Safety, tolerability, and efficacy of PBT2 in Huntington's disease: a phase 2, randomised, double-blind, placebo-controlled trial

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Summary

Background PBT2 is a metal protein-attenuating compound that might reduce metal-induced aggregation of mutant huntingtin and has prolonged survival in a mouse model of Huntington's disease. We aimed to assess the safety, tolerability, and efficacy of PBT2 in patients with Huntington's disease.

Methods In this 26-week, randomised, double-blind, placebo-controlled trial, adults (≥25 years old) with early-stage to mid-stage Huntington's disease were randomly assigned (1:1:1) by a centralised interactive response system to once daily PBT2 250 mg, PBT2 100 mg, or placebo. Randomisation was stratified by site with a block size of three. Participants, carers, the steering committee, site investigators, study staff, and the study sponsor were masked to treatment assignment. Primary endpoints were safety and tolerability. The safety population consisted of all participants who were randomly assigned and had at least one dose of study drug. The principal secondary endpoint was cognition, measured by the change from baseline to week 26 in the main composite *Z* score of five cognitive tests (Category Fluency Test, Trail Making Test Part B, Map Search, Symbol Digit Modalities Test, and Stroop Word Reading Test) and scores on eight individual cognitive tests (the five aforementioned plus the Trail Making Test Part A, Montreal Cognitive Assessment, and the Speeded Tapping Test). The intention-to-treat population comprised participants who were randomly assigned and had at least one efficacy assessment after administration of study drug. This trial is registered with ClinicalTrials.gov, NCT01590888.

Findings Between April 18, 2012, and Dec 14, 2012, 109 participants were randomly assigned to PBT2 250 mg (n=36), PBT2 100 mg (n=38), or placebo (n=35) at 19 research centres in Australia and the USA. 32 (89%) individuals on PBT2 250 mg, 38 (100%) on PBT2 100 mg, and 34 (97%) on placebo completed the study. Six serious adverse events (acute coronary syndrome, major depression, pneumonia, suicide attempt, viral infection, and worsening of Huntington's disease) occurred in five participants in the PBT2 250 mg group, three (fall with subdural haematoma, suicide attempt, and hospital admission for stabilisation of Huntington's disease) occurred in two participants in the PBT2 100 mg group, and one (increasing aggression) occurred in a participant in the placebo group. The site investigators deemed all, except the worsening of Huntington's disease, as unrelated to study drug. 32 (89%) participants on PBT2 250 mg, 30 (79%) on PBT2 100 mg, and 28 (80%) on placebo had at least one adverse event. Compared with placebo, neither PBT2 100 mg (least-squares mean 0·02, 95% CI –0·10 to 0·14; p=0·772) nor PBT2 250 mg (0·07, –0·05 to 0·20; p=0·240) significantly improved the main composite cognition *Z* score between baseline and 26 weeks. Compared with placebo, the Trail Making Test Part B score was improved between baseline and 26 weeks in the PBT2 250 mg group (17·65 s, 0·65–34·65; p=0·042) but not in the 100 mg group (0·79 s improvement, –15·75 to 17·32; p=0·925); neither dose significantly improved cognition on the other tests.

Interpretation PBT2 was generally safe and well tolerated in patients with Huntington's disease. The potential benefit on executive function will need to be confirmed in a larger study.

Funding Prana Biotechnology Limited.

Lancet Neurol 2014

Published Online
November 14, 2014
http://dx.doi.org/10.1016/S1474-4422(14)70262-5

See Online/Comment
http://dx.doi.org/10.1016/S1474-4422(14)70265-0

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Introduction

Huntington's disease is an autosomal dominant neurodegenerative disorder characterised by cognitive dysfunction, behavioural changes, and involuntary movements. Cognitive decline begins gradually in the prodromal phase,[1] progresses with the disease,[2] and contributes substantially to disease burden.[2]

PBT2 is a moderate-affinity 8-hydroxyquinoline transition metal ligand that acts as a synthetic chaperone, redistributing copper, zinc, and iron from locations where they are abundant to subcellular locations where they might be deficient.[3] These metals are highly abundant in the brain, and copper and zinc in particular are required for normal function of glutamatergic synapses.

In people with Huntington's disease and in transgenic Huntington's disease (R6/2) mice, increased concentrations of brain oxidative stress markers are associated with increased concentrations of the redox-active metals iron and copper,[4] which might promote the aggregation of mutant huntingtin.[4,5] On MRI, people with Huntington's disease have raised concentrations of iron in the basal ganglia and cortex, which are associated

See Online for appendix

with their cytosine–adenine–guanine (CAG) repeat number and disease severity.[6] Delivery of copper and zinc by PBT2 into the cytoplasm deactivates the kinase glycogen synthase kinase 3β and the phosphatase calcineurin,[7] both potential targets for Huntington's disease treatment.[8]

Exposure of huntingtin to copper in vitro induces its aggregation and promotes formation of reactive oxygen species. This aggregation is inhibited by the 8-hydroxyquinoline drug clioquinol.[4] In the R6/2 mouse model, clioquinol improves motor function, decreases brain atrophy, and reduces aggregated huntingtin.[9] PBT2 treatment in the R6/2 mouse also improves motor ability and increases body and brain weight.[10] Similarly, in the *Caenorhabditis elegans* model of Huntington's disease, PBT2 ameliorates the toxic effects of polyglutamine aggregation and increases lifespan.[10]

In aged wild-type mice, PBT2 improves cognitive ability and markers of neuronal plasticity and function.[11] In Alzheimer's disease mouse models, PBT2 inhibits accumulation of amyloid β, attenuates neuropathological effects of amyloid β, including amyloid-β-induced hyperphosphorylation of tau, and improves cognition.[12] In a 12-week, phase 2a, randomised, double-blind, placebo-controlled trial[13] in 78 individuals with mild Alzheimer's dementia, PBT2 was safe and well tolerated and significantly reduced concentrations of amyloid β_{42} in CSF. The secondary efficacy endpoints assessed cognitive effects, and participants receiving PBT2 250 mg did significantly better than those on placebo on two executive function components of a neuropsychological test battery (Category Fluency Test and Trail Making Test Part B) and on the composite executive function *Z* score. On the basis of these results, we aimed to assess the safety and tolerability of PBT2 in individuals with early-stage to mid-stage Huntington's disease, with secondary efficacy assessments including its effects on cognition.

