Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial

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Summary

Background Huntington's disease is a progressive neurodegenerative disorder, characterised by motor, cognitive, and behavioural deficits. Pridopidine belongs to a new class of compounds known as dopaminergic stabilisers, and results from a small phase 2 study in patients with Huntington's disease suggested that this drug might improve voluntary motor function. We aimed to assess further the effects of pridopidine in patients with Huntington's disease.

Methods We undertook a 6 month, randomised, double-blind, placebo-controlled trial to assess the efficacy of pridopidine in the treatment of motor deficits in patients with Huntington's disease. Our primary endpoint was change in the modified motor score (mMS; derived from the unified Huntington's disease rating scale) at 26 weeks. We recruited patients with Huntington's disease from 32 European centres; patients were aged 30 years or older and had an mMS of 10 points or greater at baseline. Patients were randomly assigned (1:1:1) to receive placebo, 45 mg per day pridopidine, or 90 mg per day pridopidine by use of centralised computer-generated codes. Patients and investigators were masked to treatment assignment. We also assessed the safety and tolerability profile of pridopidine. For our primary analysis, all patients were eligible for inclusion in our full analysis set, in which we used the last observation carried forward method for missing values. We used an analysis of covariance model and the Bonferroni method to adjust for multiple comparisons. We used a prespecified per-protocol population as our sensitivity analysis. The α level was 0·025 for our primary analysis and 0·05 overall. This trial is registered with ClinicalTrials.gov, number NCT00665223.

Findings At 26 weeks, in our full analysis set the difference in mean mMS was −0·99 points (97·5% CI −2·08 to 0·10, p=0·042) in patients who received 90 mg per day pridopidine (n=145) versus those who received placebo (n=144), and −0·36 points (−1·44 to 0·72, p=0·456) in those who received 45 mg per day pridopidine (n=148) versus those who received placebo. At the 90 mg per day dose, in our per-protocol population (n=114), the reduction in the mMS was of −1·29 points (−2·47 to −0·12; p=0·014) compared with placebo (n=120). We did not identify any changes in non-motor endpoints at either dose. Pridopidine was well tolerated and had an adverse event profile similar to that of placebo.

Interpretation This study did not provide evidence of efficacy as measured by the mMS, but a potential effect of pridopidine on the motor phenotype of Huntington's disease merits further investigation. Pridopidine up to 90 mg per day was well tolerated in patients with Huntington's disease.

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Introduction

Huntington's disease is an autosomal dominant, progressive, neurodegenerative disease caused by a cytosine–adenine–guanine (CAG) trinucleotide repeat expansion in the huntingtin gene.[1,2] Pathologically, Huntington's disease leads to widespread neuronal degeneration, especially in the striatum.[1,3–8] The disease produces a range of cognitive, behavioural, and motor deficits, including involuntary movements, motor impersistence, parkinsonism, apraxia, and abnormal gait, posture, and eye movements.[1,9] The progressive deficits of Huntington's disease substantially affect patients' daily functioning, ultimately leading to loss of independence and premature death.

The prevalence of Huntington's disease has been estimated at about 5–7 per 100 000 people,[1] but recent reports suggest that it might be at least double this number.[10,11] A Cochrane review[12] was unable to draw any firm conclusions about best medical practice for the control of motor and non-motor symptoms of the disease, although some compounds are thought to be somewhat effective. For example, tetrabenazine, the only drug licensed in North America and some European countries for Huntington's disease, is effective for the control of chorea, but is associated with risk of serious adverse events.[12] Furthermore, antipsychotic drugs are used widely off label for the treatment of chorea[13] and some behavioural symptoms.

Previous research suggests that glutamate and dopamine neurotransmission are affected in Huntington's disease; hence, the mechanism by which dopamine modulates glutamate-induced excitation in the basal ganglia and the cortex might be disrupted.[14] Pridopidine belongs to a new class of drugs called dopaminergic stabilisers. These compounds act primarily at dopamine type 2 (D2)

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receptors and cause state-dependent behavioural effects. In vivo, pridopidine normalises dysregulated psychomotor functions, while having only subtle effects on normal psychomotor activity.[15–17] An important pharmacological property of pridopidine might be explained by its ability to strengthen corticostriatal glutamate functions in various settings of perturbed neurotransmission. Pridopidine is effective in animals that have signs relevant to Huntington's disease, including depression, anxiety, and motor dysfunction. Preliminary clinical findings also suggest that pridopidine might improve motor function without worsening chorea.[18] To assess further the potential of pridopidine as a symptomatic treatment for Huntington's disease, we undertook a phase 3 study: the Multinational European Multicentre ACR16 study in Huntington's Disease (MermaiHD).

