·8)	43·3 (7·8)	44·0 (7·8)	45·5 (6·0)	43·9 (7·6)
Sex*					
Male	52 (48%)	55 (51%)	53 (50%)	19 (63%)	179 (51%)
Female	56 (52%)	52 (49%)	54 (50%)	11 (37%)	173 (49%)
Race*					
White	104 (96%)	103 (96%)	105 (98%)	28 (93%)	340 (97%)
Black	0	1 (<1%)	1 (<1%)	0	2 (<1%)
Asian	2 (2%)	0	0	1 (3%)	3 (<1%)
Other	0	1 (<1%)	0	0	1 (<1%)
Missing	2 (2%)	2 (2%)	1 (<1%)	1 (3%)	6 (2%)
Ethnicity*					
Not Hispanic or Latino	96 (89%)	95 (89%)	96 (90%)	28 (93%)	315 (89%)
Hispanic or Latino	9 (8%)	10 (9%)	9 (8%)	1 (3%)	29 (8%)
Unknown	1 (<1%)	0	1 (<1%)	0	2 (<1%)
Missing	2 (2%)	2 (2%)	1 (<1%)	1 (3%)	6 (2%)
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 diagnosis of Huntington's disease	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-TFC	11 (1·8)	11·1 (1·7)	11·2 (1·5)	11·4 (1·6)	11·1 (1·7)
UHDRS-TFC 11–13	12·2 (0·8); 36%	12·3 (0·8); 37%	12·1 (0·8); 36%	12·0 (0·9); 22%	12·2 (0·8); 35%
UHDRS-TFC ≤10	8·9 (0·8); 64%	9·2 (0·8); 63%	9·4 (0·7); 64%	9·0 (0·9); 78%	9·2 (0·8); 65%
Normalised caudate volume, mL	6·06 (1·86)	5·78 (1·82)	6·03 (1·79)	5·43 (1·28)	5·92 (1·79)

Data are mean (SD) or n (%). The intention-to-treat set (ie, all randomised patients) is used for the demographic characteristics and number of cytosine-adenosine-guanine repeats. The FAS set (ie, all randomised patients who received at least one dose of study drug and had at least one post-baseline Unified Huntington's Disease Rating Scale-Total Motor Score assessment) is used for Unified Huntington's Disease Rating Scale-Total Motor Score, Unified Huntington's Disease Rating Scale-Total Functional Capacity, and normalised caudate volume. FAS=full analysis set. *Sex, race, and ethnicity were self reported.

Table 1: **Patient demographic and disease state characteristics**

white matter volume loss, and ventricular volume for laquinimod 0·5 mg and laquinimod 1·0 mg groups all consistently showed improvements compared with placebo. The least squares mean differences from baseline to week 52 between the laquinimod dose groups and the placebo group for each of the exploratory MRI volumetric measures support these treatment effects and are shown in the appendix (p 4).

The rater-dependent exploratory clinical measures showed no significant differences between laquinimod and placebo for the rating scales assessing functional capacity (UHDRS-TFC, UHDRS-FA, and mPPT), clinical global impression (CIBIC-Plus), psychiatric conditions (PBA-s, HADS, and CDR-SB), and quality of life (Huntington's disease health-related quality-of-life, EQ-5D-5L, and WLQ; table 2). The rater-independent exploratory Q-Motor assessments showed improvements in some of the digitomotography (speeded tapping) measures (inter-onset interval and inter-tap interval in the laquinimod 0·5 mg group and the laquinimod 1·0 mg group (appendix p 7). The least squares mean differences between the laquinimod 0·5 mg group and the laquinimod 1·0 mg group versus the placebo group for all Q-Motor measures are shown in the appendix (pp 8–11). For dysdiadochomotography (pronation or supination hand tapping) and pedomotography (speeded foot tapping) there were some improvements with both laquinimod doses compared with placebo; however, for the manumotography (grip force) and choreomotography (chorea) analyses, the laquinimod doses showed no effects. The computerised HD-CAB test did not show any treatment effects of laquinimod, neither in the composite score nor in the subdomains (table 2).

Treatment-emergent adverse events were reported by 83 (77%) patients receiving placebo, 89 (83%) patients receiving laquinimod 0·5 mg, 75 (71%) receiving laquinimod 1·0 mg, and 22 (76%) receiving laquinimod 1·5 mg (table 3). The most common adverse events were headache (seven [6%] patients in the placebo group, 19 [18%] in the laquinimod 0·5 mg group, 14 [13%] in the laquinimod 1·0 mg group, and five [17%] in the laquinimod 1·5 mg group), diarrhoea (nine [8%], 12 [11%], nine [8%], and three [10%], respectively), and fall (nine [8%], 11 [10%], five [5%], and two [7%], respectively). Adverse events leading to trial discontinuation are shown in the appendix (p 12). Treatment-related adverse events occurred in 24 (22%) patients in the placebo group, 46 (43%) patients in the laquinimod 0·5 mg group, 36 (34%) in the laquinimod 1·0 mg group, and 12 (41%) in the laquinimod 1·5 mg group. Adverse events associated with the gastrointestinal system, psychiatric disorders, and infections and infestations were the most common across all treatment groups (appendix pp 13–16).