Methods

Study design and participants

We did a 26-week, randomised, double-blind, placebo-controlled study of two doses of PBT2 (100 mg and 250 mg once daily) in Huntington's disease. Participants were enrolled at 19 centres in Australia and the USA. Eligible participants were at least 25 years old and had early-stage to mid-stage Huntington's disease, defined by having clinical features of Huntington's disease, an expanded *huntingtin* allele of at least 36 CAG repeats,[14] and a total functional capacity[15] score of at least 6. Inclusion criteria included presence of a study partner (ie, a spouse, relative, or friend knowledgeable about the patient's behaviour), a score of at least 12 on the Montreal Cognitive Assessment,[16] and fluency in English. The main exclusion criteria were disorders other than Huntington's disease that could cause cognitive impairment, fluctuating doses of tetrabenazine, uncontrolled medical or psychiatric illness, and ocular disease that could worsen visual acuity during the study. Further inclusion and exclusion criteria are listed in the appendix.

The study protocol and consent forms were reviewed and approved by the US Food and Drug Administration, institutional review boards of the coordinating centre (University of Rochester, NY, USA), and each participating site, with notification to the Australian Therapeutic Goods Administration. The study was done in accordance with the Declaration of Helsinki and International Conference on Harmonisation. All participants provided written informed consent at the screening visit before the start of study activities. An independent data safety monitoring committee, which had access to unmasked safety data, monitored safety throughout the study.

Randomisation and masking

Participants were randomly assigned (1:1:1) to PBT2 250 mg, PBT2 100 mg, or placebo once daily for 26 weeks. Randomisation was stratified by site with a block size of three; the randomisation algorithm was generated by the unmasked programmer (AW) at the Department of Biostatistics, University of Rochester, using SAS. Study drugs were given in coded drug packages. Site investigators and coordinators used a centralised interactive response system to identify which study package to administer. Investigators and coordinators dispensed study drug or matching placebo, in orange-coloured capsules that were identical in appearance and taste. Participants, carers, the steering committee, site investigators, study staff, and the study sponsor were masked to treatment assignment throughout the trial.

Procedures

Participants underwent a screening visit to assess eligibility followed by a baseline visit within 28 days, at which they were allocated to a treatment assignment. Five additional on-study drug visits were done over the 26-week study (at weeks 4, 8, 12, 18, and 26) followed by a final assessment 28 days after the participant's last study drug dose (ie, at week 30). At screening, participants underwent a cognitive test battery twice, on either the same or separate days, to minimise potential practice effects.[17] Because ability on cognitive tests can improve from simply taking the test a second time, tests were repeated at screening to maximise the likelihood that any differences (or absence thereof) noted during the study were due to study intervention. Study staff administered the first dose of study drug at baseline and subsequently dispensed study drug at each visit for self-administration by participants.

Clioquinol, an 8-hydroxyquinolone, has been associated with subacute myelo-optic neuropathy,[3] which has not been noted with PBT2 in preclinical and clinical testing.[10,14] Notwithstanding this previous testing, study participants underwent an extensive ophthalmological battery at screening and week 26 and a smaller battery at week 12. The extensive battery included tests of colour vision and

visual acuity, pupillary assessment, confrontation visual field testing, intraocular pressure measurements, optical coherence tomography of the macula and nerve head, dilated ophthalmoscopy using slit lamp biomicroscopy and indirect ophthalmoscopy, and colour fundus photographs. The smaller battery consisted of the following: tests of colour vision and visual acuity, optical coherence tomography of the macula and nerve head, and dilated ophthalmoscopy using slit lamp biomicroscopy and indirect ophthalmoscopy. Additionally, we assessed visual evoked responses at sites that had the capability to undertake the test.

Outcomes

The primary objective was to assess the safety and tolerability of two doses of PBT2. For safety, we assessed treatment-emergent adverse events, vital signs, clinical laboratory findings, electrocardiograms (ECGs), physical and neurological examinations, behaviour as measured by the Neuropsychiatric Inventory,[18] and suicidality as measured by the Columbia Suicide Severity Rating Scale.[19] Tolerability was assessed by the ability to complete the trial on the assigned dose of study drug.

Our secondary objective was to assess efficacy. The primary efficacy outcome was cognition, as assessed by the main composite cognition *Z* score for five tests (Category Fluency Test, Trail Making Test Part B, Map Search, Symbol Digit Modalities Test, and Stroop Word Reading Test) and the individual test outcome measures for each of these five tests plus the Trail Making Test Part A, Montreal Cognitive Assessment, and the Speeded Tapping Test. We also assessed two other composite *Z* scores, to include an objective measure of cognition and to assess the possible effects of the drug on executive function in light of previous study results:[1,13] an exploratory composite *Z* score that comprised the main composite plus Speeded Tapping Test, and an executive function *Z* score calculated from the *Z* scores for Category Fluency Test and Trail Making Test Part B. The principal secondary (ie, primary efficacy) analyses assessed the change from baseline to week 26. Additional exploratory analyses were calculated from baseline to week 12 and from week 26 to follow-up (ie, week 30).