Methods

Participants

Between April, 2008, and November, 2009, we undertook a randomised, double-blind, placebo-controlled trial to assess the efficacy of pridopidine in treating motor deficits in patients with Huntington's disease. We recruited patients from 32 clinics in eight European countries (Austria, Belgium, France, Germany, Italy, Portugal, Spain, and the UK). We included patients with Huntington's disease (on the basis of clinical features and the presence of ≥36 CAG repeats) who were aged 30 years or older (to avoid recruitment of patients with juvenile disease), were ambulatory, and had a modified motor score (mMS; derived from the unified Huntington's disease rating scale [UHDRS]) of 10 points or greater. We included participants treated with allowed antipsychotics (amisulpride, haloperidol, olanzapine, risperidone, sulpiride, or tiapride, which are the most commonly prescribed antipsychotics in the participating countries), antidepressants, or other psychotropic drugs if they had received a stable dose for 6 weeks or longer before randomisation. We excluded patients who were pregnant, lactating, or fertile women not using contraception, patients who received disallowed antipsychotics or tetrabenazine in the 12 weeks before randomisation, and patients who used fluoxetine, paroxetine, tricyclic antidepressants, class 1 antiarrhythmics, or strong CYP2D6 inhibitors in the 6 weeks before randomisation.

Written, informed consent was obtained from patients before any study-related procedure was undertaken. Our study was done in accordance with the ethical principles of the Declaration of Helsinki. All study protocol and trial documentation was reviewed by the appropriate ethics committees and institutional review boards before our study began.

Randomisation and masking

After eligibility assessment, patients were randomly assigned by the investigator in each site by allocation of a prenumbered treatment pack (block-balanced randomisation codes were computer-generated by Catalent Pharma Solutions, Bolton, UK). Patients were stratified across groups according to antipsychotic drug use and were not identified by name on trial documents, but by their screening or randomisation number. To ensure equal distribution of patients receiving antipsychotic drugs in the different treatment groups, we used different randomisation sequences for patients either receiving or not receiving antipsychotic drugs. A separate log of patient codes, names, and addresses was maintained confidentially by the investigators at their sites. Treatment packs and tablets were identical in appearance to guarantee masking from the patient and the investigator. Placebo was matched to the study drug for taste, colour, and size. Only the independent safety committee were permitted to unmask data before the listings were compiled and locked, at which point the data were unmasked for statistical analysis. The statistical analysis plan and any exclusions from the per protocol set were finalised before unmasking.

Procedures

We randomly assigned patients (1:1:1) to receive placebo, 45 mg per day pridopidine, or 90 mg per day pridopidine (45 mg twice daily) orally for 26 weeks. Our choice of doses was based on efficacy data from a smaller, short-term study assessing the effects of pridopidine in patients with Huntington's disease[18] and on safety data generated from other studies (NeuroSearch, data on file). During the first 4 weeks, all patients received once-daily treatment with 45 mg pridopidine or placebo. Thereafter, the pridopidine dose was increased to 45 mg twice daily (morning and afternoon) in the 90 mg per day group while the 45 mg per day and placebo groups received placebo for their second daily dose. In cases of poor tolerability the afternoon capsule was stopped, resulting in a dose decrease in the 90 mg per day pridopidine group, but not in the other two groups. Compliance was assessed by capsule count at each visit. We judged as compliant all patients who took 70% or more of their capsules. Compliance greater than 100% was classified as 100% (since extra drug was provided in case a visit was delayed, some patients could have taken more than the intended amount of drug; also, some patients on the 90 mg per day dose who were de-escalated to 45mg per day could have mistakenly continued to take the second daily dose). All concomitant drug use was recorded.

Our primary outcome measure was change in the mMS from baseline to week 26. The mMS is a shortened version of the UHDRS total motor score (TMS)[19] that comprises items 4–10 (dysarthria, tongue protrusion, finger taps, pronate and supinate hands, fist–hand–palm sequencing, arm rigidity, and body bradykinesia) and 13–15 (gait, tandem walking, and retropulsion pull test), and excludes eye movements, dystonia, and chorea. This subscale has been tested on the Coenzyme Q_{10} and Remacemide Evaluation Huntington's Disease (CARE-HD) dataset,[20] and shows good internal consistency and test–retest reliability.[21,22] The rationale for our choice of the mMS as primary

endpoint was also based on results from a small, 4 week study in Scandinavian patients with Huntington's disease receiving 45 mg per day pridopidine, which suggested that the primary effects of the drug were on voluntary motor function.[18] We assessed the mMS at screening (week –2), baseline (week 0), and weeks 4, 8, 12, and 26. All investigators who administered the UHDRS–TMS were certified by the European Huntington's Disease Network.

Our prespecified secondary outcome measures were the clinical global impression improvement (CGI-I) assessment,[23] the Stroop word reading test, the UHDRS behavioural assessment, and the hospital anxiety and depression scale; secondary outcome measures were assessed at baseline (week 0) and at week 26. Our prespecified tertiary outcomes included changes in motor function, as measured by the UHDRS–TMS, and individual items within the mMS (gait and dysarthria). Our other prespecified tertiary outcomes included measures of cognitive function with the Stroop interference tests, the anxiety and depression subscales within the hospital anxiety and depression scale and the UHDRS behavioural assessment subscores, the UHDRS functional assessment, the UHDRS independence assessment, and the UHDRS functional capacity assessment. We also undertook standard safety and tolerability assessments.

Statistical analysis
To detect a between-group difference of 2·0 points (SD 3·6–4·4) in our primary outcome, with a two-sided significance level of 0·025, a power of 90%, and an assumed dropout rate of 10%, 82–122 patients would be needed per treatment group. Since we planned to undertake the statistical analysis with stratification of the sample according to use of antipsychotic drugs, it was necessary to increase the sample size to 420 patients (140 per group) to allow for the possibility of separate analyses of each stratum, should a significant interaction between strata and treatment be recorded.

