Effects of the dopaminergic stabilizer pridopidine on motor symptoms in Huntington’s disease: a meta-analysis

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Table 1. Patient demographics and baseline characteristics (all treatment groups, FAS = n = 664). Data are presented as mean (% CI). CI, confidence interval; TMS, Unified Huntington’s Disease Rating Scale Total Motor Score.

Table 2. Change from baseline (pridopidine 90 mg/day versus placebo) for the HART- and sub-scores (FAS, n = 203). Data are expressed as mean (95% CI). "Chorea and hand movements" (Figure 1) Dystonia, the mMS, eye movements, involuntary motor symptoms.

CONCLUSIONS
The meta-analysis results are in line with those of the individual studies and further indicate that pridopidine improves overall motor function in patients with-HD. This study further illustrates the specific nature of the motor effects of pridopidine, namely a consistent improvement in the UHDRS-TMS, which is most pronounced in the clinically relevant items hand movements and balance and gait. Combined with the benign safety and tolerability profile, these results indicate that pridopidine is a beneficial and well-tolerated potential new treatment for HD.

References
2. Elali K et al. Neurotherapeutics 2011;8:130.

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Figure 1. Change from baseline to the end of treatment in hand movement scores (all treatment groups, FAS, n = 664). Data are presented as mean (95% CI, confidence interval; TMS, full analysis set.

Figure 2. Change from baseline to the end of treatment in balance and gait scores (all treatment groups, FAS, n = 664). Data are presented as mean (95% CI, confidence interval; TMS, full analysis set.

Introduction
There is a significant unmet need for novel Huntington’s disease (HD) treatments. Indeed, a recent systematic review failed to recommend strongly any therapy for the symptomatic treatment of HD.1 Motor dysfunction in HD is associated with abnormalities in dopamine and glutamate transmission within the cortico-striatal pathways. Pridopidine, the first in a new class of compounds known as dopaminergics, stabilizers, has the potential to treat motor dysfunction in HD, via its actions at dopamine type 1 and 2 receptors in the cortico-striatal pathways. Thus, pridopidine is hypothesized to stimulate the direct pathway, alleviating impairments in voluntary motor function, and inhibit the indirect pathway, alleviating involuntary movements (see Water S et al at poster 163 for details).

This is in line with findings from two large clinical trials of pridopidine in patients with HD,2,3 where pridopidine 90 mg/day improved overall motor function (on the Unified Huntington’s Disease Rating Scale Total Motor Score, UHDRS-TMS).4 Specifically, there was an improvement in gait and hand movements (i.e. an improvement in impaired voluntary motor function) and a reduction in dystonia (i.e. an improvement in involuntary motor symptoms).2,3 To further understand the efficacy profile of pridopidine, a meta-analysis of the two studies was performed, enabling data from a large pool of patients to be analysed and data from the two studies compared.

Methods
Pridopidine study designs
HART study: a 3-month, phase 2b, multicentre, North American, randomized, double-blind, parallel-group trial, assessing the effects of pridopidine 20 mg/day, 45 mg/day, 90 mg/day and placebo on motor symptoms of HD.2,3 MermaHD study: a 6-month, phase 3, multicentre, European, randomized, double-blind, parallel-group trial, assessing the effects of pridopidine 45 mg/day, 90 mg/day and placebo on motor symptoms of HD.4
In both studies, patients were ambulatory, aged ≥ 30 years and had a modified Motor Score (mMS) ≥ 10 points. The primary outcome was change in the mMS from baseline to the end of treatment.2,3 Other outcome measures included change in the UHDRS-TMS from baseline.2,3 Meta-analysis population
All randomized patients who received study medication and who had at least one post-randomization efficacy assessment were eligible for inclusion in the meta-analysis (i.e. the full analysis set [FAS]). Patients in the FAS were grouped according to treatment and dose: pridopidine 20 mg/day (HART only) and pridopidine 45 mg/day, 90 mg/day or placebo (HART and MermaHD).

Statistical analyses
Data from both studies were analysed using repeated measures analysis, including baseline value, gender, antipsychotic medication use, study, week, treatment, and interaction between study and treatment, and week. The covariance matrix for observations over time (within the same patient) was fitted by a heterogenous Toeplitz covariance matrix. For the treatment group ‘pridopidine 45 mg/day’, patients could have received one of two different dosages (22.5 mg twice daily in the HART study and 45 mg once daily in the MermaHD study). These dosages were, therefore, included as two different dose strata in the initial analysis but collapsed (into one dose stratum) if they were not significantly different.

The interactions between study, treatment and week; study; treatment and week, and study and week were included, but removed if they were not significant.

Results
Patient populations
In the HART study, 58, 58, 55 and 58 patients were randomized to placebo, pridopidine 25 mg/day, 45 mg/day and 90 mg/day, respectively. For the MermaHD study, 144, 148 and 145 patients were randomized to placebo, pridopidine 45 mg/day and 90 mg/day, respectively.

All randomized patients (n = 664) were eligible for inclusion in the meta-analysis FAS (n = 202, n = 86, n = 203 and n = 203 for placebo, pridopidine 20 mg/day, 45 mg/day and 90 mg/day, respectively).

Patient demographics, baseline characteristics and disposition
Most variables were similar or showed only minor differences between groups (Table 1). Exceptions were: for pridopidine 90 mg/day, there were more females than males in each treatment group; on average, patients on placebo were younger than those in each pridopidine group. These patients also had a higher UHDRS-TMS score, and higher hand movement and dystonia scores. Balance and gait score and chorea scores were highest in the pridopidine 20 mg/day treatment group.

Discussion
In this meta-analysis, the effects of pridopidine 90 mg/day on motor symptoms of HD were consistent with those observed in the individual studies. Furthermore, these results have a higher degree of precision than those of the individual studies, due to the larger number of patients included in the analysis. Pridopidine 90 mg/day produced an improvement in the UHDRS-TMS at weeks 12 and 26, as well as in the items ‘hand movements’, ‘balance and gait’ and ‘dystonia’. This is in line with the proposed mechanism of action of pridopidine, namely a lessening of impaired voluntary motor function and an improvement in involuntary motor symptoms.