Secondary efficacy objectives included the change from baseline to week 26 on several aspects of the Unified Huntington's Disease Rating Scale (UHDRS):[15] motor function as measured by the total motor score, behaviour as measured by the sum of the product of frequency and severity for individual items, and function as measured by the independence score and total functional capacity. Additionally, the individual components of these motor, behaviour, and function tests were assessed. We measured global function, another secondary endpoint, with the investigator-assessed Clinical Global Impression Scale. We used a new exploratory patient-reported outcome called the Huntington Disease Patient Reported Outcome of Problems to identify which symptoms were most bothersome to participants (a secondary endpoint); the results, which had no predefined means for assessment in the protocol, are not reported here. All efficacy measurements were taken at baseline, week 12, and week 26, with the exception of the Montreal Cognitive Assessment, which was done only at screening and week 26.

Exploratory biomarker assessments consisted of plasma selenium, urine 8-hydroxy-2′-deoxyguanosine—a marker of oxidative DNA damage[20]—and concentrations of total and mutant huntingtin in leucocytes measured at baseline, week 12, and week 26.[21]

Statistical analysis

Sample size was based on safety and tolerability. Assuming a Poisson distribution, zero occurrences of any adverse effect in an active treatment group gave a 95% upper confidence limit of 9% for the population rate of such adverse events in a future study. Using a one-sided *t* test with a 5% significance level, we estimated that a sample size of 33 participants per group provided 80% power to detect a difference in tolerability (favouring placebo) of 30%; for example, 90% tolerability in the placebo group versus 60% in an active treatment group.

All participants who were randomly assigned and took at least one dose of study drug comprised the safety population; safety was assessed to week 30. All participants who were randomly assigned and had at least one efficacy assessment after study drug comprised the intention-to-treat population. The mean and SD of the values measured for each cognitive test at the baseline assessment were used to calculate the Z scores for each test. We created an ANCOVA model for each efficacy endpoint and included study site as a covariate. Age at baseline was also included as a covariate for all cognitive endpoints. We assessed other potential covariates—baseline total functional capacity, CAG repeat length, sex, and education—before

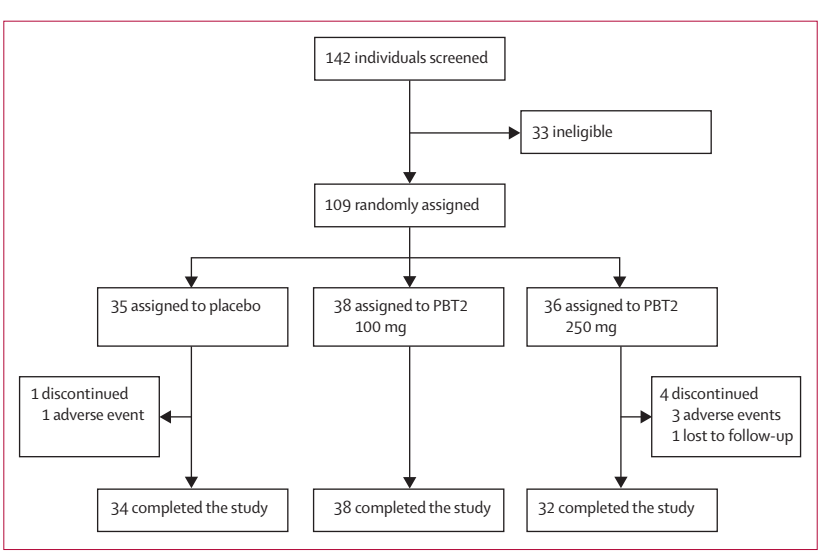

Figure: **Trial profile**

unmasking, by backwards elimination, removing at each step the covariate with the largest p value until all the remaining variables had a p value of less than 0·1. These variables were included in the final analysis of the relevant endpoint. Separate comparisons, summarised by least-squares means, their SEs, and associated p values, were made for each active treatment group with the placebo group. For efficacy analyses, in general, we calculated a total score if at least 80% of the components of a total score were present. Missing values after baseline were imputed using the last-observation-carried-forward method except for the Columbia Suicide Severity Rating Scale, for which missing values were not imputed. Because all efficacy endpoints were secondary, no adjustments were made for multiple comparisons to account for possible type I error. We used residual plots to check model validity, and did supportive analyses using non-parametric methods and mixed models.

This study is registered with ClinicalTrials.gov, NCT01590888.