Our full analysis set included all patients randomly assigned to study groups who received study drug and had a postrandomisation clinical assessment. Our per-protocol population included all patients who had 70% or greater compliance with treatment and completed the study in accordance with our protocol or with only minor violations. Events that led to exclusion from our per-protocol population were those thought to affect the validity of a patient's primary endpoint. These events included stopping the study drug more than 1 week before assessment of the primary outcome at week 26, an invalid mMS assessment at week 26 or made more than 28 days before the intended date of assessment, taking disallowed concomitant drugs, and inclusion and exclusion criteria violations and major protocol violations identified by clinical monitoring staff. The inclusion and exclusion of each patient in our per-protocol population was established before unmasking.

We assessed our primary endpoint in our full analysis set with an ANCOVA model, with treatment as the classification variable. Baseline mMS, sex, and use of antipsychotic drugs were covariates. We used the last observation carried forward method to account for missing data. We assessed the two pridopidine groups independently versus placebo and we used the Bonferroni method to adjust for multiple comparisons. The overall α level was 0·05 (0·025 for the Bonferroni adjustment). We also assessed our secondary and tertiary endpoints with the ANCOVA model with suitable baseline covariates. We report comparisons between active treatment and placebo as ANCOVA estimates unless we state otherwise.

We did predefined sensitivity analyses on our primary endpoint: to assess effects in our per-protocol population with the same ANCOVA model as for the full analysis set on observed cases; to assess interactions between treatment and study centre, use of antipsychotic drugs, and CAG repeat length; and a mixed-effects model for repeated measures without imputation for missing values, including terms for baseline mMS, sex, use of antipsychotic drugs, study week, and the interaction between study week and treatment.

We undertook exploratory post-hoc analyses to identify drivers of improvements in the mMS and the UHDRS–TMS, and to assess the effect of treatment on the mMS and the UHDRS–TMS when the CAG repeat length and age terms were included in our main effects ANCOVA model.

An independent safety committee reviewed masked data encompassing any protocol violations; numbers of patient withdrawals and the reason for withdrawal; adverse events and serious adverse events; and laboratory data. The committee was allowed to request unmasking of individual patients, the entire trial, or both, at any time, and reported its findings on a quarterly basis. This trial is registered with ClinicalTrials.gov, number NCT00665223.

Role of the funding source
This study was funded by NeuroSearch A/S. Employees of the company were involved in the study design, the collection, analysis, and interpretation of data, the writing of the report, and the decision to submit for publication. The corresponding author had full access to all the data in the study, received no payment for writing or revision of the report, and had final responsibility for the decision to submit for publication.

Results
The first visit of the first patient took place in April, 2008, and the first and last visits of the last patient took place in April and November, 2009, respectively. Figure 1 shows the trial profile. In total, 437 patients were randomly assigned and included in the full analysis set (144, 148, and 145 individuals in the placebo, 45 mg per day pridopidine, and 90 mg per day pridopidine groups,