No unexpected safety signals emerged during the study. There were no clinically meaningful changes in serum chemistry, haematological parameters, vital signs, or ECGs. Elevations in liver or pancreatic enzymes

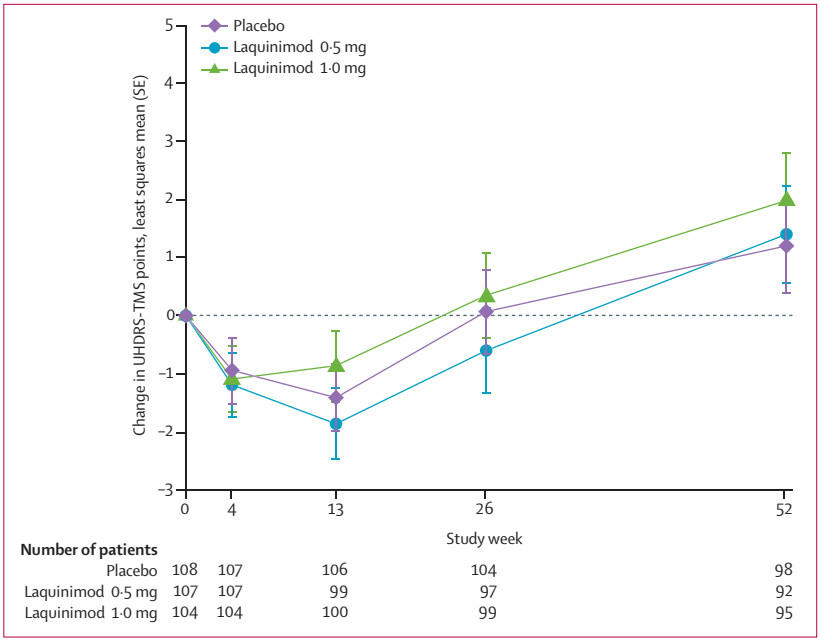

Figure 2: **UHDRS-TMS least squares mean change from baseline to week 52 in the full analysis set**
Change in points from baseline in UHDRS-TMS least squares mean score at 52 weeks for the laquinimod 1·0 mg per day group (primary endpoint) and for the laquinimod 0·5 mg per day group (exploratory endpoint). Range 1–134 points, with lower numbers indicating less severe symptoms. Changes compared with placebo are reported in table 2. UHDRS-TMS=Unified Huntington's Disease Rating Scale-Total Motor Score.

included alanine aminotransferase three or more times the upper limit of normal (one patient in the laquinimod 1·0 mg group and one patient in the laquinimod 1·5 mg group), aspartate aminotransferase three or more times the upper limit of normal (one patient in the placebo group), bilirubin 34·2 µmol/L or more (one patient in the laquinimod 1·5 mg group), and gamma glutamyl transferase more than three times the upper limit of normal (one patient in the laquinimod 0·5 mg group, two patients in the laquinimod 1·0 mg group, and one patient in the laquinimod 1·5 mg group).

Most participants in all groups showed little change in their Columbia Suicide Severity Rating Scale ratings. For suicidal ideation, answers for ten (9%), 14 (13%), 11 (10%), and ten (36%) patients changed from "yes" at baseline to "no" at week 52 for the placebo, laquinimod 0·5 mg, laquinimod 1·0 mg, and laquinimod 1·5 mg groups, and two (2%) patients in the placebo group, two (2%) in the laquinimod 1·0 mg group, and one (4%) in the laquinimod 1·5 mg group changed their answer from "no" at baseline to "yes" at week 52. For suicidal behaviour, six (6%), two (2%), five (5%), and two (7%) patients in the placebo, laquinimod 0·5 mg, laquinimod 1·0 mg, and laquinimod 1·5 mg groups, respectively, changed their answer from "yes" at baseline to "no" at week 52. One patient in the laquinimod 1·0 mg group changed their answer from "no" at baseline to "yes" at week 52.

