Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study

Ralf Reilmann, Andrew McGarry*, Igor D Grachev, Juha-Matti Savola, Beth Borowsky, Eli Eyal, Nicholas Gross, Douglas Langbehn, Robin Schubert, Anna Teige Wickenberg, Spyros Papapetropoulos, Michael Hayden, Ferdinando Squitieri, Karl Kieburtz, G Bernhard Landwehrmeyer, on behalf of the European Huntington's Disease Network and the Huntington Study Group investigators†*

Summary

Background Previous trials have shown that pridopidine might reduce motor impairment in patients with Huntington's disease. The aim of this study was to ascertain whether higher doses of pridopidine than previously tested reduce motor symptoms in a dose-dependent manner while maintaining acceptable safety and tolerability.

Methods PRIDE-HD was a randomised, placebo-controlled, phase 2, dose-ranging study in adults (aged ≥21 years) with Huntington's disease at outpatient clinics in 53 sites across 12 countries (Australia, Austria, Canada, Denmark, France, Germany, Italy, Poland, Russia, the Netherlands, the UK, and the USA). Eligible patients had clinical onset after age 18 years, 36 or more cytosine-adenine-guanine repeats in the huntingtin gene, motor symptoms (Unified Huntington's Disease Rating Scale total motor score [UHDRS-TMS] ≥25 points), and reduced independence (UHDRS independence score ≤90%). Patients were randomly assigned (1:1:1:1:1) with centralised interactive-response technology to receive one of four doses of pridopidine (45, 67·5, 90, or 112·5 mg) or placebo orally twice a day for 52 weeks. Randomisation was stratified within centres by neuroleptic drug use. The primary efficacy endpoint was change in the UHDRS-TMS from baseline to 26 weeks, which was assessed in all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment (full analysis set). Participants and investigators were masked to treatment assignment. This trial is registered with EudraCT (2013-001888-23) and ClinicalTrials.gov (NCT02006472).

Findings Between Feb 13, 2014, and July 5, 2016, 408 patients were enrolled and randomly assigned to receive placebo (n=82) or pridopidine 45 mg (n=81), 67·5 mg (n=82), 90 mg (n=81), or 112·5 mg (n=82) twice daily for 26 weeks. The full analysis set included 397 patients (81 in the placebo group, 75 in the 45 mg group, 79 in the 67·5 mg group, 81 in the 90 mg group, and 81 in the 112·5 mg group). Pridopidine did not significantly change the UHDRS-TMS at 26 weeks compared with placebo at any dose. The most frequent adverse events across all groups were diarrhoea, vomiting, nasopharyngitis, falls, headache, insomnia, and anxiety. The most common treatment-related adverse events were insomnia, diarrhoea, nausea, and dizziness. Serious adverse events occurred in the pridopidine groups only and were most frequently falls (n=5), suicide attempt (n=4), suicidal ideation (n=3), head injury (n=3), and aspiration pneumonia (n=3). No new safety or tolerability concerns emerged in this study. One death in the pridopidine 112·5 mg group due to aspiration pneumonia was considered to be possibly related to the study drug.

Interpretation Pridopidine did not improve the UHDRS-TMS at week 26 compared with placebo and, thus, the results of secondary or tertiary analyses in previous trials were not replicated. A potentially strong placebo effect needs to be ruled out in future studies.

Funding Teva Pharmaceutical Industries.

Introduction

Huntington's disease is an autosomal-dominant, neurodegenerative disorder that is caused by expansion of a cytosine-adenine-guanine triplet repeat in the huntingtin gene, resulting in a wide range of complex behavioural, cognitive, and motor symptoms that worsen over time.[1] With disease progression, patients experience functional decline,[2] increasing disability,[3] loss of independence, and premature death within 15–20 years of symptom onset.[1] Although two drugs (tetrabenazine and deutetrabenazine) are specifically approved for the management of involuntary choreatic movements in patients with Huntington's disease,[4,5] no treatment options exist for modification of voluntary motor coordination, worsening function, or disease progression.[6,7]

Pridopidine (TV-7820; formerly ACR16) is an investigational, oral, small-molecule drug in development for the treatment of patients with Huntington's disease.[7] It is a dopamine stabiliser, regulating dopamine-dependent behaviours and thus mediating striatal pathways involved in motor control via dopamine type 2 receptors.[8] Behavioural studies[9,10] in rats indicated that pridopidine

Lancet Neurol 2019; 18: 165–76

Published Online December 15, 2018 http://dx.doi.org/10.1016/S1474-4422(18)30391-0

See Comment page 131

*Contributed equally

†Investigators are listed in the appendix

George Huntington Institute, Münster, Germany (R Reilmann MD, R Schubert MS); **Department of Clinical Radiology, University of Münster, Münster, Germany** (R Reilmann); **Department of Neurodegenerative Diseases and Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany** (R Reilmann); **Movement Disorders Center, Cooper University Health Care, Camden, NJ, USA** (A McGarry MD); **Teva Pharmaceutical Industries, Frazer, PA, USA** (I D Grachev MD, B Borowsky PhD, N Gross MS); **Teva Pharmaceuticals International, Basel, Switzerland** (J-M Savola MD); **Teva Pharmaceutical Industries, Petach Tikva, Israel** (E Eyal MSc, A T Wickenberg PhD, Prof M Hayden MD); **Department of Psychiatry, University of Iowa, Iowa City, IA, USA** (Prof D Langbehn MD); **Massachusetts General Hospital, Boston, MA, USA** (S Papapetropoulos MD); **Unita' Operativa Ricerca e Cura Huntington e Malattie Rare, Istituto di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy** (F Squitieri MD); **Center for Health & Technology, University of Rochester Medical Center, Rochester, NY, USA** (Prof K Kieburtz MD); **and Department of Neurology,University of Ulm,**

Ulm, Germany
(Prof G B Landwehrmeyer MD)

Correspondence to:
Dr Ralf Reilmann, George Huntington Institute, 48149 Münster, Germany
ralf.reilmann@ghi-muenster.de

See Online for appendix

Research in context

Evidence before this study

We searched PubMed up to Feb 4, 2018, for English-language articles using the broad search terms "Huntington disease" AND "clinical trials". We performed a second search up to the same date using the terms "Huntington disease" AND "pridopidine", "ACR-16", and "(-)-OSU6162". To date, no intervention has been shown to provide symptomatic motor benefit beyond effects on chorea, and none has shown an effect on function in patients with Huntington's disease. Two large randomised controlled studies, MermaiHD and HART, investigated the effects of pridopidine up to 45 mg twice daily on motor impairment in patients with Huntington's disease. Although the primary endpoint, modified motor score (a subset of the total motor score [TMS] of the Unified Huntington's Disease Rating Scale [UHDRS]), was not met in either study, both found improvements in the overall UHDRS-TMS with pridopidine 45 mg twice daily, which resulted from changes across multiple TMS subitems assessing motor domains other than chorea.

Added value of this study

We aimed to explore the safety and efficacy of higher doses of pridopidine up to 112·5 mg twice daily. Pridopidine compared with placebo at all doses did not decrease motor impairment, as assessed by the UHDRS-TMS. Prespecified, exploratory analyses of selected quantitative motor (Q-Motor) measures revealed potential improvements with pridopidine 45 mg and 90 mg compared with placebo, although these findings are of unknown clinical significance and will need further confirmatory work. Exploratory findings of longer-term treatment (up to 52 weeks) provided some evidence that pridopidine 45 mg twice daily might have beneficial effects on global function in patients with Huntington's disease, as assessed with the total functional capacity scale of the UHDRS. However, this effect was not dose-dependent and needs independent replication.