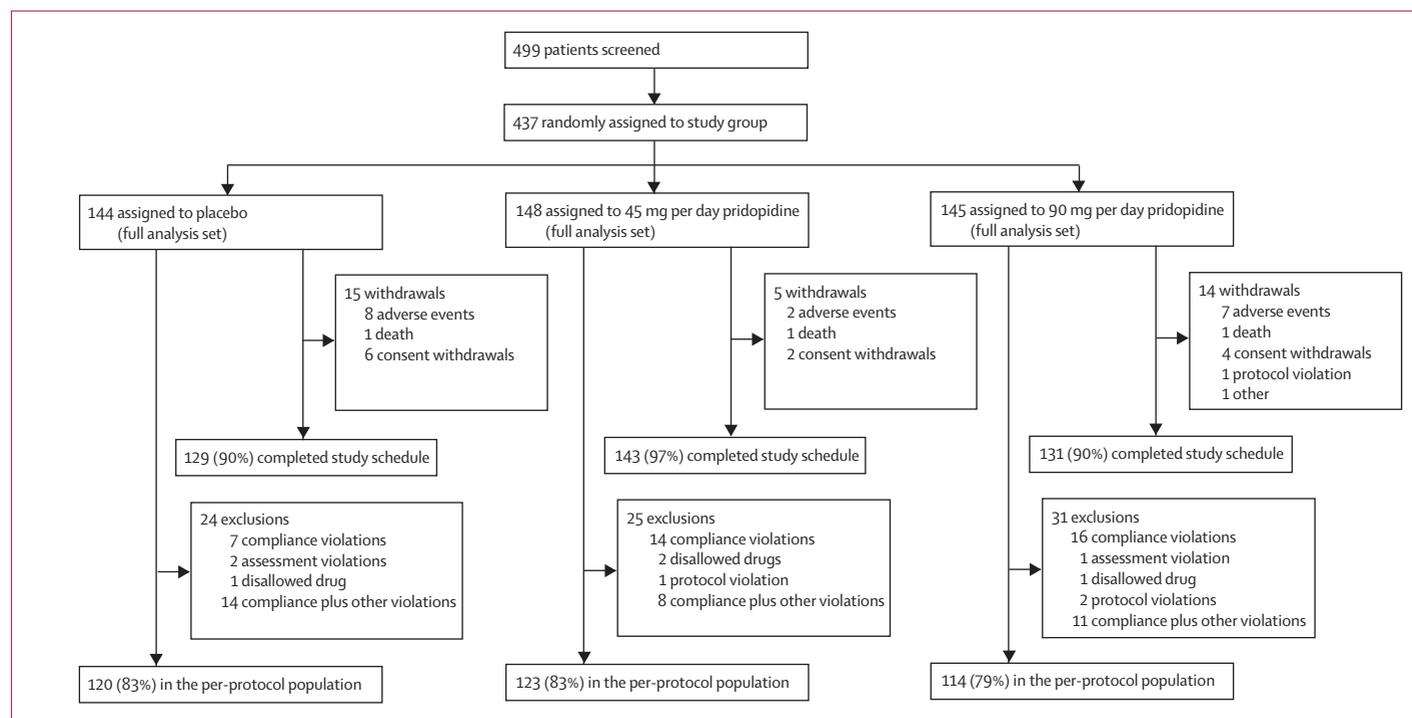*Figure 1:* Trial profile

	Placebo (n=144)	45 mg per day pridopidine (n=148)	90 mg per day pridopidine (n=145)	Total (n=437)
Sex				
Male	68 (47%)	66 (45%)	81 (56%)	215 (49%)
Female	76 (53%)	82 (55%)	64 (44%)	222 (51%)
Ethnic origin				
White	144 (100%)	145 (98%)	145 (100%)	434 (99%)
Asian	0	2 (1%)	0	2 (1%)
Latin American	0	1 (1%)	0	1 (<1%)
Age, years	49·1 (9·6)	51·0 (10·7)	51·8 (11·1)	50·6 (10·5)
Weight (kg)	68·2 (13·3)	67·2 (13·0)	69·9 (13·6)	68·4 (13·3)
Body-mass index (kg/m²)	23·9 (4·2)	24·0 (4·3)	24·2 (4·2)	24·0 (4·2)
Time since diagnosis of Huntington's disease (years)	4·8 (3·3)	4·5 (3·6)	5·1 (3·6)	4·8 (3·5)
Receiving antipsychotic drugs	64 (44%)	64 (43%)	62 (43%)	190 (43%)
CAG repeat length*	45·0 (3·5)	44·5 (3·5)	44·6 (3·4)	44·7 (3·5)
History of suicidal ideation	25 (17%)	22 (15%)	29 (20%)	76 (17%)
Total functional capacity score	7·4 (3·2)	7·9 (3·2)	7·7 (3·0)	7·7 (3·1)

Data are n (%) or mean (SD). CAG=cytosine–adenine–guanine. *CAG repeat length data were available for 426 patients.

Table 1: Baseline characteristics

respectively). Of these, 403 patients (92%) randomly assigned to study groups completed the study and 386 (88%) completed treatment (126 [88%] in the placebo group, 136 [92%] in the 45 mg per day pridopidine group, and 124 [86%] in the 90 mg per day pridopidine group). The primary reasons for discontinuation were adverse events and withdrawal of consent. Our per-protocol population included 357 patients.

Demographics and baseline characteristics of patients are shown in table 1. Patients were predominantly white. The mean age was 50·6 years (SD 10·5), with a mean time since diagnosis of Huntington's disease of 4·8 years (3·5). 190 (43%) of 437 patients were taking antipsychotic drugs. The mean CAG repeat length was 44·7 (3·5).

34 patients (8%) needed dose de-escalation: ten patients (7%) in the placebo group, 11 (7%) in the 45 mg per day pridopidine group, and 13 (9%) in the 90 mg per day pridopidine group. Compliance was similar in all treatment groups. Throughout our study, the proportion of patients judged to be compliant was 94% (136 patients) in the placebo group, 93% (137) in the 45 mg per day pridopidine group, and 94% (137) in the 90 mg per day pridopidine group. This compares with 88% (126), 89% (132), and 83% (120), respectively, during the last 3 months of the study. 400 patients (92%) were taking concomitant drugs: 92% (132 patients) in the placebo group, 92% (136) in the 45 mg per day group pridopidine, and 91% (132) in the 90 mg per day pridopidine group.

At baseline, the mean mMS was 19·43 points (SD 8·28) in the placebo group and scores were similar in the pridopidine groups (18·38 points [6·76] in the 45 mg per day pridopidine and 18·57 [6·90] in the 90 mg per day pridopidine group). By week 26, the mean mMS had decreased in the 90 mg per day pridopidine group relative to placebo (table 2), but there was no between-group difference because the p value did not reach our

prespecified threshold of p<0·025. Change from baseline at week 26 was 0·22 points (97·5% CI –0·55 to 0·99) in the placebo group, –0·14 (–0·90 to 0·63) in the 45 mg per day pridopidine group, and –0·77 (–1·54 to 0·00) in the 90 mg per day pridopidine group (figure 2).