Cardiovascular adverse events in the LEGATO-HD study included one first-degree atrioventricular block and one defect intraventricular conduction in the laquinimod

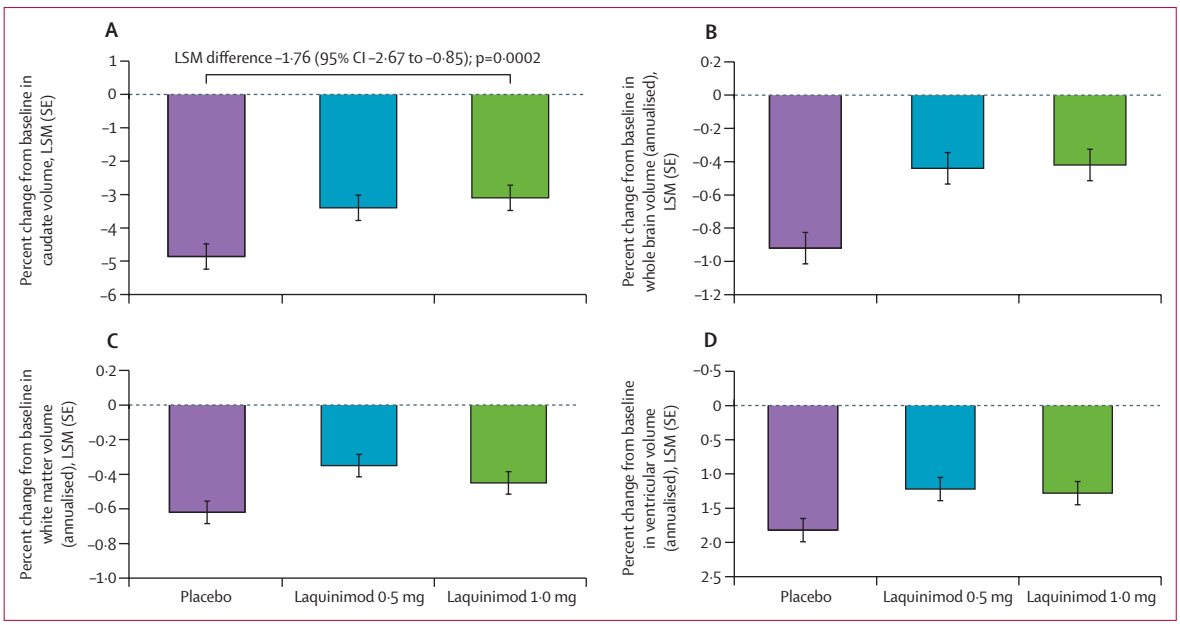

Figure 3: **Percent change in MRI measures from baseline to week 52 in the full analysis set**
Percent change in caudate volume, with laquinimod 1·0 mg dose versus placebo being the secondary endpoint of LEGATO-HD, and in brain volume, white matter volume, and ventricular volume, with both laquinimod doses versus placebo being exploratory endpoints. LSM=least squares mean.

1·5 mg group, and one left ventricular hypertrophy and four tachycardias in the laquinimod 1·0 mg group. There was one death during the study: one patient in the placebo group died due to multiple injuries in a road traffic accident. Serious adverse events were reported by eight (7%) patients in the placebo group, seven (7%) in the laquinimod 0·5 mg group, five (5%) in the laquinimod 1·0 mg group, and one (3%) in the laquinimod 1·5 mg group (appendix pp 17–18).

Discussion

In this placebo-controlled study of patients with early Huntington's disease, laquinimod showed no evidence for significant differences between groups on the primary endpoint UHDRS-TMS. The UHDRS-TMS is a well established clinical rating scale for the assessment of motor function in Huntington's disease.[17] All raters were experienced and certified annually.[10] We observed a 1–2 point decrease in UHDRS-TMS across groups until about 13 weeks, which resembles a placebo effect, as seen in previous trials.[18–20] After week 13, all groups progressed approximately 3 points by week 52. This change is similar to previous data,[21] which suggest UHDRS-TMS worsening by about 3 points within a year.

However, laquinimod showed a statistically significant reduction in volume loss in the caudate for the 1·0 mg laquinimod dose. There were also reductions in volume loss in the caudate for the 0·5 mg laquinimod dose, and volume loss for whole brain and white matter for both doses, which is consistent with the caudate findings. Progressive volume losses in the striatum, which are best assessable in the caudate, but also seen in various other brain regions (white matter, grey matter, and whole brain) are well established hallmarks of Huntington's disease pathology.[22,23] Caudate volume loss, in particular, is a sensitive marker very early in premanifest and manifest Huntington's disease, and correlates with disease progression and motor, specifically Q-Motor, and other clinical outcomes in long-term observational studies. Based on historical observational data, approximately 3% caudate volume loss was expected at 52 weeks.[14] In our study, a considerably larger caudate volume loss of 4·9% was observed in the placebo group, but the changes in the other brain volume measures are consistent with the observation of an effect of laquinimod in the caudate and might support the validity and relevance of the findings of decreased brain volume loss. However, there is no obvious or consistent dose effect in any imaging measure.

