



Clinical trial results:

A Phase 2, Dose-Finding, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Study, Evaluating the Safety and Efficacy of Pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg Twice-Daily versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease

Summary

EudraCT number	2013-001888-23
Trial protocol	DE IT NL AT PL DK
Global end of trial date	07 July 2016

Results information

Result version number	v2 (current)
This version publication date	12 June 2021
First version publication date	09 March 2018
Version creation reason	• Correction of full data set Change of sponsor name and additional information

Trial information

Trial identification

Sponsor protocol code	TV7820-CNS-20002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02006472
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor study acronym: PRIDE-HD

Notes:

Sponsors

Sponsor organisation name	Prilenia Neurotherapeutics
Sponsor organisation address	Hamenofim 10, Herzliya, Israel, 4672561
Public contact	Henk Schuring, Prilenia Neurotherapeutics Ltd., clinicaltrials@prilenia.com
Scientific contact	Michal Geva, Prilenia Neurotherapeutics Ltd., clinicaltrials@prilenia.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2015
Global end of trial reached?	Yes
Global end of trial date	07 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of pridopidine 45 to 112.5 mg twice daily (bid) on motor impairment in patients with Huntington's Disease (HD) after 26 weeks of treatment using the Unified Huntington's Disease Rating Scale Total Motor Score (TMS).

The trial was initially designed as a 26-week study to evaluate the effect of pridopidine on motor function. Due to the recognition that the Primary target of pridopidine is S1R, suggesting a therapeutic potential beyond motor function, the ongoing trial was extended from 26 to 52 weeks in order to allow the assessment of pridopidine on total functional capacity (TFC). A minimum of 52 are needed for the placebo group to decline in TFC and allow a window to detect an effect of treatment on TFC.

Approximately 19% of patients completed 26 weeks (period 1) of the study before IRB approvals for the extension and did not continue into period 2 with a duration of up to 52 weeks.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 50
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	United States: 63

Worldwide total number of subjects	408
EEA total number of subjects	262

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	360
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 492 patients were screened; of these, 408 were randomized. The main reason for not randomizing patients was noncompliance with the eligibility criteria.

Period 1

Period 1 title	Period 1 (through Week 26)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Pridopidine matching placebo (hard capsules)

Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 45 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 67.5 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 90 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 112.5 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Number of subjects in period 1	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid
Started	82	81	82
Completed	70	59	65
Not completed	12	22	17
Consent withdrawn by subject	3	9	3
Adverse event, non-fatal	5	6	11
Not specified	1	5	-
Non-compliance	2	1	1
Protocol deviation	1	1	1
Lack of efficacy	-	-	1

Number of subjects in period 1	Pridopidine 90 mg bid	Pridopidine 112.5 mg bid
Started	81	82
Completed	67	62
Not completed	14	20
Consent withdrawn by subject	-	3
Adverse event, non-fatal	11	14
Not specified	2	3
Non-compliance	-	-
Protocol deviation	1	-
Lack of efficacy	-	-

Period 2

Period 2 title	Period 2 (Week 26 through Week 52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Pridopidine matching placebo (hard capsules)

Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Placebo
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Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine matching placebo (hard capsules)

Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 45 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 67.5 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 90 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm title	Pridopidine 112.5 mg bid
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Arm description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Arm type	Experimental
Investigational medicinal product name	pridopidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Number of subjects in period 2^[1]	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid
Started	57	49	54
Completed	52	43	44
Not completed	5	6	10
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	1	2
Adverse event, non-fatal	1	4	5
Not specified	-	1	-
Non-compliance	1	-	-
Did not receive study drug	-	-	2
Sponsor decision	-	-	1
Lack of efficacy	1	-	-

Number of subjects in period 2^[1]	Pridopidine 90 mg bid	Pridopidine 112.5 mg bid
Started	56	46
Completed	53	44
Not completed	3	2
Adverse event, serious fatal	1	1
Consent withdrawn by subject	-	-
Adverse event, non-fatal	-	-

Not specified	1	-
Non-compliance	-	-
Did not receive study drug	-	-
Sponsor decision	-	-
Lack of efficacy	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients who did not enter the second study period from the first study period were lost due to prolonged IRB review periods at some clinical sites.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Pridopidine matching placebo (hard capsules)	
Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 45 mg bid
Reporting group description:	
Pridopidine given as hard capsules, twice daily	
Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 67.5 mg bid
Reporting group description:	
Pridopidine given as hard capsules, twice daily	
Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 90 mg bid
Reporting group description:	
Pridopidine given as hard capsules, twice daily	
Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 112.5 mg bid
Reporting group description:	
Pridopidine given as hard capsules, twice daily	
Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	

Reporting group values	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid
Number of subjects	82	81	82
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	50.3	51.9	51.0
standard deviation	± 11.34	± 11.75	± 11.83
Gender categorical			
Units: Subjects			
Female	40	40	41
Male	42	41	41
Race			
Units: Subjects			
White	73	75	78
Black	0	0	1
Asian	1	0	0
Other	0	1	0