Implications of all the available evidence

Pridopidine does not have detectable motor benefit, as assessed by the UHDRS-TMS. In view of the emerging preclinical properties of pridopidine, signs of potential efficacy in exploratory analyses of Q-Motor measures, and the favourable safety profile of the drug, further investigation might be warranted owing to the substantial unmet therapeutic needs of patients with Huntington's disease.

could modify pharmacologically induced hyperactive and hypoactive states. In 2016, unique pharmacological properties of pridopidine were reported, which suggested that the drug has additional effects on non-dopaminergic neurotransmission.[11] In particular, pridopidine exhibited high affinity for the sigma-1 receptor chaperone protein (half maximal inhibitory concentration around 100 nM),[12,13] a molecule that is believed to modify multiple pathways known to be impaired in Huntington's disease and other neurodegenerative diseases.[14]

Two large randomised controlled studies have investigated the effects of pridopidine on motor impairment in patients with Huntington's disease: MermaiHD[15] and HART.[16] Neither study found a significant difference between pridopidine and placebo groups in the primary endpoint, the modified motor score, which is a subset of the total motor score (TMS) of the Unified Huntington's Disease Rating Scale (UHDRS).[17] However, both studies provided exploratory evidence that pridopidine 45 mg twice daily might improve the overall UHDRS-TMS compared with placebo.[15,16] The improvement was small but consistent in amplitude across both studies. Furthermore, it was seen in TMS subdomains that assess motor functions other than chorea, suggesting potential efficacy in domains for which no treatment is available.[18] No effects were seen for lower doses of pridopidine (10 mg and 22·5 mg twice daily in HART or 45 mg once daily in MermaiHD), and doses higher than 45 mg twice daily were not assessed. In all studies,[15,16,19–21] pridopidine up to 45 mg twice daily was generally well tolerated, with a favourable safety profile up to 1 year of treatment in the open-label extension study of MermaiHD[19] and up to 3 years in the open-label extension study of HART.[20]

In view of pridopidine's safety profile and potential to improve motor symptoms, we designed the Pridopidine Dose Evaluation in Huntington Disease (PRIDE-HD) trial to investigate whether higher doses of pridopidine are associated with dose-dependent improvements in the UHDRS-TMS, while being safe and well tolerated.

For the **PRIDE-HD protocol** see http://www.ghi-muenster.de/protocols/pride-hd

For the **European Huntington Disease Network** see www.ehdn.org

For the **Huntington Study Group** see www.huntingtonstudygroup.org

Methods

Study design and participants

PRIDE-HD (protocol number TV7820-CNS-20002) was a randomised, double-blind, placebo-controlled, dose-ranging, phase 2 trial done at 53 member sites of the European Huntington Disease Network (EHDN; in Austria, Denmark, France, Germany, Italy, Poland, Russia, the Netherlands, and the UK; appendix) and the Huntington Study Group (HSG; in Australia, Canada, and the USA). Eligible patients were aged 21 years and older and had genetically confirmed presence of 36 or more cytosine-adenine-guanine repeats in one huntingtin gene and symptoms clinically indicative of Huntington's disease, as defined by diagnostic confidence level 4 (ie, motor abnormalities that are unequivocal signs of Huntington's disease [99% confidence]).[22] Clinical onset after age 18 years was required to avoid recruitment of individuals with juvenile-onset Huntington's disease. Participants had to be clinically symptomatic and ambulatory, with screening values of at least 25 points for the UHDRS-TMS and 90% or less for the UHDRS independence score. The availability and willingness of a caregiver or companion (someone attending to the

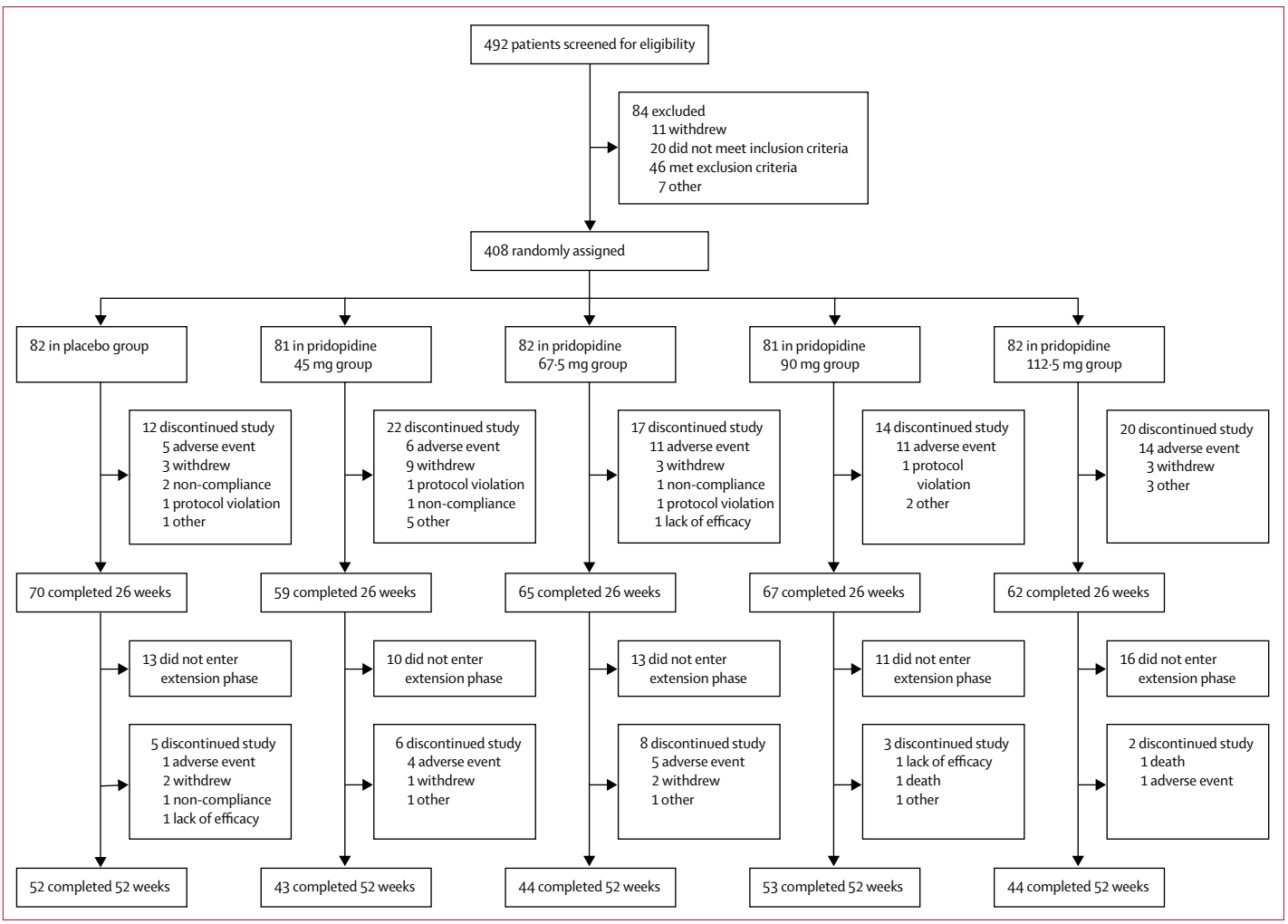

Figure 1: **Trial profile**
Patients in the pridopidine groups received the stated dose twice daily.

participant at least two to three times per week for at least 3 h each time) to accompany the participant to study visits was mandatory to assess caregiver feedback in secondary endpoints. Participants treated with permitted neuroleptics, antidepressants, or other psychotropic medications were required to have been on a stable dose for 6 weeks or more before randomisation.

Exclusion criteria were pregnant or lactating women; inadequate contraception (either sex); history of epilepsy or seizures within the past 5 years; use of disallowed neuroleptics, strong cytochrome P450 2D6 inhibitors, or tetrabenazine within 6 weeks of randomisation and throughout the study; and a known history or risk of long QT syndrome, prolonged QT corrected for heart rate with Fridericia's correction (QTcF) intervals (>450 ms) on electrocardiogram (ECG), or clinically significant heart disease. Patients with previous exposure to pridopidine or any investigational product within 6 weeks of screening were also excluded.

The study was initiated in February, 2014, with an intended duration of 26 weeks, and amended in January, 2015 (before the primary endpoint analysis), to 52 weeks to enable longer-term assessment of safety and, in view of the drug's potential for non-dopaminergic effects,[11–13] to perform an exploratory efficacy analysis of effects beyond motor function.

An independent data safety monitoring board (DSMB) reviewed anonymised data for protocol violations, withdrawals and reasons for withdrawal, adverse events and serious adverse events, and laboratory data. The DSMB could request unmasking of individual patients or the entire trial at any time and reported its findings regularly.

Ethical approval was obtained from institutional review boards or independent ethics committees at participating sites. The trial was done in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before

	Placebo group (n=82)	Pridopidine 45 mg group (n=81)	Pridopidine 67·5 mg group (n=82)	Pridopidine 90 mg group (n=81)	Pridopidine 112·5 mg group (n=82)
Age (years)	50·3 (11·3)	51·9 (11·8)	51·0 (11·8)	51·3 (12·7)	47·5 (11·4)
Sex					
Female	40 (49%)	40 (49%)	41 (50%)	43 (53%)	39 (48%)
Male	42 (51%)	41 (51%)	41 (50%)	38 (47%)	43 (52%)
White	73 (89%)	75 (93%)	78 (95%)	75 (93%)	77 (94%)
Bodyweight (kg)	72·7 (12·3)	69·5 (14·0)	69·9 (12·8)	70·5 (11·8)	70·7 (14·6)
CAG repeats	44·4 (3·2)	44·1 (4·1)	45·0 (4·7)	44·5 (4·9)	45·3 (3·7)
Stage 1–2 disease†	62 (76%)	64 (79%)	55 (67%)	56 (69%)	59 (72%)
Neuroleptics use	31 (38%)	31 (38%)	32 (39%)	31 (38%)	32 (39%)

Data are mean (SD) or n (%). CAG=cytosine-adenine-guanine. *Includes all randomised participants who received at least one dose of study drug. †Stages 1 and 2 are defined as total functional capacity scores of 11–13 and 7–10, respectively.