In our per-protocol population, the between-group difference between 90 mg per day pridopidine and placebo was significant at week 26 (table 2). The interaction terms "pooled study centre by treatment" and "antipsychotic medication use by treatment" had no significant effect on treatment (p=0·196 and p=0·649, respectively), so we did not identify any independent statistically significant relation between the effects of the treatment and the different study centres or the use (or not) of antipsychotic drugs. The effect of CAG repeat length was statistically significant (p=0·009) although the interaction between CAG repeat length and treatment was not (p=0·470). By use of the mixed-effects model for repeated measures, we identified similar results as for our primary analysis: at week 26, the mean between-group difference for 90 mg per day pridopidine versus placebo in the full analysis set was –1·11 points (97·5% CI –2·25 to 0·03; p=0·029).

For our secondary outcomes, by week 26, none of the changes from baseline were statistically significant. In our CGI-I assessment, mean changes were 4·02 points (95% CI 3·86 to 4·19) in the placebo group, 4·03 (3·86 to 4·19) in the 45 mg per day pridopidine group, and 4·00 (3·84 to 4·16) in the 90 mg per day pridopidine group—a score of 4 points represents no overall change in CGI-I. Mean changes in the Stroop word reading test were –1·30 points (95% CI –3·31 to 0·71) in the placebo group, –1·10 (–2·81 to 0·61) in the 45 mg per day pridopidine group, and –0·80 (–2·77 to 1·17) in the 90 mg per day pridopidine group. Respective changes in the total UHDRS behavioural assessment were 0·12 points (95% CI –2·13 to 2·37), –0·41 (–3·13 to 2·31), and –2·22 (–4·02 to –0·42), and in the total hospital anxiety and depression scale score were –0·10 (–1·13 to 0·93), –0·73 (–1·85 to 0·39), and 0·13 (–0·87 to 1·13).

At baseline, the mean UHDRS–TMS was 42·78 points (SD 17·28) in the placebo group, and scores were similar in the pridopidine groups (41·14 [15·83] in the 45 mg per day pridopidine group and 41·81 [14·87] in the 90 mg per day pridopidine group). The mean UHDRS–TMS change from baseline to week 26 was 1·77 points (95% CI 0·35 to 3·19) in the placebo group, 0·90 (–0·50 to 2·29) in the 45 mg per day pridopidine group, and –1·19 (–2·60 to 0·22) in the 90 mg per day pridopidine group (full analysis set; figure 3). The between-group difference (90 mg per day pridopidine vs placebo) of –2·96 points (–4·96 to –0·97) was significant (p=0·004; table 3). Figure 4 shows the mean difference between 90 mg per day pridopidine and placebo in the change in individual UHDRS–TMS items from baseline to study end. Other tertiary motor and non-motor endpoints did not reach statistical significance.

	Population	Between-group differences vs placebo (97·5% CI)	p value
90 mg per day	Full analysis set (n=437)	–0·99 (–2·08 to 0·10)	0·042
45 mg per day	Full analysis set (n=437)	–0·36 (–1·44 to 0·72)	0·456
90 mg per day	Per-protocol population (n=357)	–1·29 (–2·47 to –0·12)	0·014
45 mg per day	Per-protocol population (n=357)	–0·63 (–1·78 to 0·53)	0·222

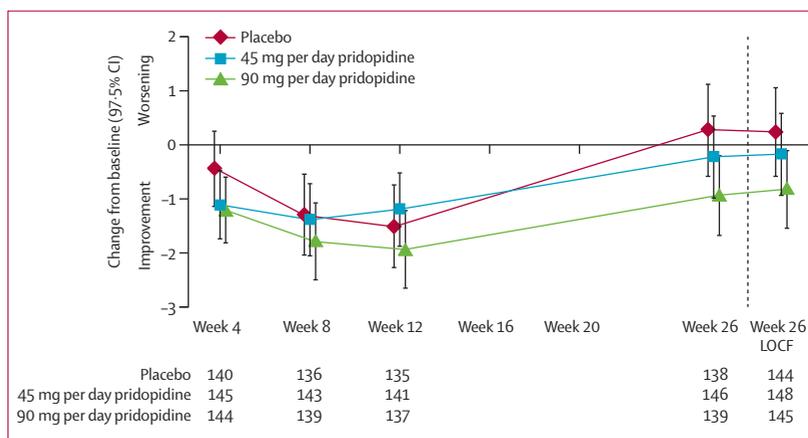*Table 2:* Change from baseline to week 26 in the modified motor score

Figure 2: Mean change from baseline in the modified motor score
Data at week 26 are also shown after adjustment for non-completers with last observation carried forward (LOCF).
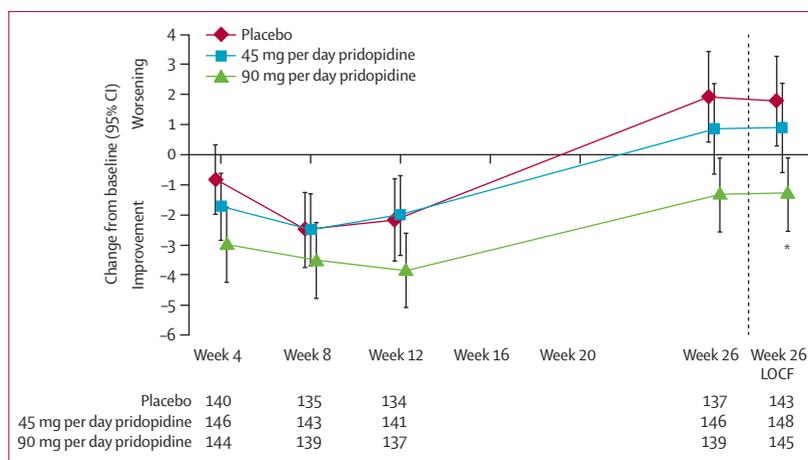