	Placebo (n=35)	PBT2 100 mg (n=38)	PBT2 250 mg (n=36)	All participants (n=109)
Age (years)	51·2 (10·4)	54·1 (12·1)	50·3 (10·4)	51·9 (11·0)
Sex				
Men	16 (46%)	19 (50%)	19 (53%)	54 (50%)
Women	19 (54%)	19 (50%)	17 (47%)	55 (50%)
Ethnic origin				
Hispanic or Latino	0 (0%)	0 (0%)	2 (6%)	2 (2%)
Not Hispanic or Latino	35 (100%)	38 (100%)	34 (94%)	107 (98%)
Race				
White	35 (100%)	38 (100%)	35 (97%)	108 (99%)
Other	0 (0%)	0 (0%)	1 (3%)	1 (1%)
Education (years)	14·7 (2·7)	15·4 (3·2)	15·5 (3·1)	15·2 (3·0)
Height (cm)	171·2 (10·8)	170·2 (10·5)	171·7 (10·5)	171·0 (10·5)
Weight (kg)	79·5 (19·3)	74·2 (17·2)	76·2 (20·8)	76·6 (19·1)
Body-mass index (kg/m^2)	27·1 (6·0)	25·4 (4·5)	25·5 (4·9)	26·0 (5·2)
CAG repeat length	44·1 (3·9)	43·2 (2·8)	44·4 (4·6)	43·9 (3·8)
Cognition measures				
Category Fluency Test (number of correct words)	12·7 (5·9)	13·5 (5·4)	11·7 (5·0)	12·6 (5·4)
Trail Making Test Part A (time to complete; s)	55·5 (26·5)	56·4 (41·9)	58·1 (34·4)	56·7 (34·7)
Trail Making Test Part B (time to complete; s)	144·7 (67·9)	131·0 (70·8)	158·1 (67·8)	144·3 (69·2)
Map Search (number correct in 1 min)	18·9 (10·3)	18·2 (9·7)	18·3 (11·7)	18·5 (10·5)
Map Search (number correct in 2 min)	34·8 (18·5)	33·8 (16·2)	33·6 (18·6)	34·0 (17·6)
Symbol Digit Modalities Test (total correct)	25·0 (12·4)	27·0 (13·8)	24·9 (13·7)	25·6 (13·2)
Stroop Word Reading Test (number of words correctly read)	64·0 (21·7)	69·2 (22·8)	66·6 (21·9)	66·7 (22·1)
Montreal Cognitive Assessment (total score)	22·5 (4·2)	23·5 (3·7)	23·0 (3·9)	23·0 (3·9)
Speeded Tapping Test (mean inter-tap interval; ms)	499·9 (250·9)	559·9 (420·8)	490·0 (296·2)	517·1 (329·6)
Unified Huntington's Disease Rating Scale measures				
Total motor score	32·7 (16·3)	31·1 (15·8)	32·9 (16·8)	32·2 (16·2)
Total functional capacity score	9·3 (1·6)	9·3 (2·3)	9·0 (2·2)	9·2 (2·1)
Total behavioural score	10·7 (9·5)	7·7 (9·7)	13·2 (12·3)	10·5 (10·7)
Total independence scale score	82·3 (11·7)	81·3 (14·2)	81·1 (10·6)	81·6 (12·2)
Neuropsychiatric Inventory				
Total score	9·7 (10·5)	9·2 (11·8)	10·4 (11·7)	9·8 (11·3)
Total distress score	5·8 (7·4)	4·5 (5·8)	5·2 (5·7)	5·2 (6·3)

Data are mean (SD) or number (%). CAG=cytosine–adenine–guanine.

Table 1: **Demographics and baseline characteristics**

Role of the funding source

The funder assisted in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author (ERD) and the study biostatistician (DO) had full access to all the data in the study, and all other authors could have accessed the data if they wished. The corresponding author (ERD) had final responsibility for the decision to submit for publication.

Results

From April 18, 2012, to Dec 14, 2012, we screened 142 individuals, 109 of whom were enrolled in the study (figure). Of the 104 participants who completed the study, 32 (89%) received PBT2 250 mg, 38 (100%) received PBT2 100 mg, and 34 (97%) received placebo. Baseline characteristics were similar across the three groups (table 1). Three individuals in the PBT2 250 mg group did not complete the study because of headache, acute coronary syndrome, and major depression, and one individual was lost to follow-up. One individual receiving placebo did not complete the study because of migraines.

Ten serious adverse events were reported (table 2). Six events (acute coronary syndrome, major depression, pneumonia, suicide attempt, viral infection, and worsening of Huntington's disease) occurred in five individuals in the PBT2 250 mg group. The acute coronary syndrome was diagnosed by ECG changes at week 4 and eventually resulted in an uncomplicated cardiac bypass surgery. The participants with major depression, pneumonia, and viral infection needed hospital admission. The suicide attempt occurred in an individual who reported having suicidal thoughts, subsequently walked into a river with their dog, and aborted the attempt after the dog became distressed. The worsening of Huntington's disease occurred after the individual had completed study drug at the 26-week visit. Three serious adverse events (fall with subdural haematoma, suicide attempt, and hospital admission for stabilisation of Huntington's disease) occurred in two individuals taking PBT2 100 mg. An elderly individual had an unwitnessed fall and subsequently developed a subdural haematoma that needed surgical evacuation. The subdural bleeding re-occurred, resulting in an expressive aphasia and a second surgical evacuation before it resolved. The suicide