Table 1: **Demographic and clinical characteristics (safety population*)**

randomisation and for the study extension. This study was endorsed by the EHDN and the HSG.

Randomisation and masking

Patients were randomly assigned (1:1:1:1:1) with interactive response technology (ClinIntel; PAREXEL International, Waltham, MA, USA), using dynamic randomisation and applying the method of Pocock and Simon,[23] to receive placebo or pridopidine 45 mg, 67·5 mg, 90 mg, or 112·5 mg orally twice a day. Randomisation was stratified within centres by neuroleptic drug use. Placebo was matched to study drug on taste, colour, size, and treatment packaging. Participants, caregivers, the steering committee, site investigators, study staff, and the study sponsor were masked to treatment allocation.

Procedures

Participants were progressively titrated to their target dose over 4 weeks (appendix), followed by full-dose treatment up to week 26 or week 52. Participants were then assessed for safety for 2 weeks after the last dose. All participants in the full-dose treatment phase (pridopidine and placebo groups) took three capsules in the morning and three capsules in the afternoon; dose adjustments were not permitted. Compliance was assessed by investigators at each visit; participants who took at least 80% of their capsules were considered compliant. Primary efficacy assessments were done at screening (weeks –12 to –1); baseline (week 0); weeks 4, 8, 12, 16, 20, 26, and 52; and follow-up (week 54 or week 28 for participants who did not enter the extension phase).

Outcomes

The primary outcome was change from baseline to week 26 in the TMS of the UHDRS.[24] The TMS is a categorical scale (range 0–124) consisting of 31 subitems that assess eye movements, dysarthria, tongue protrusion, voluntary hand function, involuntary motor signs, and gait or balance.

The prespecified secondary outcome was the modified physical performance test at week 26,[25] which has been shown to correlate with established functional status assessments and gait.[26] Patients were timed while performing a series of nine standardised tasks mimicking basic and complex activities of daily living. Times for completion of tasks were converted to a categorical score of 0–4, where 0 represented inability to complete a task. The maximum score on the nine-item modified physical performance test is 36, with a higher score indicating better performance.

Prespecified exploratory endpoints included the total functional capacity (TFC),[27] independence,[24] and functional assessment[24] scales of the UHDRS; the short version of the problem behaviours assessment for Huntington's disease;[28] quantitative motor (Q-Motor) tests (ie, digitomotography [finger tapping], dysdiadochomotography [alternating pronate–supinate hand tapping], manumotography [precision grip force], choreomotography [chorea assessment], and pedomotography [foot tapping]);[29,30] TMS gait and balance subitems;[17] and the timed up and go test.[26] Cognition was assessed with the Huntington's disease Cognitive Assessment Battery.[31] Global assessments of change and quality of life were done with the Clinical Global Impression of Change scale, the Clinician's Interview-Based Impression of Change Plus Caregiver Input scale, the Physical Disability Scale, the Huntington's disease health-related quality-of-life questionnaire, and the European Quality of Life Five Dimension Five Level assessment. Exploratory assessments were done at baseline and weeks 4, 12, 26, and 52. Additional assessments were done at week 20 for the TFC scale and at weeks 20 and 28 for the independence scale.

Standard safety and tolerability assessments included adverse events, serious adverse events (defined in the protocol), laboratory tests, vital signs, 12-lead ECG, and the Columbia Suicide Severity Rating Scale.[32] At the request of the DSMB, additional safety monitoring measures were implemented and individual-patient discontinuation criteria were updated during the study to collect additional data and ensure participant safety considering the suicidality risk in patients with Huntington's disease.[33]

Statistical analysis

We estimated that 80 participants per group would provide 84% power to detect at least a 4·0-point change from baseline to week 26 in the TMS, assuming a SD of 8·5[15] and a type I error of 5%. This sample size also provided 71% power to detect a change from baseline to week 26 of 2·0 points or more in the modified physical performance test, assuming a SD of 5·0 and a type I error of 5%.

All primary and secondary efficacy analyses were done on the full analysis set at week 26, which included all randomised participants who received at least one dose of study drug and had at least one post-baseline efficacy assessment. The safety population included all

	Placebo group (n=81)	Pridopidine 45 mg group (n=75)	Pridopidine 67·5 mg group (n=79)	Pridopidine 90 mg group (n=81)	Pridopidine 112·5 mg group (n=81)
Total motor score					
Baseline†	42·9 (13·96)	40·5 (13·28)	42·9 (14·17)	43·0 (15·02)	42·7 (12·25)
Week 26†‡	38·4 (15·93)	37·3 (16·42)	39·8 (15·52)	39·0 (15·99)	39·7 (14·94)
Mean (SE) change from baseline	−4·5 (0·96)	−3·2 (0·92)	−3·1 (1·02)	−4·0 (1·02)	−3·0 (0·86)
LSM (SE) change from baseline	−4·79 (0·99)	−3·37 (1·05)	−3·09 (1·02)	−4·13 (1·00)	−2·74 (1·01)
LSM difference *vs* placebo§	..	1·42 (−1·39 to 4·23); 0·32	1·70 (−1·06 to 4·46); 0·23	0·66 (−2·07 to 3·39); 0·63	2·04 (−0·71 to 4·80); 0·14
Week 52†	40·4 (16·45)	38·5 (15·97)	41·9 (16·07)	41·4 (18·28)	41·7 (15·75)
Mean (SE) change from baseline	−2·5 (1·07)	−2·0 (0·92)	−1·0 (1·08)	−1·6 (1·30)	−1·0 (1·02)
LSM (SE) change from baseline	−2·03 (1·25)	−1·43 (1·36)	0·54 (1·32)	−0·29 (1·27)	0·71 (1·34)
LSM difference *vs* placebo§	..	0·60 (−3·02 to 4·22); 0·74	2·57 (−0·98 to 6·13); 0·16	1·74 (−1·74 to 5·22); 0·33	2·73 (−0·86 to 6·32); 0·14
Modified physical performance test					
Baseline†	25·5 (6·10)	24·9 (5·77)	26·1 (5·31)	25·7 (5·52)	25·7 (5·61)
Week 26†	26·2 (5·99)	25·6 (5·55)	26·6 (5·33)	26·6 (5·18)	26·6 (6·38)
Mean (SE) change from baseline	0·7 (0·39)	0·7 (0·36)	0·4 (0·44)	0·6 (0·42)	0·8 (0·45)
LSM (SE) change from baseline	0·71 (0·41)	0·75 (0·42)	0·64 (0·41)	0·70 (0·40)	1·00 (0·40)
LSM difference *vs* placebo§	..	0·04 (−1·09 to 1·17); 0·95	−0·07 (−1·20 to 1·05); 0·90	−0·01 (−1·12 to 1·10); 0·99	0·29 (−0·82 to 1·40); 0·61
Week 52†	25·8 (6·20)	25·5 (5·72)	26·2 (5·66)	26·0 (5·95)	25·8 (6·70)
Mean (SE) change from baseline	0·3 (0·44)	0·6 (0·39)	0·0 (0·47)	0·1 (0·47)	0·0 (0·55)
LSM (SE) change from baseline	0·05 (0·54)	0·51 (0·57)	0·22 (0·57)	−0·28 (0·54)	−0·42 (0·57)
LSM difference *vs* placebo§	..	0·46 (−1·07 to 2·00); 0·55	0·17 (−1·37 to 1·71); 0·83	−0·33 (−1·82 to 1·16); 0·66	−0·47 (−2·00 to 1·06); 0·55

LSM=least square mean. *Includes all randomised participants who received at least one dose of study drug and had at least one post-baseline efficacy assessment. †Data are mean (SD). ‡Primary endpoint; the change in total motor score from baseline to 26 weeks in the 45 mg group was not included in the primary analysis. §Data are LSM (95% CI); p value.

Table 2: **Primary and secondary efficacy assessments (full analysis set*)**

randomised participants who received at least one dose of study drug. All evaluations at week 52 were for exploratory purposes.