Figure 3: Mean change from baseline in the UHDRS–TMS
Data at week 26 are also shown after adjustment for non-completers using last observation carried forward (LOCF). UHDRS–TMS=unified Huntington's disease rating scale total motor score. *p=0·004 for the between-group difference (90 mg per day pridopidine vs placebo).

	Population	Between-group differences vs placebo (95% CI)	p value
90 mg per day	Full analysis set (n=437)	–2·96 (–4·96 to –0·97)	0·004
45 mg per day	Full analysis set (n=437)	–0·87 (–2·86 to 1·11)	0·387
90 mg per day	Per-protocol population (n=357)	–2·93 (–5·13 to –0·74)	0·009
45 mg per day	Per-protocol population (n=357)	–0·94 (–3·09 to 1·22)	0·392

Table 3: Change from baseline to week 26 in unified Huntington's disease rating scale total motor score
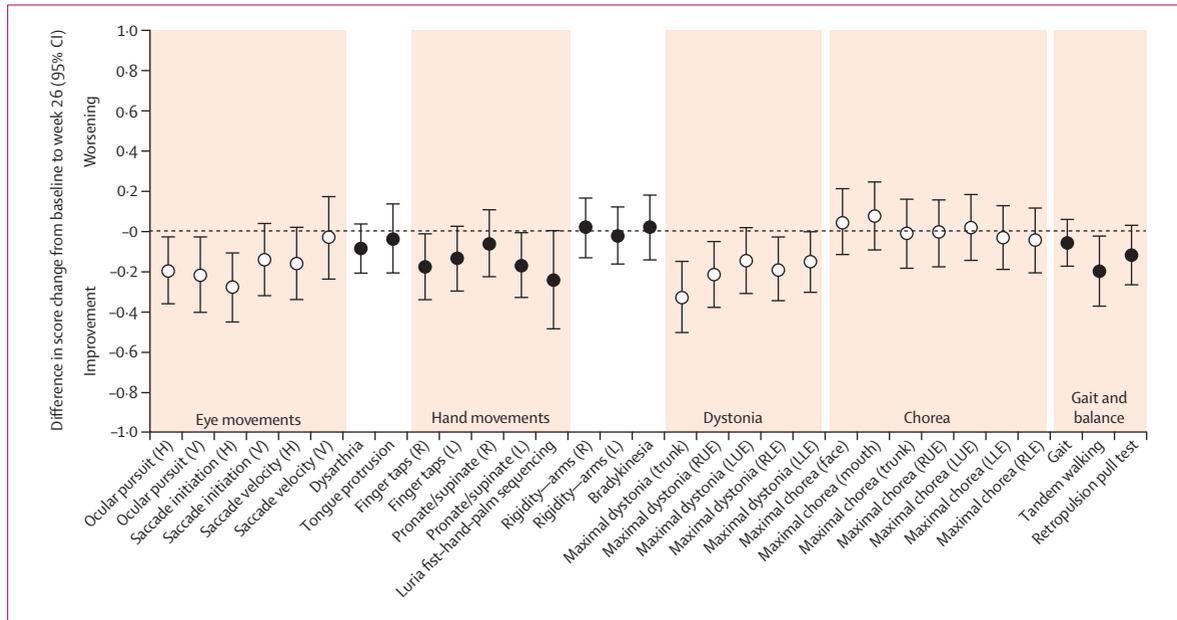
Figure 4: **Mean difference between 90 mg per day pridopidine and placebo in the change from baseline to week 26 for individual items in the UHDRS–TMS**
Black circles represent items included in the modified motor score. Shading denotes groups of similar items. H=horizontal. L=left. LLE=left lower extremity. LUE=left upper extremity. R=right. RLE=right lower extremity. RUE=right upper extremity. V=vertical. UHDRS–TMS=unified Huntington's disease rating scale total motor score.

	Difference (95% CI)	p value
Eye movements*	–1·07 (–1·85 to –0·30)	0·007
Dystonia	–1·03 (–1·64 to –0·42)	0·001
Chorea	0·14 (–0·67 to 0·95)	0·74
Hand movements†	–0·70 (–1·26 to –0·14)	0·015
Gait and balance‡	–0·35 (–0·66 to –0·04)	0·028

*Equivalent to the sum of unified Huntington's disease rating scale total motor score (UHDRS–TMS) items 1–3 (ocular pursuit, saccade initiation, and saccade velocity). †Equivalent to the sum of UHDRS–TMS items 6–8 (finger taps, pronate and supinate hands, and Luria fist–hand–palm sequencing). ‡Equivalent to the sum of UHDRS–TMS items 13–15 (gait, tandem walking, and retropulsion pull test).