An effect of laquinimod on preserving brain volume loss has also been reported in patients with relapsing-remitting multiple sclerosis in three large phase 2 and phase 3 studies (ALLEGRO [n=1106], BRAVO [n=1331], and CONCERTO [n=2199]), in which laquinimod 0·6 mg and laquinimod 1·2 mg decreased whole brain volume loss.[4–6] Further exploratory analyses in patients with relapsing-remitting multiple sclerosis showed that, similar to what was observed in LEGATO-HD, there was a substantial reduction in both white and grey matter brain volume loss in people treated with laquinimod compared with those who received placebo.[24] A phase 2 study (ARPEGGIO [n=252]) of patients with primary progressive multiple sclerosis suggested reduced brain

	Laquinimod 0·5 mg *vs* placebo	Laquinimod 1·0 mg *vs* placebo
UHDRS-Total Motor Score	0·20 (–1·98 to 2·39); p=0·8543	0·78 (–1·42 to 2·98); p=0·4853*
UHDRS-Total Functional Capacity	0·06 (–0·40 to 0·51); p=0·8109	0·35 (–0·11 to 0·81); p=0·1320
UHDRS-Functional Assessment	–0·17 (–0·95 to 0·62); p=0·6790	0·48 (–0·30 to 1·26); p=0·2250
HD-CAB composite	–0·05 (–0·13 to 0·04); p=0·2954	0·01 (–0·08 to 0·10); p=0·8153
Symbol Digit Modalities Test	–1·07 (–3·14 to 1·00); p=0·3095	0·31 (–1·76 to 2·38); p=0·7670
Emotion recognition	–0·23 (–1·18 to 0·72); p=0·6361	–0·11 (–1·06 to 0·85); p=0·8251
Trail Making Test	–1·59 (–11·63 to 8·45); p=0·7554	–10·24 (–20·54 to -0·41); p=0·0414
Hopkins Verbal Learning Test—revised	–1·15 (–2·84 to 0·53); p = 0·1779	–0·49 (–2·17 to 1·18); p=0·5624
Paced-tapping (at 3 Hz)	0·21 (–1·713 to 2·134); p=0·8297	1·659 (–0·268 to 3·585); p=0·0913
One Touch Stockings of Cambridge (abbreviated 10 trial version)	–1·67 (–4·70 to 1·36); p=0·2790	–0·57 (–3·58 to 2·44); p=0·7097
Clinician's Interview-Based Impression of Change	0·15 (–0·06 to 0·35); p=0·1567	0·03 (–0·17 to 0·24); p=0·7453
Modified Physical Performance Test total score	0·64 (–0·23 to 1·51); p=0·1484	0·19 (–0·67 to 1·05); p=0·6669
Huntington's Disease health-related quality-of-life total score		
Participant	5·75 (–2·79 to 14·28); p=0·1863	–0·36 (–8·86 to 8·17); p=0·9363
Companion	7·49 (–0·68 to 15·66); p=0·0722	–1·22 (–9·40 to 6·95); p=0·7690
EuroQoL-5 Dimensions Questionnaire		
Mobility	0·08 (–0·14 to 0·30); p=0·4727	–0·15 (–0·36 to 0·07); p=0·1866
Self-care	–0·03 (–0·18 to 0·13); p=0·7293	0·02 (–0·13 to 0·18); p=0·7958
Usual activities	0·07 (–0·14 to 0·27); p=0·5389	0·01 (–0·20 to 0·22); p=0·9251
Pain or discomfort	0·06 (–0·12 to 0·23); p=0·5249	0·07 (–0·10 to 0·24); p=0·4419
Anxiety or depression	0·00 (–0·22 to 0·22); p=0·9794	–0·10 (–0·32 to 0·12); p=0·3560
Health state	1·70 (–3·00 to 6·40); p=0·4766	1·94 (–2·76 to 6·63); p=0·4174
Work Limitations Questionnaire		
Time management	5·08 (–3·83 to 14·00); p=0·2613	1·57 (–6·51 to 9·65); p=0·7010
Physical tasks	11·89 (–1·26 to 25·04); p=0·0761	15·61 (3·52 to 27·70); p=0·0117
Mental interpretation	–0·17 (–9·06 to 8·73); p=0·9707	–4·74 (–12·99 to 3·51); p=0·2583
Output tasks	7·28 (–1·20 to 15·75); p=0·0919	–1·53 (–9·29 to 6·24); p=0·6981
Clinical Dementia Rating–Sum of Boxes	0·16 (–0·60 to 0·92); p=0·6802	–0·23 (–0·99 to 0·52); p=0·5431
Hospital Anxiety and Depression Scale	0·60 (–0·99 to 2·19); p=0·4562	–0·50 (–2·08 to 1·08); p=0·5328
Problem Behaviors Assessment-short form	1·43 (–2·17 to 5·03); p=0·4351	–1·42 (–5·00 to 2·16); p=0·4357

Data are least squares mean difference (95% CI). HD-CABHD-CAB=Huntington's Disease-Cognitive Assessment Battery. UHDRS=Unified Huntington's Disease Rating Scale. *Primary endpoint.