We analysed changes from baseline using a repeated measures model that included an interaction term between categorical week in trial and treatment as a fixed effect, as well as country, neuroleptic drug use, and baseline TMS score, as fixed effects. Country, not site, was used as a fixed-effect covariate in the model because many sites recruited too few patients to allow estimation of treatment effect within sites. We used an unstructured covariance matrix for repeated observations within patients to account for potential temporal fluctuations in variance within groups. Thus, the results were essentially equivalent to separate dose comparisons at the individual follow-up times using analysis of covariance.

We compared mean changes from baseline to week 26 in TMS between the active treatment groups and the placebo group. The comparison of the 45 mg twice a day group with the placebo group was not included in the primary efficacy analysis to reduce the penalty in the α value due to multiple comparisons but served as a comparator to previous pridopidine studies[15,16] and was included in exploratory efficacy analyses. The change from baseline to week 26 in the modified physical performance test was analysed with the same methods as used for the primary efficacy endpoint except that baseline modified physical performance test scores were included in the model instead of baseline TMS. We used

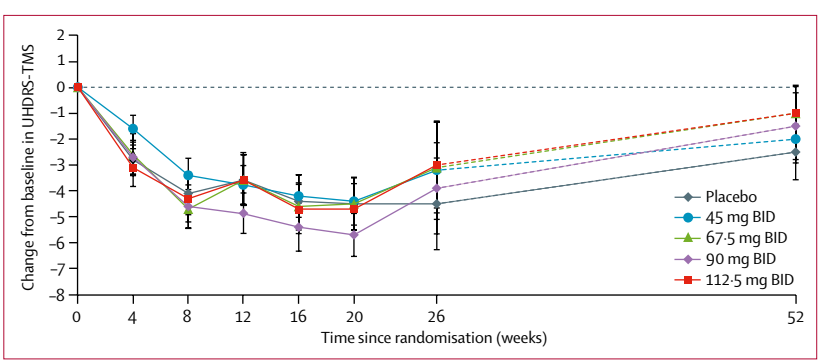

Figure 2: **Change from baseline in UHDRS-TMS (full analysis set)**
Data are means with SEs. BID=twice daily. UHDRS-TMS=Unified Huntington's Disease Rating Scale total motor score.

Hochberg's Step-Up method for multiple comparisons between treatment groups and hierarchical testing of the primary and secondary efficacy endpoints,[34] to maintain an experiment-wise type I error of 5%.

Prespecified exploratory efficacy endpoints were analysed at weeks 26 and 52. The p values for these exploratory endpoints are nominal and not corrected for multiple comparisons; they are a relative measure of strength of evidence among these outcomes and should not be interpreted as measures of statistical significance relative to traditional standards (p≤0·05).

To reduce the number of Q-Motor outcomes analysed, and identify the measures from each task that are most representative of the main dimension of variation

	Placebo group (n=82)	Pridopidine 45 mg group (n=81)	Pridopidine 67·5 mg group (n=82)	Pridopidine 90 mg group (n=81)	Pridopidine 112·5 mg group (n=82)
Any adverse event	62 (76%)	63 (78%)	69 (84%)	71 (88%)	67 (82%)
Treatment-related adverse event	27 (33%)	26 (32%)	40 (49%)	38 (47%)	36 (44%)
Adverse events leading to treatment discontinuation	6 (7%)	10 (12%)	16 (20%)	12 (15%)	15 (18%)
Gastrointestinal disorders					
Diarrhoea	9 (11%)	9 (11%)	11 (13%)	12 (15%)	10 (12%)
Nausea	4 (5%)	4 (5%)	7 (9%)	4 (5%)	3 (4%)
Vomiting	4 (5%)	5 (6%)	6 (7%)	6 (7%)	4 (5%)
Toothache	3 (4%)	1 (1%)	2 (2%)	4 (5%)	2 (2%)
Constipation	1 (1%)	3 (4%)	4 (5%)	2 (2%)	0
Dysphagia	1 (1%)	0	4 (5%)	4 (5%)	1 (1%)
Dry mouth	0	0	3 (4%)	2 (2%)	4 (5%)
General disorders					
Fatigue	7 (9%)	3 (4%)	6 (7%)	7 (9%)	1 (1%)
Infections					
Nasopharyngitis	7 (9%)	14 (17%)	12 (15%)	13 (16%)	15 (18%)
Urinary tract infection	4 (5%)	3 (4%)	6 (7%)	4 (5%)	5 (6%)
Injury, poisoning, and procedural complications					
Falls	17 (21%)	19 (23%)	21 (26%)	14 (17%)	16 (20%)
Contusion	3 (4%)	6 (7%)	6 (7%)	0	3 (4%)
Laceration	2 (2%)	2 (2%)	3 (4%)	0	4 (5%)
Ligament sprain	1 (1%)	4 (5%)	0	0	0
Investigations					
Increased blood creatine phosphokinase	4 (5%)	4 (5%)	4 (5%)	4 (5%)	0
Decreased bodyweight	3 (4%)	4 (5%)	3 (4%)	3 (4%)	7 (9%)
Decreased clearance of renal creatinine	1 (1%)	5 (6%)	2 (2%)	3 (4%)	5 (6%)
Musculoskeletal disorders					
Back pain	3 (4%)	4 (5%)	3 (4%)	6 (7%)	5 (6%)
Nervous system disorders					
Headache	8 (10%)	7 (9%)	7 (9%)	11 (14%)	8 (10%)
Balance disorder	3 (4%)	2 (2%)	5 (6%)	1 (1%)	3 (4%)
Dyskinesia	3 (4%)	2 (2%)	0	4 (5%)	3 (4%)
Dizziness	2 (2%)	2 (2%)	6 (7%)	5 (6%)	6 (7%)
Akathisia	1 (1%)	0	4 (5%)	1 (1%)	1 (1%)
Chorea	1 (1%)	4 (5%)	13 (16%)	3 (4%)	7 (9%)
Psychiatric disorders					
Irritability	7 (9%)	4 (5%)	6 (7%)	5 (6%)	2 (2%)
Depression	4 (5%)	0	2 (2%)	2 (2%)	4 (5%)
Insomnia	3 (4%)	5 (6%)	11 (13%)	9 (11%)	9 (11%)
Anxiety	2 (2%)	6 (7%)	7 (9%)	7 (9%)	5 (6%)
Restlessness	0	0	4 (5%)	1 (1%)	1 (1%)
Suicidal ideation	0	2 (2%)	8 (10%)	2 (2%)	1 (1%)
Respiratory disorders					
Cough	2 (2%)	5 (6%)	2 (2%)	1 (1%)	5 (6%)
Skin disorders					
Rash	0	4 (5%)	3 (4%)	1 (1%)	1 (1%)

(Table 3 continues on next page)

between study participants, we did a cross-sectional principal component analysis of all 34 Q-Motor measures at baseline (ten measures for each of the three tapping paradigms [ie, digitomotography, dysdiadochomotography, and pedomotography], two for manumotography, and two for choreomotography). The selected measures are reported as mean (SE) values from the right and left hand or foot. Tapping measures (eg, inter-onset and inter-peak intervals[30]) were reported as mean time (to assess movement speed) or mean SDs (to assess variability in motor coordination).

We performed additional post-hoc analyses for weeks 4 and 12 to explore the timeline of responses observed in Q-Motor measures (reported in figures only). Exploratory post-hoc analyses were also done to identify drivers of improvements in TFC scale scores in subgroups of patients with higher function, defined according to Shoulson–Fahn criteria as Huntington's disease stage 1 (TFC scores 11–13) or stage 2 (TFC scores 7–10).[27]

Statistical analyses were done with SAS, version 9.1.3. This study is registered with EudraCT (2013-001888-23) and ClinicalTrials.gov (NCT02006472).

Role of the funding source

The funder was involved in study design, data collection, data analysis, data interpretation, revision of the manuscript, and the decision to submit for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 13, 2014, and July 5, 2016, 492 patients were screened for eligibility, of whom 408 were enrolled and randomly assigned to treatment (figure 1). 323 patients completed 26 weeks of the study, of whom 260 continued to participate and receive treatment in the 52 weeks of the extended study. 68 patients could not continue because of delayed approval of the protocol extension at certain sites. In total, 236 patients completed the full 52 weeks of the study.

Demographic and clinical baseline characteristics were well balanced between groups (table 1). The majority of participants were white and had early-stage Huntington's disease (table 1). Treatment compliance was high in all groups: 338 (83%) of 408 randomised patients were compliant with study medications during the first 26 weeks of the study.