	Placebo (n=35)		PBT2 100 mg (n=38)		PBT2 250 mg (n=36)		All PBT2 treatment (n=74)		All participants (n=109)		3-category χ^2 p value
	Participants (%)	Events	Participants (%)	Events	Participants (%)	Events	Participants (%)	Events	Participants (%)	Events	
At least one adverse event	28 (80%)	132	30 (79%)	149	32 (89%)	175	62 (84%)	324	90 (83%)	456	0·463
Serious adverse events	1 (3%)	1	2 (5%)	3	5 (14%)	6	7 (9%)	9	8 (7%)	10	0·214
Common adverse events											
Diarrhoea	5 (14%)	7	6 (16%)	8	5 (14%)	5	11 (15%)	13	16 (15%)	20	1·000
Headache	5 (14%)	9	5 (13%)	9	4 (11%)	8	9 (12%)	17	14 (13%)	26	0·938
Falls	2 (6%)	2	4 (11%)	4	7 (19%)	11	11 (15%)	15	13 (12%)	17	0·193
Dizziness	3 (9%)	3	2 (5%)	2	6 (17%)	7	8 (11%)	9	11 (10%)	12	0·291
Anxiety	4 (11%)	4	1 (3%)	1	5 (14%)	5	6 (8%)	6	10 (9%)	10	0·205
Nausea	3 (9%)	3	1 (3%)	2	6 (17%)	6	7 (9%)	8	10 (9%)	11	0·097
Fatigue	1 (3%)	2	2 (5%)	2	6 (17%)	6	8 (11%)	8	9 (8%)	10	0·115
Upper respiratory tract infection	2 (6%)	2	3 (8%)	6	3 (8%)	4	6 (8%)	10	8 (7%)	12	1·000
Irritability	2 (6%)	2	4 (11%)	4	1 (3%)	1	5 (7%)	5	7 (6%)	7	0·445
Back pain	1 (3%)	2	1 (3%)	2	4 (11%)	7	5 (7%)	9	6 (6%)	11	0·317
Chorea	2 (6%)	2	2 (5%)	2	2 (6%)	2	4 (5%)	4	6 (6%)	6	1·000
Constipation	0 (0%)	0	3 (8%)	3	2 (6%)	2	5 (7%)	5	5 (5%)	5	0·368
Myalgia	0 (0%)	0	3 (8%)	3	2 (6%)	3	5 (7%)	6	5 (5%)	6	0·368
Urinary tract infection	2 (6%)	2	3 (8%)	4	0 (0%)	0	3 (4%)	4	5 (5%)	6	0·322
Dry mouth	0 (0%)	0	1 (3%)	1	3 (8%)	3	4 (5%)	4	4 (4%)	4	0·214
Visual acuity reduced	1 (3%)	1	3 (8%)	3	0 (0%)	0	3 (4%)	3	4 (4%)	4	0·267
Gait disturbance	0 (0%)	0	2 (5%)	2	1 (3%)	1	3 (4%)	3	3 (3%)	3	0·772
Influenza	0 (0%)	0	2 (5%)	2	1 (3%)	1	3 (4%)	3	3 (3%)	3	0·772
Dysgeusia	0 (0%)	0	0 (0%)	0	3 (8%)	3	3 (4%)	3	3 (3%)	3	0·065
Viral infection	0 (0%)	0	0 (0%)	0	3 (8%)	3	3 (4%)	3	3 (3%)	3	0·065

Table 2: **Adverse events that occurred in at least three participants in any treatment group**

attempt occurred in an individual who reported suicidal thoughts after a relationship break-up and subsequently took an overdose of gabapentin. The individual was admitted to hospital after reporting the overdose to study staff and was subsequently discharged. The hospital admission was to stabilise symptoms of Huntington's disease, which was successful. One serious adverse event (increasing aggression) occurred in an individual receiving placebo. On the basis of their assessment, the site investigators deemed all, except the worsening of Huntington's disease, as unrelated to study drug. No deaths were reported.

90 individuals reported at least one adverse event: 32 (89%) on PBT2 250 mg, 30 (79%) on PBT2 100 mg, and 28 (80%) on placebo (table 2). The most common adverse events were diarrhoea, headache, falls, dizziness, anxiety, nausea, and fatigue. No clinically significant differences were noted on vital signs, ECGs, the Neuropsychiatric Inventory, or laboratory assessments (including plasma copper, iron, and zinc concentrations; data not shown). On the Columbia Suicide Severity Rating Scale, one individual in the placebo group and two in the PBT 250 mg group had suicidal ideation at baseline, and one individual in the placebo group, two in the PBT2 100 mg group, and five in the PBT2 250 mg group reported suicidal ideation during the study (p=0·0753; Mantel-Haenszel χ^2 test). Of the five people in the PBT2 250 mg group who reported suicidal ideation, one report occurred after the individual completed the 26-week visit and was off study drug. One individual in each of the PBT2 100 mg and 250 mg groups and no individuals in the placebo group displayed suicidal behaviour.

An extensive ophthalmological battery revealed no significant differences between the PBT2 and placebo groups (data not shown). 43 individuals (15 on PBT2 250 mg, 14 on PBT2 100 mg, and 14 on placebo) underwent visual evoked response testing, and no significant differences in P100 latency or amplitude were noted (data not shown).

Neither dose of PBT2 significantly improved the main composite cognition *Z* score compared with placebo at 26 weeks (table 3; appendix). On the Trail Making Test Part B, those taking PBT2 250 mg had improved performance compared with those on placebo at 26 weeks (least-squares mean 17·65 s, 95% CI 0·65–34·65; p=0·042), whereas participants in the 100 mg group had no significant difference from the placebo group (0·79 s improvement, –15·75 to 17·32; p=0·925). The other seven cognitive outcome measures were not significantly improved in either PBT2 group compared with placebo at 26 weeks. Uncorrected for multiple comparisons,