Table 2: **Rater-dependent and patient-reported primary endpoint and exploratory outcome measures in the full analysis set**

volume loss in treated participants compared with those who received placebo at 24 weeks, which did not persist at the end of the study at 48 weeks.[7] The development of laquinimod for multiple sclerosis was discontinued on the basis of inconsistent findings,[4–7] as other evidence-based approved treatments are available. However, given the absence of treatments that influence the course of Huntington's disease, the beneficial effects on brain volume loss in the multiple sclerosis studies are valuable when assessing the potential of laquinimod and immune modulation in Huntington's disease.

The key question of central importance when observing changes in brain volume is whether these changes convey a biological or clinical effect. Glial dysfunction and neuroinflammation are thought to be early characteristics of Huntington's disease and might contribute to neuronal dysfunction and degeneration.[25–29] Laquinimod treatment reduced inflammatory cytokine IL-6 concentrations and striatal atrophy in the YAC128

	Placebo (n=108)	Laquinimod 0·5 mg (n=107)	Laquinimod 1·0 mg (n=106)	Laquinimod 1·5 mg (n=29)
Any adverse event	83 (77%)	89 (83%)	75 (71%)	22 (76%)
Treatment-related adverse event	24 (22%)	46 (43%)	36 (34%)	12 (41%)
Adverse event leading to treatment discontinuation	6 (6%)	6 (6%)	9 (8%)	3 (10%)
Patients with at least one serious adverse event*	8 (7%)	7 (7%)	5 (5%)	1 (3%)
Blood and lymphatic system disorders	4 (4%)	1 (1%)	5 (5%)	0
Anaemia	4 (4%)	1 (1%)	5 (5%)	0
Gastrointestinal disorders	27 (25%)	34 (32%)	27 (25%)	12 (41%)
Diarrhoea	9 (8%)	12 (11%)	9 (8%)	3 (10%)
Abdominal pain	1 (1%)	7 (7%)	2 (2%)	1 (3%)
Vomiting	3 (3%)	7 (7%)	4 (4%)	2 (7%)
Nausea	4 (4%)	5 (5%)	5 (5%)	4 (14%)
Abdominal pain upper	0	4 (4%)	2 (2%)	1 (3%)
Constipation	3 (3%)	3 (3%)	3 (3%)	2 (7%)

(Table 3 continues on next page)

	Placebo (n=108)	Laquinimod 0·5 mg (n=107)	Laquinimod 1·0 mg (n=106)	Laquinimod 1·5 mg (n=29)
(Continued from previous page)				
General disorders and administration site conditions	8 (7%)	8 (7%)	9 (8%)	0
Fatigue	4 (4%)	5 (5%)	3 (3%)	0
Pyrexia	2 (2%)	1 (1%)	5 (5%)	0
Infections and infestations	39 (36%)	41 (38%)	36 (34%)	4 (14%)
Nasopharyngitis	19 (18%)	10 (9%)	10 (9%)	0
Influenza	7 (6%)	8 (7%)	7 (7%)	0
Upper respiratory tract infection	7 (6%)	3 (3%)	2 (2%)	1 (3%)
Urinary tract infection	5 (5%)	1 (1%)	2 (2%)	2 (7%)
Injury, poisoning, and procedural complications	25 (23%)	19 (18%)	13 (12%)	5 (17%)
Fall	9 (8%)	11 (10%)	5 (5%)	2 (7%)
Ligament sprain	2 (2%)	1 (1%)	1 (1%)	2 (7%)
Contusion	6 (6%)	0	1 (1%)	1 (3%)
Investigations (laboratory tests)	12 (11%)	19 (18%)	23 (22%)	9 (31%)
Amylase increased	0	8 (7%)	6 (6%)	1 (3%)
Lipase increased	0	3 (3%)	4 (4%)	1 (3%)
Alanine aminotransferase increased	0	2 (2%)	4 (4%)	2 (7%)
Pancreatic enzymes increased	0	2 (2%)	2 (2%)	2 (7%)
Blood folate decreased	0	2 (2%)	2 (2%)	2 (7%)
Haemoglobin decreased	0	1 (1%)	3 (3%)	3 (10%)
Musculoskeletal and connective tissue disorders	20 (19%)	20 (19%)	22 (21%)	5 (17%)
Back pain	7 (6%)	8 (7%)	8 (8%)	2 (7%)
Arthralgia	5 (5%)	5 (5%)	4 (4%)	2 (7%)
Neck pain	1 (1%)	4 (4%)	1 (1%)	0
Nervous system disorders	17 (16%)	32 (30%)	23 (22%)	11 (38%)
Headache	7 (6%)	19 (18%)	14 (13%)	5 (17%)
Chorea	3 (3%)	3 (3%)	0	2 (7%)
Balance disorder	0	1 (1%)	0	2 (7%)
Psychiatric disorders	22 (20%)	19 (18%)	19 (18%)	7 (24%)
Irritability	4 (4%)	6 (6%)	3 (3%)	1 (3%)
Insomnia	4 (4%)	4 (4%)	2 (2%)	2 (7%)
Anxiety	4 (4%)	3 (3%)	1 (1%)	2 (7%)
Depression	5 (5%)	0	3 (3%)	2 (7%)
Respiratory, thoracic, and mediastinal disorders	12 (11%)	5 (5%)	11 (10%)	2 (7%)
Cough	4 (4%)	3 (3%)	6 (6%)	0
Skin and subcutaneous disorders	10 (9%)	7 (7%)	10 (9%)	1 (3%)
Hyperhidrosis	0	1 (1%)	4 (4%)	0