The full analysis set consisted of 397 patients, including 81 in the placebo group, 75 in the pridopidine 45 mg group, 79 in the pridopidine 67·5 mg group, 81 in the pridopidine 90 mg group, and 81 in the pridopidine 112·5 mg group. Pridopidine treatment did not lead to any significant change in the UHDRS-TMS from baseline to week 26 at any dose compared with placebo (table 2, figure 2), and the differences were still not significant at 52 weeks (table 2). Similarly, scores on the modified physical performance

test did not significantly improve with pridopidine compared with placebo at either timepoint (table 2).

Pridopidine at all treatment doses was generally well tolerated. Most adverse events in all groups were mild or moderate in severity (data not shown). Diarrhoea, vomiting, nasopharyngitis, falls, headache, insomnia, and anxiety were the most frequently reported (≥5% of patients) adverse events in all groups (table 3). 13 patients (all in pridopidine groups; table 3) reported suicidal ideation and four (one each in the pridopidine 45 mg and 90 mg groups and two in the pridopidine 112·5 mg group) reported suicide attempt. This imbalance in reports of suicidal ideation between pridopidine and placebo groups was less apparent when suicidality was assessed by prespecified, per-protocol procedures with the Columbia Suicide Severity Rating Scale, which showed a change from negative to positive in four (5%) of 82 patients in the placebo group, two (2%) of 81 patients in the pridopidine 45 mg group, seven (9%) of 82 patients in the pridopidine 67·5 mg group, one (1%) of 81 patients in the pridopidine 90 mg group, and three (4%) of 82 patients in the pridopidine 112·5 mg group.

Overall, 35 participants, all in pridopidine groups, reported at least one serious adverse event (table 3). The most frequent serious adverse events were falls (four in the 45 mg group and one in the 90 mg group), suicidal ideation (one each in the 67·5 mg, 90 mg, and 112·5 mg groups), head injury (two in the 45 mg group and one in the 112·5 mg group), and aspiration pneumonia (one each in the 67·5 mg, 90 mg, and 112·5 mg groups). The frequency of adverse events leading to treatment discontinuation was higher in the pridopidine groups than in the placebo group, and of the pridopidine groups, was lowest in the 45 mg group, suggesting a decrease in tolerability with increasing doses of pridopidine (table 3).

The most common treatment-related adverse events were insomnia (in one patient in the placebo group, four in the pridopidine 45 mg group, three each in the pridopidine 67·5 mg and 90 mg groups, and seven in the pridopidine 112·5 mg group), diarrhoea (in one patient each in the placebo and pridopidine 45 mg groups, five each in the pridopidine 67·5 mg and 90 mg groups, and three in the pridopidine 112·5 mg group), nausea (in one patient in the placebo group, four in the pridopidine 45 mg group, three each in the pridopidine 67·5 mg and 90 mg groups, and one in the pridopidine 112·5 mg group), and dizziness (in one patient in the placebo group, four each in the pridopidine 67·5 mg and 90 mg groups, and two in the pridopidine 112·5 mg group). Two deaths occured during the study: a woman in the 90 mg group experienced a lethal accident (fall), which was deemed to be unrelated to the study drug, and a man in the 112·5 mg group died of aspiration pneumonia, which was considered as possibly related to the study drug.

Cardiac safety monitoring showed a mild dose-dependent increase in heart rate, with no effect on blood pressure. QTcF increased in a dose-dependent manner; the maximal post-baseline QTcF value calculated during the study was 497 ms in the pridopidine 112·5 mg group. No patient had a value of 500 ms or higher or less than 480 ms accompanied by a change in QTcF greater than 60 ms (based on the mean value from triplicate ECG measurements). Abnormal QTcF values observed in the study are presented in the appendix. Mild increases of serum creatinine concentrations were seen in all pridopidine groups, showing clear dose dependency, but generally they remained within the normal range and changes were not deemed to be clinically meaningful. The values observed at the follow-up visit, after a washout period of 2 weeks, indicated a de-challenge effect (trend towards recovery). No other abnormalities in clinical laboratory parameters were observed.

We did prespecified exploratory analyses of ten Q-Motor measures that had the highest correlations with the first principal component in a joint analysis of all Q-Motor tasks (appendix). We found evidence of improvements in Q-Motor finger tapping inter-onset and inter-peak intervals in the pridopidine 45 mg and 90 mg groups (figure 3; appendix). No improvements in Q-Motor finger tapping were detected in the placebo group, which showed slight increases in these intervals over the course of the study. Similarly, within-participant SDs of Q-Motor finger tapping inter-onset and inter-peak intervals appeared to increase in the placebo group, whereas they were improved in the pridopidine 90 mg group compared with the placebo group at week 26 (figure 3; appendix).

	Placebo group (n=82)	Pridopidine 45 mg group (n=81)	Pridopidine 67·5 mg group (n=82)	Pridopidine 90 mg group (n=81)	Pridopidine 112·5 mg group (n=82)
(Continued from previous page)					
Vascular disorders					
Hypertension	1 (1%)	0	1 (1%)	5 (6%)	2 (2%)
Serious adverse events	0	8 (10%)	9 (11%)	9 (11%)	9 (11%)
Cardiac†	0	0	1 (1%)	0	0
Eye†	0	0	0	0	1 (1%)
Gastrointestinal†	0	0	3 (4%)	4 (5%)	1 (1%)
Infection or infestations†	0	0	1 (1%)	2 (2%)	1 (1%)
Injury, poisoning, or procedural complications†	0	11 (14%)	0	1 (1%)	3 (4%)
Investigations†	0	1 (1%)	0	0	0
Neoplasms†	0	2 (2%)	0	1 (1%)	1 (1%)
Nervous system†	0	0	2 (2%)	1 (1%)	1 (1%)
Psychiatric†	0	2 (2%)	3 (4%)	2 (2%)	4 (5%)
Renal or urinary†	0	0	0	1 (1%)	0
Reproductive system and breast†	0	0	1 (1%)	1 (1%)	0
Respiratory, thoracic, or mediastinal†	0	0	2 (2%)	1 (1%)	1 (1%)

Data are number of patients (%), unless otherwise stated. Adverse events occurring in ≥5% of patients in any group are shown. *Includes all randomised participants who received at least one dose of study drug. †Data are number of events (%).