Table 4: **Between-group differences (90 mg per day pridopidine vs placebo) for the change from baseline to week 26 in groups of items from the UHDRS-TMS**

	Placebo (n=144)	45 mg per day pridopidine (n=148)	90 mg per day pridopidine (n=145)
Any adverse event	92 (64%)	91 (61%)	99 (68%)
Fall	9 (6%)	7 (5%)	13 (9%)
Chorea	9 (6%)	7 (5%)	10 (7%)
Diarrhoea	5 (3%)	10 (7%)	9 (6%)
Dizziness	6 (4%)	11 (7%)	7 (5%)
Nausea	9 (6%)	10 (7%)	5 (3%)
Nasopharyngitis	5 (3%)	8 (5%)	9 (6%)
Depression	8 (6%)	6 (4%)	6 (4%)
Fatigue	8 (6%)	7 (5%)	4 (3%)
Insomnia	5 (3%)	5 (3%)	8 (6%)

Both the worsening of a pre-existing symptom or disorder and the appearance of any new symptom or disorder were reported as adverse events.

Table 5: **Adverse events**

Within the mMS, the main drivers of improvement were hand movements and gait and balance. In addition to these, the main drivers of improvement in the UHDRS–TMS were eye movements and dystonia (table 4). Results of our exploratory analysis on the mMS, including both CAG repeat length and age, confirmed that the effect of CAG repeat length was statistically significant (p=0·007), but the effect of age was not (p=0·171); the treatment difference between 90 mg per day pridopidine and placebo was –1·12 (p=0·024). For the UHDRS–TMS, between-group differences for 90 mg per day pridopidine versus placebo were similar to those in our main model including the CAG repeat length interaction with treatment (–2·91 points, 95% CI –4·91 to –0·92) and the CAG repeat length and age interaction (–3·02, –5·02 to –1·01).

Overall, the mean exposure to study drug was 169·4 days (SD 44·1; median 182, IQR 180–188) and was similar across the three groups: 170·5 days (SD 42·9; median 182, IQR 180–188) in the placebo group, 172·5 (SD 38·9; median 182, IQR 181–188) in the 45 mg per day pridopidine group, and 165·0 (SD 49·9; median 182, IQR 179–188) in the 90 mg per day pridopidine group. Pridopidine was well tolerated and had an adverse event profile similar to that of placebo. Most patients in each group reported at least one adverse event (table 5). The most common adverse events were falls, chorea, diarrhoea, dizziness, and nausea. 47 patients (11%) experienced an adverse event that needed intervention or withdrawal of study drug, and 185 (42%) reported an adverse event judged to be related to study drug (65 patients [45%] in the placebo group, 56 [38%] in the

45 mg per day pridopidine group, and 64 [44%] in the 90 mg per day pridopidine group). The incidence of serious adverse events was similar across all groups (11 [8%], ten [7%], and nine [6%], respectively). There were three deaths during our study: one in the placebo group (suicide) reported as possibly related to study drug, one in the 45 mg per day pridopidine group (urosepsis), and one in the 90 mg per day pridopidine group (subarachnoid haemorrhage). The deaths in the pridopidine groups were judged unlikely to be related to study drug.

Discussion

Our findings show that the mean reduction of 0·99 points in the mMS in patients receiving 90 mg per day pridopidine compared with those receiving placebo (p=0·042) fell short of the threshold that we predefined for multiple comparisons in our full analysis set (p<0·025). We did not identify any statistically significant improvements in non-motor secondary and tertiary outcome measures, which assessed deficits in cognition and functional capacity, and were included to test potential effects of pridopidine on symptom domains other than motor function. In view of the complexity of the disease, it is perhaps unsurprising that significance was not reached on these non-motor endpoints. Also, the scales might have been insensitive to changes over the timescale of our study. For example, the UHDRS functional capacity assessment encompasses five diverse areas such as the ability to handle financial affairs, to keep a job, or to maintain independence in activities of normal daily living.[19] Patients in the present study had a baseline score of 7 points on this scale and an improvement of one point would constitute a major change, such as being able to be at home (2 points) rather than requiring chronic care (1 point), or being able to perform a job partially (1 point) or not at all (0 points). Thus, it seems unlikely that a change of this size would occur over a 6 month period with a symptomatic intervention.

Our sensitivity analyses on the primary endpoint revealed similar findings to the primary analysis and suggest that pridopidine might have some effect on motor function. Indeed, for our tertiary endpoint the UHDRS–TMS (from which the mMS is derived), there was a significant improvement with 90 mg per day pridopidine, which was driven by improvements in dystonia and eye movements. The motor symptoms that improved in our study (hand movements, and gait and balance) are recognised by physicians as clinically meaningful. For example, the improvement in hand movements might mean that a patient becomes able to handle cutlery and feed himself or herself, and the improvement in gait and balance might mean that the patient is less likely to fall.