	Week 12				Week 26			
	PBT2 100 mg *vs* placebo		PBT2 250 mg *vs* placebo		PBT2 100 mg *vs* placebo		PBT2 250 mg *vs* placebo	
	Least-squares mean (SE)	p value	Least-squares mean (SE)	p value	Least-squares mean (SE)	p value	Least-squares mean (SE)	p value
Main composite cognition *Z* score*	0·04 (0·05)	0·352	0·12 (0·05)	0·020	0·02 (0·06)	0·772	0·07 (0·06)	0·240
Category Fluency Test (number of correct words)*†	−0·22 (0·86)	0·796	0·84 (0·89)	0·350	−0·99 (0·82)	0·231	0·63 (0·85)	0·461
Trail Making Test Part A (time to complete; s)*	2·60 (6·22)	0·677	−0·65 (6·45)	0·919	−5·40 (5·04)	0·287	−3·45 (5·22)	0·510
Trail Making Test Part B (time to complete; s)*†	−7·62 (6·82)	0·267	−25·63 (7·04)	<0·0001	−0·79 (8·31)	0·925	−17·65 (8·54)	0·042
Map Search (number correct in 1 min)*†	1·22 (1·48)	0·411	1·84 (1·53)	0·232	2·00 (1·79)	0·266	0·03 (1·86)	0·985
Map Search (number correct in 2 min)	1·32 (2·53)	0·603	1·51 (2·63)	0·566	1·54 (2·53)	0·543	−1·36 (2·63)	0·608
Symbol Digit Modalities Test (total correct)*†	0·33 (1·02)	0·744	−0·14 (1·05)	0·895	0·54 (1·19)	0·649	−1·29 (1·23)	0·297
Stroop Word Reading Test (number of words correctly read)*†	2·29 (1·80)	0·209	−2·32 (1·87)	0·217	2·04 (2·11)	0·336	2·00 (2·18)	0·362
Montreal Cognitive Assessment (total score)*	..	..	..	..	−0·73 (0·65)	0·261	0·19 (0·66)	0·774
Speeded Tapping Test (mean inter-tap interval; ms)*	−11·25 (62·05)	0·857	−105·13 (64·05)	0·105	−47·03 (44·48)	0·294	−17·22 (46·66)	0·713
Exploratory composite *Z* score	0·03 (0·05)	0·549	0·13 (0·05)	0·016	0·02 (0·06)	0·732	0·06 (0·06)	0·310
Executive function *Z* score	0·02 (0·09)	0·810	0·27 (0·09)	0·005	−0·10 (0·10)	0·324	0·19 (0·10)	0·069

Data are change in score from baseline. *Principal secondary (ie, primary efficacy) endpoints. †Included in the main composite cognition *Z* score.

Table 3: **Cognitive outcome measures**

	Week 12				Week 26			
	PBT2 100 mg *vs* placebo		PBT2 250 mg *vs* placebo		PBT2 100 mg *vs* placebo		PBT2 250 mg *vs* placebo	
	Least-squares mean (SE)	p value	Least-squares mean (SE)	p value	Least-squares mean (SE)	p value	Least-squares mean (SE)	p value
Unified Huntington's Disease Rating Scale								
Total motor score	1·09 (1·48)	0·462	0·01 (1·54)	0·996	2·24 (1·82)	0·222	0·96 (1·91)	0·616
Total behavioural score	0·54 (1·98)	0·787	1·60 (2·07)	0·441	1·67 (3·18)	0·602	−2·37 (3·33)	0·478
Total functional capacity score	..	..	..	..	0·08 (0·33)	0·812	0·29 (0·34)	0·386
Total independence score	..	..	..	..	−0·54 (1·63)	0·739	2·10 (1·67)	0·212
Clinical Global Impression-Severity efficacy index	−0·06 (0·13)	0·677	−0·12 (0·14)	0·384	0·13 (0·14)	0·356	0·15 (0·15)	0·317

Data are change in score from baseline.

Table 4: **Secondary efficacy outcome measures**

	Week 12					Week 26				
	Number of patients	PBT2 100 mg *vs* placebo		PBT2 250 mg *vs* placebo		Number of patients	PBT2 100 mg *vs* placebo		PBT2 250 mg *vs* placebo	
		Least-squares mean (SE)	p value	Least-squares mean (SE)	p value		Least-squares mean (SE)	p value	Least-squares mean (SE)	p value
Selenium (μg/L)	90	4·06 (4·32)	0·350	4·27 (4·41)	0·337	100	−3·83 (4·45)	0·392	−2·36 (4·48)	0·600
8-hydroxy-2′-deoxyguanosine*	104	0·18 (0·28)	0·517	0·08 (0·29)	0·798	100	0·50 (0·33)	0·128	0·09 (0·34)	0·792
Mutant huntingtin†	72	7·35 (2·76)	0·010	8·05 (2·95)	0·009	78	2·46 (3·10)	0·431	0·67 (3·31)	0·841
Total huntingtin†	72	3·36 (1·47)	0·026	3·70 (1·55)	0·021	78	0·29 (1·55)	0·853	0·73 (1·63)	0·658

Data are change in score from baseline. *Normalised to creatinine concentrations. †Normalised to lysate protein concentrations.

Table 5: **Blood biomarker measures**

PBT2 250 mg improved cognition at 12 weeks for several outcomes, including the main composite outcome, but the changes in other cognitive measures at week 12 were not significantly different from placebo (table 3). No significant differences were reported in the change between week 26 and the week 30 follow-up visit off study drug (data not shown).

We noted no significant differences in the change from baseline to week 26 in motor, behavioural, functional, or global assessments (table 4). We did not identify any gross outliers in the data on residual plots and supportive non-parametric and mixed models analyses gave results similar to those for the primary efficacy analysis (data not shown).

Regarding the exploratory biomarkers, we noted no significant difference in plasma selenium concentrations (table 5). No significant differences were noted across groups in urine 8-hydroxy-2′-deoxyguanosine concentrations normalised to creatinine. The concentrations of mutant huntingtin and total huntingtin, normalised to lysate protein concentrations, were increased at 12 weeks in individuals on PBT2 100 mg and 250 mg (table 5), respectively, compared with placebo. We noted no differences in the treatment groups at 26 weeks.