Table 3: **Summary of adverse events (safety population*)**

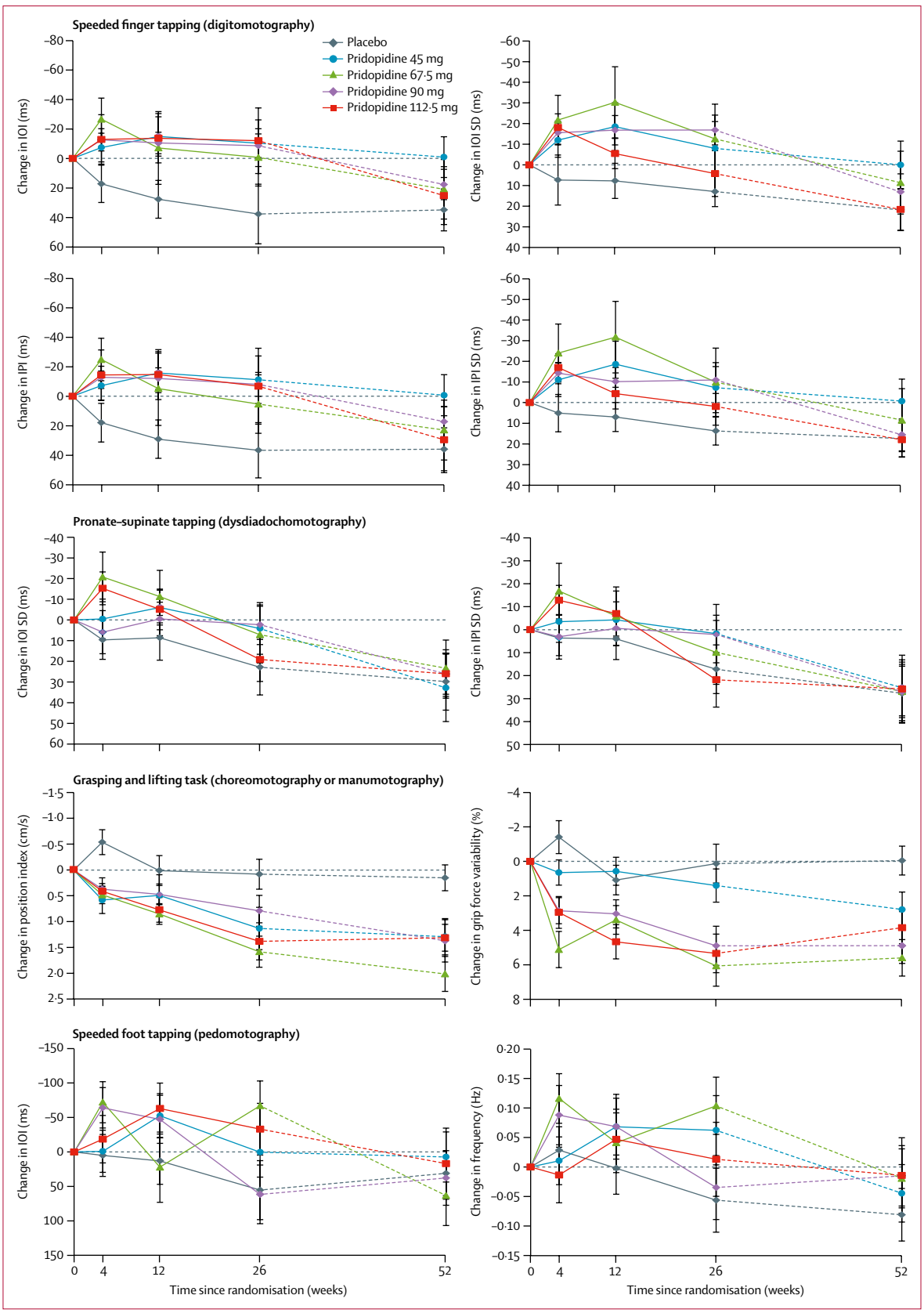

Figure 3: **Changes from baseline in quantitative motor measures (full analysis set)**
Data are means with SEs. IOI and IPI SDs reflect the within-participant variability in motor performance at difference visits. IOI=inter-onset interval. IPI=inter-peak interval.

There was some evidence of improvement in pronation–supination hand tapping in the groups treated with pridopidine: compared with placebo at 26 weeks, variability in the inter-onset interval was reduced in the 45 mg and 90 mg groups and variability in the inter-peak interval was reduced in the 45 mg group (figure 3; appendix). The lift position index (chorea analysis) was increased in all pridopidine groups compared with placebo at 26 and 52 weeks, and grip-force variability (grasping-force analysis) was increased in the pridopidine 67·5 mg, 90 mg, and 112·5 mg groups at 26 weeks and in all pridopidine groups at 52 weeks (appendix). No improvements were seen in other Q-Motor assessments (appendix).

At 26 weeks, no dose of pridopidine had caused any significant improvement in TFC scale scores compared with placebo. Exploratory analyses at week 52 suggested a possible effect on function for pridopidine 45 mg twice daily (figure 4; appendix). No linear dose-dependency was observed for the effect on TFC. Post-hoc analyses showed that this effect for 45 mg pridopidine on TFC was most evident at 52 weeks in patients with early-stage Huntington's disease (stages 1 and 2; appendix). The evidence was also strongest for this subgroup at week 26 (appendix). All domains of the TFC scale, except occupation, contributed substantially to improvements on this scale in this early-stage subpopulation at week 56 (appendix).

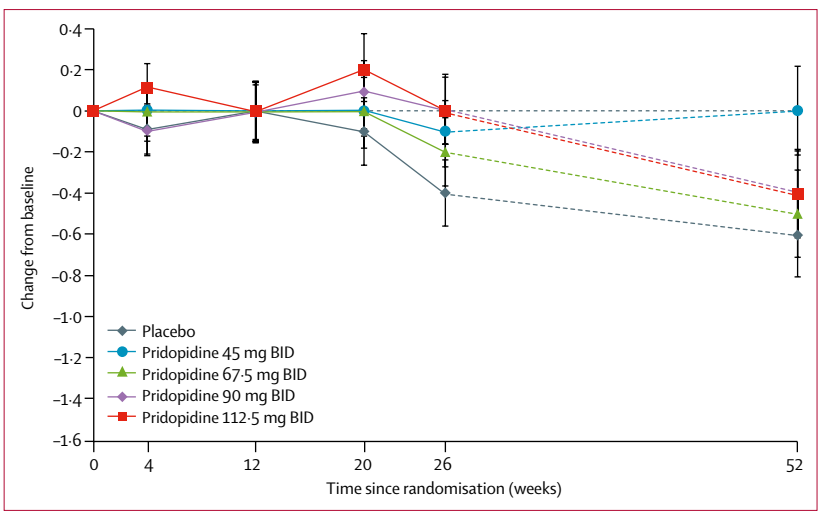

Figure 4: **Change from baseline in total functional capacity (full analysis set)**
Data are means with SEs.

Discussion

This phase 2 study was designed to investigate the symptomatic effects of high doses of pridopidine on motor function over 26 weeks in patients with Huntington's disease, with extension of the trial to 52 weeks to explore safety and symptomatic efficacy. The study did not meet its primary or secondary endpoints at 26 weeks; compared with placebo, no dose of pridopidine significantly decreased motor impairment, as assessed with the UHDRS-TMS and modified physical performance test.

Changes in motor impairment from baseline to week 26 in all treatment groups were of similar magnitude to those observed with pridopidine 45 mg twice daily in previous studies.[8,9] The placebo effect for the primary endpoint was large, with the mean TMS in the placebo group decreasing by about 5 points between baseline and 26 weeks (a numerically larger effect than those seen for all active treatment groups). Placebo effects in the TMS are common in clinical trials in patients with Huntington's disease. Factors that might have contributed to the sizeable placebo effect include high expectations of participants and investigators based on motor improvements observed in previous studies and the high allocation ratio (4:1) to active treatment versus placebo.[35] The rater-independent motor effects observed with the Q-Motor measures of finger-tapping (digitomotography) and pronation–supination hand tapping (dysdiadochomotography) in the pridopidine 45 mg and 90 mg groups, changes in chorea (choreomotography) and grip force (manumotography) assessments across all dose groups, and the minimal changes in Q-Motor measures in the placebo group support the notion that a rater-induced placebo effect might have impeded the detection of a treatment effect on the TMS. Future clinical trials, particularly phase 1 and 2 trials, should address these factors, using rater-independent, quantitative outcomes to minimise placebo effects and detect efficacy signs.[7]

We included the modified physical performance test as a secondary efficacy endpoint in this study to characterise pridopidine's effects on activities of daily living. Data on how well the test performs over the course of the disease or in response to treatment are scarce.[36] No significant difference between placebo and pridopidine treatment groups or trend towards improvement were seen in scores on this test.

Pridopidine was generally well tolerated in this study, and we did not observe any new safety or tolerability findings. Psychiatric adverse events, such as depression, suicidal ideation, and suicide attempt, are common symptoms of Huntington's disease[37] and were seen in all groups. There was a small imbalance between active treatment groups and the placebo group in reports of suicidality and serious adverse events (none were reported in the placebo group). This imbalance was less apparent when suicidality was assessed with the Columbia Suicide Severity Rating Scale, which showed a change from negative to positive in all groups, including the placebo group. Natural history studies reported that the prevalence of suicidal ideation increased from about 9% of those at risk of Huntington's disease without motor signs or symptoms to about 20% of those with early signs of the disease and about 24% of those who had possible early-stage Huntington's disease.[32] Therefore, suicidality would be expected in studies in patients with symptomatic Huntington's disease. Nevertheless, we acknowledge that suicidal ideation and suicide attempts should be carefully

monitored in any future study of pridopidine. We also acknowledge that the proportion of patients who discontinued treatment was higher in the treated groups than in the placebo group and that the data suggest a possible dose-dependency. This finding should be considered in future studies, although our observations do not appear to preclude the doses used from further exploration.

Among exploratory endpoints, we observed a possible effect of pridopidine on function, as assessed by TFC scores, at 52 weeks. This effect was seen only in patients receiving pridopidine 45 mg twice daily and was most evident in the early clinical stages of Huntington's disease. It is unclear why this effect was not dose-dependent or whether a more robust effect in earlier clinical stages of the disease reflects a stage-dependent response. Given the number of exploratory outcomes studied, this effect could be due to chance and needs independent replication. Preclinical data from the YAC128 mouse model of Huntington's disease support a larger effect of pridopidine on motor and behavioural domains for early stages than for later stages of the disease.[38] Functional capacity declines throughout the course of the disease but more steeply in earlier than in later stages; patients with early-stage Huntington's disease show a TFC decline of 0·8–1·2 points per year.[2]

No placebo effect was observed for TFC, with an annual decline in the placebo group that was similar to that reported previously.[37,39] It is not clear how pridopidine would prevent a decline in functional capacity without corresponding improvements in other measures. Converging evidence for the pridopidine 45 mg twice daily dose from the exploratory Q-Motor efficacy measures suggests that attenuation of functional decline, as measured by TFC, might reflect small improvements in multiple clinical domains. Some of these improvements in categorical clinical outcomes might have been too modest to detect but could be reflected in aggregate via the TFC.