Although the UHDRS–TMS results are interesting, this was only a tertiary endpoint and limited conclusions can be made from these findings. However, these have been reproduced in a phase 2b trial run in parallel with our study,[24] suggesting that they warrant further investigation. The UHDRS–TMS is a scale of 31 items used to rate different motor deficits in patients with Huntington's disease, such as incoordination, akinesia, chorea, dystonia, and ocular movements. The scale has a maximum score of 124 points. By comparison, the mMS (with a maximum score of 52 points) focuses mainly on clinical deficits related to akinesia and includes only 13 items (chorea, dystonia, and ocular movements are excluded). Our choice of mMS as the primary endpoint was based on the findings of a 4 week phase 2 study that used the UHDRS–TMS and did not show an effect of treatment on the excluded items.[18] We expected the exclusion of these items from the mMS in our study to reduce potential noise in the motor results. In retrospect, the UHDRS–TMS would have been chosen as a primary endpoint rather than the mMS; although the effects of 90 mg per day pridopidine on the mMS in our study were not statistically significant, they were detectable in a broader spectrum of motor symptoms than we expected. This finding might be due to the fact that some neurological symptoms and signs take longer to respond to treatment than others. For example, the improvement in dystonia that we recorded might have been possible because of a longer study duration than that of the previous phase 2 study, allowing changes in synaptic plasticity (ie, improvements in dystonia might need longer treatment).[25]

There is an unmet need for treatments for patients with Huntington's disease. Tetrabenazine is effective for the treatment of chorea[27] and other drugs, including neuroleptics, are also used to treat chorea, to treat other dyskinesias, and to mitigate psychotic behaviour.[13] However, previous studies have not shown any significant improvements in a range of voluntary motor symptoms or the overall motor phenotype. Indeed, a

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Panel: **Research in context**

Systematic review

We reviewed references within a recent Cochrane systematic review[12] and searched PubMed (from 2007 to December, 2010) with the terms "Huntington's disease", "HD", "Huntington's disease treatment efficacy", and the limits "human, randomized controlled trial, English". We also undertook an unlimited search of PubMed with the terms "pridopidine", "ACR16" (the development name for pridopidine) and "(–)-OSU6162" (a pridopidine-related compound). By use of the quality of evidence criteria described in the *Guide to Clinical Preventative Services*,[26] one study was identified as level 1 (class A): TETRA-HD,[27] reporting the symptomatic treatment of chorea with tetrabenazine.

Interpretation

Our study is a level 1 (class A) study; pridopidine did not produce a statistically significant change in the primary endpoint or in any functional assessment scales, but 90 mg per day pridopidine produced a slight improvement in a tertiary endpoint, the unified Huntington's disease rating scale total motor score. Whether pridopidine might complement available treatments in patients with Huntington's disease, by improving motor deficits other than chorea, merits further investigation.

Cochrane review[12] concludes that no statement can be made on the best medical practice for the control of motor and non-motor symptoms of Huntington's disease (panel). Pridopidine has the potential to complement available treatments by improving a different range of motor deficits. Its lack of severe side-effects, irrespective of antipsychotic use, suggests that pridopidine might be useful, even for those patients who are treated at sites that are not centres of excellence for Huntington's disease.

The pharmacological mode of action of pridopidine entails fast-off competitive inhibition of D2 receptors[28] and enhanced cortical levels of synaptic dopamine. Cortical dopamine activates synaptic NMDA receptor-mediated transmission,[17] strengthening corticostriatal connectivity. Preclinically, the major behavioural consequence is normalisation of disrupted motor activity (eg, hypoactivity, dyskinesias, and hyperactivity).[29] This seems to correlate with a clinical improvement of hypokinetic and hyperkinetic features. These benefits might be linked to the effects of pridopidine on D2 receptors, and to an indirect enhancement of the corticostriatal connectivity. Eye movement abnormalities are one of the first signs of Huntington's disease[30] and might be directly related to weakened corticostriatal connectivity.[31]

Our study has certain limitations. First, our primary hypothesis was not met. However, we believe the UHDRS–TMS data we present, which are from a larger and longer study than those data reported previously,[18] warrant further investigation. Second, the sensitivity to treatment effects of the mMS has not been validated; however, there is no intervention for Huntington's disease against which it could have been validated (tetrabenazine targets only chorea). Although our last observation carried forward method has the potential to introduce bias, especially if large numbers of patients drop out, sensitivity analyses with our per-protocol population and our mixed-effects model for repeated measures (observed cases only) yielded similar results to the primary analysis, in terms of effect size and significance. Furthermore, few patients dropped out of our study, suggesting that any potential bias with the last observation carried forward would be very low. Reduced motor performance is known to be associated with functional impairment,[32] and improvements were identified in clinically relevant domains such as hand movements and balance and gait. However, the improvements in recorded motor performance did not translate into an overall functional improvement, as measured by the UHDRS independence, functional capacity, and functional assessments. This might be because the size of the change was insufficient to produce a functional effect. However, in view of the aforementioned limitations of the functional scales and their insensitivity to detect a change, it is also possible that a functional effect could have been detected with a

more granular scale (ie, consisting of smaller incremental changes, providing greater resolution). Inclusion of more granular scales is warranted in future studies. Finally, no symptoms worsened and pridopidine was well tolerated, suggesting a potentially favourable risk–benefit profile.

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