*For a listing of serious adverse events per group see appendix (pp 17–18).

Table 3: **Adverse events that occurred ≥5% in any treatment group in the safety analysis set**

Huntington's disease mouse model[30] and improved motor function and increased striatal *BDNF* expression in the R6/2 Huntington's disease mouse model.[31]

We hypothesised that normalising glial function with laquinimod might ameliorate these Huntington's disease-related processes, leading to a reduction in clinical symptoms. However, none of the rater-dependent clinical outcomes in the cognitive, functional, or behavioural domains, including the clinical primary endpoint UHDRS-TMS, detected significant treatment effects. In our study, exploratory analyses of the rater-independent, objective Q-Motor assessments showed effects of laquinimod on motor coordination in the finger tapping assessment (digitomotography[32]) in the laquinimod 0·5 mg and laquinimod 1·0 mg groups, supporting the hypothesis of a neuronal correlate for the changes in the brain volume measurements. The Q-Motor measures of finger tapping, such as the inter-onset interval and the inter-peak interval, detected Huntington's disease progression in the TRACK-HD study[15,22] and treatment effects in studies such as PRIDE-HD[18] and others.[20,33] Q-Motor measures were correlated with imaging and clinical measures in Huntington's disease-biomarker studies[14,15,22,32] and, as seen in previous studies, they were less susceptible to placebo effects than clinical measures such as the UHDRS-TMS.[10,18,20,32] The clinical relevance of the amplitude of the changes observed remains to be established and not all Q-Motor measures exhibited effects; however, the significant treatment effects on brain volume and the changes in Q-Motor measures jointly suggest a possible central effect of laquinimod, albeit of unknown clinical significance. This observation is important, as it is derived from a large clinical trial and generates first in-human evidence for a proof-of-concept of possibly beneficial effects of immune modulation in the neurodegenerative process observed in Huntington's disease.

A clear limitation of LEGATO-HD was the duration of the study. Clinical observations in the multiple sclerosis studies were reported at 24 months. However, neurodegeneration in Huntington's disease develops over decades, thus, detecting treatment effects over 12 months is challenging when using traditional clinical measures.[14] Also, possible effects of immune modulation might take time to manifest. We observed that the decline in Q-Motor finger tapping performance seems to attenuate in the laquinimod groups (after visits at week 13 and week 26, slopes declined more slowly), whereas the opposite seemed to occur in the placebo group (slopes declined more quickly); thus, the treatment groups might diverge from placebo more rapidly towards the end of the study. We appreciate that we are speculating and the divergence is based on exploratory data, but we share the observation of this attenuation since it was detected by a sensitive and objective measure, given the need for new therapies in Huntington's disease. We also appreciate that MRI assessments done across multiple sites and standardisation of MRI imaging across sites can be challenging. However, the validity of our MRI findings is supported by the site qualification process applied by the contract research organisation, which was similar to the process used in the TRACK-HD study,[14,15,22,34] and by the obligatory use of three Tesla MRI scanners across all sites.