The pridopidine 45 mg group performed better on Q-Motor tapping measures than did the other dose groups between 26 weeks and 52 weeks. Although choreomotography showed a slight induction of involuntary activity across doses, grip-force variability was not increased with pridopidine 45 mg twice daily, thus favouring the low dose. The fact that this constant motor variability was only seen with the low dose might reflect a narrow window of efficacy for pridopidine but, in view of the multiple exploratory analyses, this result might be spurious. Further studies are required to substantiate these observations. Additionally, these data suggest that doses above 45 mg twice daily deserve less consideration in future Huntington's disease clinical trials.

Although we assessed several exploratory endpoints other than TFC and Q-Motor measures to identify possible endpoints for future trials of pridopidine, none showed an effect of pridopidine. The effects observed on some of the Q-Motor measures in the pridopidine groups might be explained by the higher sensitivity of rater-independent quantitative assessments than rater-dependent clinical scales, as shown in tracking the progression of pre-manifest and early-stage Huntington's disease cohorts in TRACK-HD,[30,40] and in detecting drug effects in a previous randomised clinical trial[41] in patients with Huntington's disease (particularly in the finger-tapping task). High standardisation across sites and the absence of placebo responses[17] are other important characteristics of Q-Motor measures that facilitate establishing proof-of-concept for drug effects and assessment of dose–response relationships. However, the clinical meaningfulness of changes in these measures is not yet defined and is the subject of ongoing research.[7,17] Nevertheless, the response profiles shown for the Q-Motor measures are consistent with a possible CNS effect of pridopidine, with the timeline of these responses being suggestive of a dopamine receptor-mediated effect. This effect is important when considering development of pridopidine beyond Huntington's disease.

Although speculative, it is conceivable that a functional effect of pridopidine could be mediated via the sigma-1 receptor, an endoplasmic reticulum-resident transmembrane protein. Evidence for activity of pridopidine at the sigma-1 receptor was provided in the Q175 knock-in mouse model of Huntington's disease, wherein pridopidine led to sigma-1 receptor-dependent increases in BDNF concentrations and activation of pathways known to promote neuronal plasticity and survival in cell cutures.[17] Further evidence for a possible beneficial effect of pridopidine comes from studies in the YAC128 mouse model of Huntington's disease: in one study, sigma-1 receptor was shown to be upregulated by excessive calcium in the endoplasmic reticulum.[14] Impaired calcium homeostasis in the endoplasmic reticulum is known to be abnormal in patients with Huntington's disease.[42] Pridopidine prevented spine loss in medium spiny neurons in a sigma-1 receptor-dependent manner[11,14] and normalised endoplasmic reticulum calcium homoeostasis.[14] In receptor occupancy studies in rats,[12] compared with higher doses, lower doses of pridopidine disproportionately favoured the role of sigma-1 receptor over receptors of other neurotransmitters.[12] Further investigation is necessary to clarify whether these preclinical sigma-1 receptor-mediated effects can translate into functional benefits in patients with Huntington's disease. PRIDE-HD was not designed to assess disease-modifying effects of pridopidine, and we do not intend to convey such properties on the basis of the data obtained in this study. However, this information might be considered for possible future studies of pridopidine.

This study has several limitations. First, no formal correction for type 1 error across multiple comparisons was done for the prespecified exploratory endpoints. Second, the non-stratified loss of patients in all study groups between weeks 26 and 52 due to delays in approval of the trial extension at some sites might have limited the

reliability of the 52-week exploratory analysis. However, in view of the novel preclinical findings that were published while PRIDE-HD was ongoing,[11–14] the findings for TFC and Q-Motor measures seem of value for future clinical development of pridopidine, although longer study periods might be needed to understand pridopidine's effect on endpoints of function.

In conclusion, pridopidine did not improve motor impairment at 26 weeks compared with placebo, as assessed clinically with the UHDRS-TMS. Given that improvements were seen in some exploratory, rater-independent Q-Motor assessments, a higher than expected placebo effect might have affected the primary outcome. Evidence from these exploratory endpoints must be considered as provisional, and in the context of multiple comparisons, we cannot claim statistical significance for these results. Treatment over 52 weeks suggested that pridopidine 45 mg twice daily might have some potential functional benefit. Further investigation of this finding might be considered in light of pridopidine's relatively favourable safety profile and the absence of therapies that affect global function.[7] A sufficiently powered study designed to minimise placebo effects (eg, a larger relative placebo sample size, longer follow-up, and endpoints less affected by rater bias) is needed to clarify the possible effect of pridopidine on overall function and motor symptoms in patients with Huntington's disease.

Contributors

RR served as the principal investigator for Europe; was involved in study design, data collection, data analysis, and data interpretation; did Q-Motor analyses; and wrote the first draft of the manuscript. AM served as co-principal investigator for North America and Australia and was involved in data analysis, data interpretation, and drafting of the manuscript. IDG was the sponsor's responsible medical officer and project physician and was involved in study design, medical monitoring, data analysis, safety reviews, interpretation of study results, and writing of the manuscript. J-MS, BB, NG, SP, and MH were involved in study design, data analysis, data interpretation, and writing of the manuscript. EE did the statistical analyses and was involved in study design, data interpretation, and writing of the manuscript. DL was involved in data analysis, data interpretation, the principal component analysis of Q-Motor data, critical statistical review, and writing of the manuscript. RS was involved in Q-Motor data analyses, the principal component analysis of Q-Motor data, data interpretation, and writing of the manuscript. ATW was involved in study design, study implementation, data interpretation, and writing of the manuscript. FS was involved in study design, data collection, and revising the manuscript. KK was the principal investigator for North America and Australia and was involved in study design, data analysis, data interpretation, and writing of the manuscript. GBL served as global principal investigator and was involved in study design, data collection, data analysis, data interpretation, and writing of the manuscript.

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 serves as an elected member of the steering committees of the EHDN and the HSG, co-chair of the Task Force on Huntington's Disease, and member of the Task Force on Technology of the International Parkinson and Movement Disorder Society. He has provided consulting services, advisory board functions, clinical trial services, Q-Motor analyses, or lectures for Actelion Pharmaceuticals, Amarin Neuroscience, AOP Orphan Pharmaceuticals, Cure Huntington Disease Initiative Foundation (CHDI), Desitin, Hoffmann-La Roche, Ionis Pharmaceuticals, Ipsen, Lundbeck, Link Medicine, Meda Pharma, Medivation, Mitoconix, Neurocrine Biosciences, Neurosearch, Novartis, Omeros, Pfizer, Prana Biotechnology, Prilenia Therapeutics, Raptor Pharmaceuticals, Siena Biotech, Temmler Pharma, Teva Pharmaceuticals, uniQure, Vaccinex, Wave Life Sciences, and Wyeth Pharmaceuticals. He has received grant support from Bundesministerium für Bildung und Forschung (BMBF), CHDI, Deutsche Forschungsgemeinschaft (DFG), Deutsches Zentrum für Neurodegeneration und Entzündung, European Union Seventh Framework Program (EU-FP7), EHDN, High Q Foundation, and National Science Foundation. AM has received grant support from, and participated on advisory boards and lectured for, Teva Pharmaceuticals. NG and J-MS are employed by Teva Pharmaceuticals. RS is an employee of the George Huntington Institute and received funding from the EU-FP7 for the further development of Q-Motor measures for clinical trial use. FS provided consulting and participated on advisory boards for Teva Pharmaceuticals, Pfizer, Raptor, Omani Ministry of Health, and Istituto per la Sicurezza Sociale di San Marino. He is co-founder of, and scientific officer and consultant for, the not-for-profit organisation Italian League for Research on Huntington and related diseases. BB, EE, IDG, ATW, SP, and MH were employed by Teva Pharmaceuticals at the time of study and manuscript preparation. SP has patents pending for use of pridopidine to treat dystonias and functional decline. KK has received consulting fees from Acorda, Astellas Pharma, AstraZeneca, BioMarin Pharmaceutica, Biotie, Britannia, CHDI, Clearpoint Strategy Group, Clintrex, Corium International, Cynapsus, Forward Pharma, Genzyme, INC Research, Intec, Lundbeck, Medivation, Melior Discovery, Neuroderm, Neurmedix, Orion Pharma, Otsuka, Pfizer, Pharma2B, Prana Biotechnology, Prothena, Neotope, Elan Pharmaceutical, Raptor Pharmaceuticals, Remedy Pharmaceuticals, Hoffmann-La Roche, Sage Bionetworks, Sanofi, Serina, Sunovion, Synagile, Titan, Upsher-Smith, US WorldMeds, Vaccinex, Vertex Pharmaceuticals, Weston Brain Institute. KK has also received grants or research support from National Institutes of Health National Institute of Neurological Disorders and Stroke, Michael J Fox Foundation, and Teva Pharmaceuticals. GBL has provided consulting services, advisory board functions, clinical trial services, or lectures for Alnylam, Amarin, AOP Orphan Pharmaceuticals, Bayer Pharma, Desitin, GlaxoSmithKline, Hoffmann-La Roche, Ipsen, Ionis Pharmaceuticals, Lundbeck, Neurosearch, Medesis, Medivation, Medtronic, Novartis, Pfizer, Prana Biotechnology, PTC Therapeutics, Raptor Pharmaceuticals, Sangamo and Shire, Siena Biotech, Temmler Pharma, Teva Pharmaceuticals, UniQure, and Wave Life Sciences and has received grants from CHDI, BMBF, DFG, and EU-FP7. His study site, University of Ulm, has received compensation in the context of the observational REGISTRY-Study of EHDN and the observational Enroll-HD study from CHDI, as well as from Teva Pharmaceuticals. DL declares no competing interests.