Discussion

In this phase 2 study, PBT2 at doses up to 250 mg once daily was generally safe and well tolerated in individuals with early-stage to mid-stage Huntington's disease. Numerically more serious adverse events occurred in individuals exposed to PBT2 compared with placebo, but, with the exception of worsening of Huntington's disease in an individual in the PBT2 250 mg group (which occurred after study drug was stopped), none were deemed by the site investigator to be related to study drug. Two suicide attempts (one in each of the two PBT2 dose groups) occurred, and suicidal ideation was numerically more common in the treatment groups than in the placebo group. About 25% of individuals with Huntington's disease attempt suicide at least once,[22] and the rate of attempts in this study (two for about 35 participant-years of observation) was similar to what would be expected in this population.[23] Nonetheless, on the basis of results of this study and the high frequency of suicidal behaviour in Huntington's disease, careful observation and assessment of suicidality is important in future investigations of PBT2. Consistent with previous investigations, we did not find any evidence of subacute myelo-optic neuropathy or other ophthalmological side-effects.

Cognitive outcomes on some cognitive scales were improved with PBT2 250 mg compared with placebo. The cognitive improvement of PBT2 250 mg on Trail Making Test Part B is consistent with results from the phase 2a trial of PBT2 in Alzheimer's disease.[13] The Trail Making Test Part B is a sensitive measure of executive function,[24] which is impaired early in Huntington's disease course.[25,26]

Although temporary (12 weeks), the association of increased concentrations of leucocyte huntingtin with PBT2 treatment can be interpreted as maintenance of soluble total huntingtin and mutant huntingtin. This increase contrasts with the usual diminution noted in these measures with disease progression and suggests reduced conversion of mutant huntingtin monomers to toxic oligomers;[27] since the oligomerisation of huntingtin is copper dependent,[28] this could be an effect of PBT2 treatment. The biological effect of PBT2 on huntingtin in the brain in this study is unknown; however, this finding suggests that PBT2 might be able to engage huntingtin as a target.

The limitations of this study pertain to its sample size, the possibility of type I and II errors (panel), the clinical significance of the findings, and the ability to assess biological activity. The study was powered to detect only large differences in safety events. A larger trial is needed to better assess the safety profile of the drug. The sample size and entry criteria also limit the potential generalisability of the results to the broader Huntington's disease population. Additionally, the efficacy results, as secondary outcomes in this phase 2 study, contained multiple comparisons and thus should be interpreted with caution. The results need to be replicated in a larger study that has greater power to detect differences in efficacy measures and that assesses cognition as its primary outcome. The present study, because of its small sample size and primary focus on safety and tolerability, was underpowered to detect potentially meaningful changes in the efficacy outcomes, which will have to be addressed in a phase 3 trial. Also, the clinical value of an improvement in Trail Making Test Part B or other cognitive outcomes has to be considered and weighed against the absence of any effective treatment for cognitive dysfunction in Huntington's disease. Finally,

Panel: Research in context

Systematic review

We searched PubMed up to Feb 12, 2014, for randomised controlled trials in Huntington's disease that assessed cognition, with the following search terms: "huntington disease", "randomized controlled trial", and "cognition." We identified 13 controlled masked studies of 12 drugs. Only one study, of latrepirdine, reported a significant cognitive benefit (on the Mini-Mental State Examination),[29] which was not confirmed in a subsequent study.[30] In one small study (n=20) of atomoxetine,[31] executive function specifically was examined as a primary outcome measure, but no effect was noted. In a 2011 evidenced-based review of treatment for Huntington's disease,[32] 12 drugs reportedly "failed to prove a benefit" on cognition.

Interpretation

Highlighting the need for a cognitive treatment for Huntington's disease, only one previous phase 2 study has identified a positive cognitive benefit in response to drug treatment,[29] and that was not confirmed in a phase 3 study.[30] In this study, PBT2 was generally safe and well tolerated. In view of the multiple cognitive endpoints in this phase 2 study, our findings of a possible benefit of PBT2 on cognition will need to be replicated in a manner that minimises the possibility for type I error.

the interpretation of the exploratory biomarker results in this study is not certain and highlights the need for biological assays of drugs and disease activity in Huntington's disease.

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Contributors

ERD wrote the manuscript. CH and CWR wrote the study protocol. CH, CWR, and DO wrote the statistical analysis plan. DO was the chief trial biostatistician and was assisted by SGa. AW (unmasked programmer) created the randomisation assignments and prepared interim safety reports for the data safety and monitoring board. JS recommended the cognitive battery and oversaw its use and implementation in the study; her team included KB and IL. DAn, CH, and CSt oversaw study implementation. MM-L and SH conducted and oversaw the biomarker analysis. SF and ME-D oversaw the ophthalmological battery. CWR and CV were the medical monitors. EK was the director of project management and KH was the project manager; both were assisted by CC and CO. JC-B, PKP, HDR, RM, DAm, AG, PA, AC, SJ, KM, CSi, SK, VS, RK, KA, PC, CD, MN, EM, SC, MSLD, and CL were site investigators. MW and RR were members of the steering committee. SGl, JGo, LLe, NY, MM, RC, HMo, NP, AD, DG, LLi, HMa, BH, SGu, AI, BJ, JGr, and PM were study coordinators and staff at the research sites. AF, SE, BRL, and SW formed the data safety and monitoring board. RT, ST, and CWR were study consultants. All authors revised the paper and approved the final manuscript.