Overall, safety data from this study indicate that treatment with laquinimod was generally safe and well

tolerated in patients with Huntington's disease. In two multiple sclerosis studies,[6,7] incidences of ischaemic heart disease had occurred at higher laquinimod doses. As a safety precaution, we discontinued the laquinimod 1.5 mg treatment group and there were no reports of ischaemic heart disease in LEGATO-HD. No new safety signals were identified in patients with Huntington's disease as compared with studies in multiple sclerosis.[4–7]

For patients with Huntington's disease, given the absence of treatment options that alter the disease process, we were disappointed that we did not observe a clinical benefit with laquinimod for the primary endpoint. However, this study was primarily planned as an exploratory trial to obtain clinical and biomarker evidence, specifically on imaging and Q-Motor measures, to inform the design of a possible longer pivotal trial to follow. The absence of effects on clinical scales could be due to confounders, such as the relatively short treatment period and the limited sensitivity and reliability of the clinical rating scales, which might be affected by rater error and bias in spite of the annual UHDRS-TMS online certification that was obligatory for the primary endpoint in this study.[10] In our judgement, the evidence available while this study was being designed did not justify embarking on a longer treatment period and large sample size that would typically be utilised for a phase 3 study, and a longer treatment period does not always mean that results are positive (eg, as seen in the CREST-E study of creatine in individuals with Huntington's disease).[35] Our findings in the objective MRI and exploratory Q-Motor measures raise the question of whether a properly powered long-term treatment with immunomodulatory agents should be considered in people with Huntington's disease. We do acknowledge that Q-Motor assessments were exploratory and analyses were not corrected for multiple comparisons, which due to the number of variables tested included a possibility of chance findings; however, all nominally significant changes and all mean changes were consistently in the direction of improvement across Q-Motor tests performed and no single variable showed worsening. Another point to consider is that individuals in earlier stages of Huntington's disease might benefit more from immune modulating treatments than those with later stage disease. Effects of such treatments in the prodromal or premanifest stages might be explored in future studies. In fact, to our knowledge, the only other clinical trial in Huntington's disease that reported preservation of brain volume, the PRECREST trial of creatine was done in individuals with prodromal Huntington's disease.[36]

Considering a further exploration of the risks and benefits of immunomodulatory therapies in Huntington's disease, it should be appreciated that their safe application in other diseases for several years offers perspectives for early and long lasting treatment regimens, which are required in a slowly developing neurodegenerative disease. Although LEGATO-HD was conducted a few years ago, several promising approaches using antisense-oligonucleotides recently showed no benefit for people with Huntington's disease compared with placebo in phase 2 and phase 3 trials.[37] Careful consideration of the evidence available for other treatment approaches is therefore timely. Immune modulation is available orally and could be distributed easily and applied for long periods within current medical care systems. If proven to have a clinical effect in future studies, such therapy could be used alone or in combination with other possible therapeutic approaches to modulate the course of Huntington's disease.

Contributors

RR served as the global coordinating principal investigator of LEGATO-HD; was a member of the steering committee; was involved in study design, data collection, data analysis, and data interpretation; did the Q-Motor analyses; and wrote the first draft of the manuscript. KEA and AF served as co-principal investigators; were members of the steering committee; were involved in study design, data collection, data analysis, and data interpretation; and critically reviewed the manuscript. SJT, BRL, JCS, and PP were members of the steering committee; were involved in study design, data collection, data analysis and interpretation; and critically reviewed the manuscript. RS was involved in study design, data collection, data analysis, and data interpretation; did the Q-Motor analyses; and critically reviewed the manuscript. PL was involved in data collection, data analysis, and data interpretation, and wrote the first draft of the manuscript. AW and BB were clinical study leads; were involved in study design, data collection, data analysis, and data interpretation; and critically reviewed the manuscript. GR, RV, TL, J-MS, and MH were involved in study design, data collection, data analysis, and data interpretation, and critically reviewed the manuscript. MFG served as clinical study lead, was involved in data collection, data analysis, and data interpretation, and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript, had access to all study data, and were given figures and tables of the study results and participated in discussions about study results. All authors verified the data.

Declaration of interests

RR is founding director and owner of the George Huntington Institute, a private research institute focused on clinical and preclinical research in Huntington's disease, and QuantiMedis, a clinical research organisation providing Q-Motor services in clinical trials and research. He served as an elected member of the executive committees of the European Huntington's Disease Network and the Huntington's Study Group, and as co-chair of the Task Force on Huntington's Disease of the International Parkinson and Movement Disorder Society. He has provided consulting services to Teva Pharmaceuticals, all payments to institution. He reports receiving payments for clinical trial services (global coordinating principal investigator role, patient recruitment, and quantitative motor assessment) and consulting services from Actelion, Alnylam, Amarin, AOP Orphan Pharmaceuticals, AskBio, Cure Huntington Disease Initiative Foundation, Desitin, Hoffmann-La Roche, IONIS, Ipsen, Lundbeck, MEDA Pharma, Medivation, Mitoconix, Neurocrine, Neurosearch, Novartis, Omeros, Pfizer, Prana Biotechnology, Prilenia, PTC Therapeutics, Raptor, Sage, Siena Biotech, Solaxa, Temmler Pharma, Teva, uniQure, Vaccinex, Voyager, Wave Life Sciences, and Zevra, all payments to institution. KEA reports that salary support was paid by Teva to her institution, Georgetown University, for work as co-principal investigator for North American sites, and that she has received honoraria from Teva for giving lectures and participation in advisory boards. She is also a paid consultant to Novartis Pharmaceuticals, Azevan Pharmaceuticals, Cure Huntington Disease Initiative Foundation, the Lundbeck Foundation, and Neurocrine Pharmaceuticals. She receives salary support, paid to her institution, from the Griffin Foundation and the Huntington Study Group. She receives salary support, paid to her institution, as a site investigator for