Acknowledgments

We acknowledge the help and enthusiasm of the participants and caregivers and the investigators and staff at the participating sites; the support received from EHDN and HSG; the efforts of the DSMB under the leadership of Roger Albin; and Kathleen Blatt (former employee of Teva Pharmaceuticals), Helena Knebel (employee of Teva Pharmaceuticals), Gina Pastino (employee of Teva Pharmaceuticals), Leehee Navon-Perry (employee of Teva Pharmaceuticals), and Matthew D Davis (employee of Teva Pharmaceuticals) for their contributions to the study. Medical writing assistance (collation of comments, preparation of data tables, and final styling) was provided by Anita Chadha-Patel of ACP Clinical Communications and funded by Teva Branded Pharmaceutical Products R & D (Frazer, PA). This study was funded by Teva Pharmaceuticals.

References

1 Walker FO. Huntington's disease. *Lancet* 2007; **369:** 218–28.
2 Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. *Neurology* 2000; **54:** 452–58.
3 Ross CA, Pantelyat A, Kogan J, Brandt J. Determinants of functional disability in Huntington's disease: role of cognitive and motor dysfunction. *Mov Disord* 2014; **29:** 1351–58.
4 Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* 2006; **66:** 366–72.

5 Frank S, Testa CM, Stamler D, et al. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. *JAMA* 2016; **316:** 40–50.

6 Killoran A, Biglan KM. Current therapeutic options for Huntington's disease: good clinical practice versus evidence-based approaches? *Mov Disord* 2014; **29:** 1404–13.

7 Kieburtz K, Reilmann R, Olanow CW. Huntington disease: current and future therapeutic prospects. *Mov Disord* 2018; **33:** 1033–41.

8 Waters S, Tedroff J, Ponten H, Klamer D, Sonesson C, Waters N. Pridopidine: overview of pharmacology and rationale for its use in Huntington's disease. *J Huntingtons Dis* 2018; **7:** 1–16.

9 Ponten H, Kullingsjo J, Sonesson C, Waters S, Waters N, Tedroff J. The dopaminergic stabilizer pridopidine decreases expression of L-DOPA-induced locomotor sensitisation in the rat unilateral 6-OHDA model. *Eur J Pharmacol* 2013; **698:** 278–85.

10 Rung JP, Rung E, Helgeson L, et al. Effects of (-)-OSU6162 and ACR16 on motor activity in rats, indicating a unique mechanism of dopaminergic stabilization. *J Neural Transm* 2008; **115:** 899–908.

11 Geva M, Kusko R, Soares H, et al. Pridopidine activates neuroprotective pathways impaired in Huntington disease. *Hum Mol Genet* 2016; **25:** 3975–87.

12 Sahlholm K, Sijbesma JW, Maas B, et al. Pridopidine selectively occupies sigma-1 rather than dopamine D2 receptors at behaviorally active doses. *Psychopharmacology* 2015; **232:** 3443–53.

13 Squitieri F, DiPardo A, Favellato M, Amico E, Maglione V, Frati L. Pridopidine, a dopamine stabilizer, improves motor performance and shows neuroprotective effects in Huntington disease R6/2 mouse model. *J Cell Mol Med* 2015; **19:** 2540–48.

14 Ryskamp D, Wu J, Geva M, et al. The sigma-1 receptor mediates the beneficial effects of pridopidine in a mouse model of Huntington disease. *Neurobiol Dis* 2017; **97:** 46–59.

15 de Yebenes JG, Landwehrmeyer B, Squitieri F, et al. Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2011; **10:** 1049–57.

16 Huntington Study Group. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. *Mov Disord* 2013; **28:** 1407–15.

17 Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. *Handb Clin Neurol* 2017; **144:** 209–25.

18 Reilmann R. The pridopidine paradox in Huntington's disease. *Mov Disord* 2013; **28:** 1321–24.

19 Squitieri F, Landwehrmeyer B, Reilmann R, et al. One-year safety and tolerability profile of pridopidine in patients with Huntington disease. *Neurology* 2013; **80:** 1086–94.

20 McGarry A, Kieburtz K, Abler V, et al. Safety and exploratory efficacy at 36 months in Open-HART, an open-label extension study of pridopidine in Huntington's disease. *J Huntingtons Dis* 2017; **6:** 189–99.

21 Lundin A, Dietrichs E, Haghighi S, et al. Efficacy and safety of the dopaminergic stabilizer pridopidine (ACR16) in patients with Huntington's disease. *Clin Neuropharmacol* 2010; **33:** 260–64.

22 Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. *Mov Disord* 2014; **29:** 1335–41.

23 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.

24 Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996; **11:** 136–42.

25 Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The Physical Performance Test. *J Am Geriatr Soc* 1990; **38:** 1105–12.

26 Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39:** 142–48.

27 Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. *Neurology* 1979; **29:** 1–3.

28 Kingma EM, van Duijn E, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. *Gen Hosp Psychiatry* 2008; **30:** 155–61.

29 Reilmann R, Bohlen S, Klopstock T, et al. Grasping premanifest Huntington's disease—shaping new endpoints for new trials. *Mov Disord* 2010; **25:** 2858–62.

30 Bechtel N, Scahill RI, Rosas HD, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. *Neurology* 2010; **75:** 2150–60.

31 Stout JC, Queller S, Baker KN, et al. HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease (1,2,3.). *Mov Disord* 2014; **29:** 1281–88.

32 Posner K, Brown GK, Stanley B, et al. The Columbia Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011; **168:** 1266–77.

33 Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. *Am J Psychiatry* 2005; **162:** 725–31.

34 Huang Y, Hsu JC. Hochberg's step-up method: cutting corners off Holm's step-down method. *Biometrika* 2007; **94:** 965–75.

35 Reilmann R, McGarry A, Landwehrmeyer GB, et al. Efficacy, safety, and tolerability of pridopidine in Huntington's disease (HD): results from the phase II dose-ranging study, Pride-HD. *Mov Disord* 2017; **32** (suppl 2)**:** 323–24.

36 Busse M, Quinn L, Khalil H, McEwan K. Optimising mobility outcome measures in Huntington's disease. *J Huntingtons Dis* 2014; **3:** 175–88.

37 Papapetropoulos S, Jin Y, Ahadieh S, Liu J. Model-based meta-analyses (MBMA) of UHDRS-total motor score, total functional capacity and total chorea score in Huntington's disease (HD) clinical trials. 9th Annual Huntington's Disease Therapeutics Conference; Palm Springs, CA; Feb 24–27, 2014.

38 Garcia-Miralles M, Geva M, Tan JY, et al. Early pridopidine treatment improves behavioral and transcriptional deficits in YAC128 Huntington disease mice. *JCI Insight* 2017; **2:** 95665.

39 Dorsey ER, Beck CA, Darwin K, et al. Natural history of Huntington disease. *JAMA Neurol* 2013; **70:** 1520–39.

40 Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013; **12:** 637–49.

41 Reilmann R, Rouzade-Dominguez ML, Saft C, et al. A randomized, placebo-controlled trial of AFQ056 for the treatment of chorea in Huntington's disease. *Mov Disord* 2015; **30:** 427–31.

42 Raymond LA. Striatal synaptic dysfunction and altered calcium regulation in Huntington disease. *Biochem Biophys Res Commun* 2017; **483:** 1051–62.