Declaration of interests

ERD has received grants from Prana Biotechnology; grants and personal fees from Huntington Study Group, Lundbeck, and Medtronic; and personal fees from Clintrex, Roche, Optio, Transparency Life Sciences, and Amgen. HDR has received a research contract from Prana Biotechnology and personal fees from Pfizer. CH and DAn are employees of and shareholders in Prana Biotechnology. CWR and ME-D have received personal fees from Prana Biotechnology. DO, SGa, AW, KB, and CL have received grant support from Prana Biotechnology. JS has received grants from Prana Biotechnology and CHDI Foundation, personal fees from Roche and Prana Biotechnology, research contracts from Teva Pharmaceuticals and Omeros, and personal fees and non-financial support from GlaxoSmithKline. IL has received grants from Monash University. CSt is an employee of Prana Biotechnology. RR has received grants from CHDI Foundation, DFG, EU-FP7, European Huntington's Disease Network, DZNE, and BMBF; has been an advisory board member for Novartis, Pfizer, Siena Biotech, Ipsen, Teva, Lundbeck, ISIS Pharma, and CHDI Foundation; has received honoraria from Novartis, Pfizer, Siena Biotech, NeuroSearch, Ipsen, Teva, Lundbeck, ISIS Pharma, CHDI Foundation, Wyeth, Link Medicine, Prana Biotechnology, Medivation, MEDA Pharma, Temmler Pharma, and AOP Orphan Pharmaceuticals; has received consultancy payments from Pfizer, Siena Biotech, NeuroSearch, Ipsen, Teva, Lundbeck, ISIS Pharma, CHDI Foundation, Wyeth, Link Medicine, and Prana Biotechnology; and has provided clinical trial services or quantitative motor analyses for Novartis, Teva, Pfizer, Ipsen, CHDI Foundation, BMBF, and DZNE. SH has received grants and personal fees from Prana Biotechnology; and personal fees from Pfizer and Azevan Pharmaceuticals. RM has received grants from Prana Biotechnology, Neurocrine, Medivation, and Teva. DAm was a member of a data safety and monitoring board for Prana Biotechnology. KM has received grants from CHDI Foundation, HDSA, the National Institutes of Health 1 UL 1 RR024156, P0412196, NS036630, and Parkinson's Disease Foundation. CSi has received personal fees from Lundbeck. SK's institution received research funding from Prana Biotechnology through the University of Rochester for this study; financial support from NeuroSearch for participation in HART-HD and OPEN-Hart; financial support from Auspex Pharmaceutical for participation in the First HD and Arc HD trials; and funding for participation in the ENROLL-HD. SK has received grants from Huntington's Disease Society of America, Lundbeck, NuroSearch, Auspex Pharmaceuticals, and CHDI Foundation, and personal fees from Lundbeck. PC's institution has received financial support from Prana Biotechnology through the University of Rochester for participation in the Reach2HD study. PC has received grant support from Teva Pharmaceuticals. MN has received grants from Prana Biotechnology through the University of Rochester, Teva, NeuroSearch, Medivation/Pfizer, Impax Pharmaceuticals, Schering-Plough, Biotie, and personal fees from Lundbeck. MSLD has received grants from Prana Biotechnology, Omeros, Auspex, and CHDI Foundation; and personal fees from Lundbeck, UCB Pharma, Teva, USWorldMeds, Mayo Clinic, and Elsevier. AD's institution received research funding from Prana Biotechnology through the University of Rochester for this study; from NeuroSearch in conjunction with the Huntington Study Group for participation in HART-HD and OPEN-Hart; and from Auspex Pharmaceutical in conjunction with the Huntington Study Group for participation in First HD and Arc HD. AD has received grants from Huntington's Disease Society of America, and funding from CHDI Foundation for participation in ENROLL-HD. PM has received personal fees from Novartis Pharma, Bayer, and Roche. SE has received personal fees from Huntington Study Group, Prana Biotechnology, Millennium/Takeda, Pfizer, Roche, Novartis, Achaogen, Averion, Massachusetts General Hospital, Harvard Clinical Research Institute, TARIS, Boston University, Alcon, Cubist, Merck, Chelsea Therapeutics, Mannkind, QRx Pharma, IMMPACT, Intermune,

Genentech, Affymax, FzioMed, CIS Biotech, Auspex, Sunovion, GlaxoSmithKline, Boehringer Ingelheim, Alcon, American Statistical Association, American Neurological Association, Beth Israel Deaconess Medical Center, US Food and Drug Administration, Osaka University, Statistical Society of Australia, Interfarma, Muscle Study Group, Society for Clinical Trials, Harvard Medical School, Biopharmaceutical Applied Statistics Symposium, Phamaceutical Education and Research Institute, Graybill Conference, Deming Conference, Midwest Biopharmaceutical Statistics Workshop, New Jersey Chapter of American Statistical Association, American Statistical Association, Drug Information Association, Merck, Johns Hopkins University, Schering-Plough, HIV/AIDS Network Coordination, HIV Neurobehavioral Research Center, and grant funding from the National Institutes of Health and Fogarty International Center. BRL has received personal fees from Prana Biotechnology, Novartis, Isis Pharmaceuticals, Pfizer, Neurosearch, Teva, Lundbeck, Roche, Aequus, Auspex, and Omeros. RT reports personal fees from Prana Biotechnology. ST reports personal fees and equity interest from Prana Biotechnology; grants from Pfizer, Forum Pharmaceuticals, and Civitas Pharmaceuticals; and personal fees from Functional Neuromodulation. MW, MM-L, SF, CV, EK, KH, CC, CO, JC-B, PKP, AG, PA, AC, SJ, VS, RK, KA, CD, EM, SC, SGl, JGo, LLe, NY, MM, RC, HMa, NP, DG, LLi, HMo, BH, SGu, AI, BJ, JGr, AF, and SW declare no competing interests.

Acknowledgments

This study was funded by Prana Biotechnology. Development of the huntingtin assay was supported by a National Institutes of Health grant NS071789 (SMH and MML). The 2B7 antibody was provided by the Novartis Institute for Biomedical Research. We thank Byron L Lam for his help undertaking ophthalmological assessments in the study.

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