clinical trials for SAGE Pharmaceuticals and Prilenia Pharmaceuticals. She has received salary support, paid to her institution, as a site investigator for observational studies from Cure Huntington Disease Initiative Foundation. AF served as chair of the Huntington Study Group from 2018 to 2022. He is on the data and safety monitoring board for Alzheimer's Disease Cooperative Study/Alzheimer's Therapeutic Research Institute and chairs a data and safety monitoring board for PTC Therapeutics. He has received institutional grant support to New York University, as a co-principal investigator of the LEGATO-HD study. He has also received grants to his institution, New York University, from Prilenia Therapeutics and the Huntington Study Group, and consulting fees from AskBio and Annexon. SJT reports receiving a research contract from Teva Pharmaceuticals to run LEGATO-HD at the University College London Hospital site. SJT reports receiving grant support from the following groups: the Cure Huntington Disease Initiative Foundation, Vertex Pharmaceuticals, UK Medical Research Council, Wellcome Trust, and UK Dementia Research Institute. SJT reports that consultancy fees for advisory services were paid to University College London Consultants, a wholly-owned subsidiary of University College London from the following companies: F Hoffman LaRoche, Annexon Biosciences, PTC Therapeutics, Takeda Pharmaceuticals, Vertex Pharmaceuticals, Alnylam Pharmaceuticals, Genentech, LoQus23 Therapeutics, Triplet Therapeutics, Novartis, Atalanta, Spark Therapeutics, Horama, University College Irvine, Rgenta Therapeutics, Locanobio, Adrestia Therapeutics, Alchemab, Biogen, Design Therapeutics, HCD Economics, Ipsen Bioscience, Iris Medicine, Latus Therapeutics/8V, Life Edit Therapeutics, Pfizer, Prilenia Therapeutics, Regeneron Pharmaceutics, Remix Therapeutics, Sanofi, and Unique. SJT reports consulting fees and advisory services with payment directly to SJT from Alphasight, Guidepoint, and Iqvia, and reports a patent issued on application number 2105484·6, 25 licensed to Adrestia Therapeutics. BRL reports grant support from Teva Pharmaceuticals to his university, University of British Columbia, as a site for LEGATO-HD. BRL reports receiving grant support to his university, University of British Columbia, from the following groups: Huntington Society of Canada, Canadian Institutes of Health Research, and NanoMedicines Innovation Network. BRL reports receiving consulting fees as a scientific consultant from the following companies: uniQure, Teva Pharmaceuticals, Takeda, Triplet, Novartis, PTC, Remix, LifeEdit, Spark, Design, Scientetica, Roche/Genentech, and Camp4, and reports many patents with University of British Columbia and Incisive Genetics. BRL is chief executive officer, board member, and co-founder of Incisive Genetics, a biotech startup, and holds stock in this company. BRL has participated on the scientific advisory board for sRNAlytics and has received stock options. He is co-editor-in-chief of the *Journal of Huntington's Disease*, an unpaid position which receives some expense reimbursement. JCS was director of Stout Neuropath (now Zindametrix), a commercial research service that provided assistance in implementing the HD-CAB for the LEGATO-HD study. Stout Neuropath neuropsychology staff were masked to participant group assignment during the LEGATO-HD study. PP reports receiving grant support from Cure Huntington Disease Initiative Foundation, Parkinson's UK, the UK Medical Research Council, and the Michael J Fox Foundation. RS is an employee of the George Huntington Institute, a private research institute focused on clinical and preclinical research in Huntington's disease, and QuantiMedis, a clinical research organisation providing Q-Motor services in clinical trials and research. PL, GR, RV, TL, and MFG are employees of Teva Pharmaceuticals and own stock. AW is a former employee of Teva Pharmaceuticals and current employee of Novo Nordisk. BB is a former employee of Teva Pharmaceuticals and current employee of Novartis Pharmaceuticals. J-MS is a former employee of Teva Pharmaceuticals and current employee of Spark Therapeutics. MH is the former head of Teva Global Research and Development and is currently the founder and chief executive officer of Prilenia Therapeutics.

Data sharing

The data sets used and analysed for the study described in this manuscript are available on reasonable request. Qualified researchers can request access to patient-level data and related study documents. Patient-level data will be de-identified and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please visit www.clinicalstudydatarequest.com to make your request.

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