Missing	8	5	3
Use of Neuroleptics			
Antipsychotic drugs to treat psychiatric or behavioral problems associated with HD.			
Units: Subjects			
Neuroleptics use	31	31	32
Neuroleptics no use	51	50	50
CYP2D6 Genotype			
CYP2D6 is an enzyme. An association between CYP2D6 genotypes (genetic make-up) and phenotypes (response to treatment, specifically rate of metabolism of the drug) is believed to exist.			
Units: Subjects			
Poor	1	5	4
Extensive	72	70	70
Intermediate	8	5	8
Ultra-rapid	1	1	0
Number of Cytosine-Adenosine-Guanine (CAG) Repeats			
The normal huntington protein contains multiple repeats of a sequence of three DNA bases, cytosine-adenine-guanine (CAG), which encodes the amino acid glutamine. When more than 36 repeats are present in the protein, stemming from a mutation in the huntingtin gene, an abnormal protein is produced. This mutant form of the protein is more prone to aggregation than versions of the protein with a normal number of repeats. Individuals with 36–40 CAG repeats may or may not develop symptoms of HD, while people with more than 40 repeats will develop the disorder during a normal lifetime.			
Units: repeats			
arithmetic mean	44.4	44.1	45.0
standard deviation	± 3.23	± 4.12	± 4.73

Reporting group values	Pridopidine 90 mg bid	Pridopidine 112.5 mg bid	Total
Number of subjects	81	82	408
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	51.3	47.5	
standard deviation	± 12.69	± 11.40	-
Gender categorical			
Units: Subjects			
Female	43	39	203
Male	38	43	205
Race			
Units: Subjects			
White	75	77	378
Black	0	0	1
Asian	1	0	2
Other	1	0	2
Missing	4	5	25
Use of Neuroleptics			
Antipsychotic drugs to treat psychiatric or behavioral problems associated with HD.			
Units: Subjects			
Neuroleptics use	31	32	157
Neuroleptics no use	50	50	251
CYP2D6 Genotype			

CYP2D6 is an enzyme. An association between CYP2D6 genotypes (genetic make-up) and phenotypes (response to treatment, specifically rate of metabolism of the drug) is believed to exist.

Units: Subjects			
Poor	2	4	16
Extensive	74	69	355
Intermediate	5	9	35
Ultra-rapid	0	0	2
Number of Cytosine-Adenosine-Guanine (CAG) Repeats			
The normal huntington protein contains multiple repeats of a sequence of three DNA bases, cytosine-adenine-guanine (CAG), which encodes the amino acid glutamine. When more than 36 repeats are present in the protein, stemming from a mutation in the huntingtin gene, an abnormal protein is produced. This mutant form of the protein is more prone to aggregation than versions of the protein with a normal number of repeats. Individuals with 36–40 CAG repeats may or may not develop symptoms of HD, while people with more than 40 repeats will develop the disorder during a normal lifetime.			
Units: repeats			
arithmetic mean	44.5	45.3	
standard deviation	± 4.90	± 3.66	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Pridopidine matching placebo (hard capsules) Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 45 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 67.5 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 90 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 112.5 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Placebo
Reporting group description: Pridopidine matching placebo (hard capsules) Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 45 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 67.5 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 90 mg bid
Reporting group description: Pridopidine given as hard capsules, twice daily Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.	
Reporting group title	Pridopidine 112.5 mg bid

Reporting group description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients in this study were administered 3 capsules twice daily (ie, 3 capsules in the morning and 3 capsules in the afternoon). Capsules either contained pridopidine in doses of 22.5 mg or 45 mg or placebo (sized to match the two active doses to assure the blind) and were supplied by the sponsor in medication packs to support the assigned treatment. Patients in the Placebo arm were only supplied placebo capsules which were taken from Day 1 to Week 52.

Subject analysis set title	Pridopidine 45 mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients in this study were administered 3 capsules twice daily (ie, 3 capsules in the morning and 3 capsules in the afternoon). Capsules either contained pridopidine in doses of 22.5 mg or 45 mg or placebo (sized to match the two active doses to assure the blind) and were supplied by the sponsor in medication packs to support the assigned total daily dose of 90mg. Doses were titrated during the first 4 weeks, starting at a total daily dose of 45 mg, up to the assigned total daily dose of 90 mg which was taken from Day 28 to Week 52.

Subject analysis set title	Pridopidine 67.5 mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients in this study were administered 3 capsules twice daily (ie, 3 capsules in the morning and 3 capsules in the afternoon). Capsules either contained pridopidine in doses of 22.5 mg or 45 mg or placebo (sized to match the two active doses to assure the blind) and were supplied by the sponsor in medication packs to support the assigned total daily dose of 135 mg. Doses were titrated during the first 4 weeks, starting at a total daily dose of 45 mg, up to the assigned total daily dose of 135 mg which was taken from Day 28 to Week 52.

Subject analysis set title	Pridopidine 90 mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients in this study were administered 3 capsules twice daily (ie, 3 capsules in the morning and 3 capsules in the afternoon). Capsules either contained pridopidine in doses of 22.5 mg or 45 mg or placebo (sized to match the two active doses to assure the blind) and were supplied by the sponsor in medication packs to support the assigned total daily dose of 180mg. Doses were titrated during the first 4 weeks, starting at a total daily dose of 45 mg, up to the assigned total daily dose of 180 mg which was taken from Day 28 to Week 52.

Subject analysis set title	Pridopidine 112.5 mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients in this study were administered 3 capsules twice daily (ie, 3 capsules in the morning and 3 capsules in the afternoon). Capsules either contained pridopidine in doses of 22.5 mg or 45 mg or placebo (sized to match the two active doses to assure the blind) and were supplied by the sponsor in medication packs to support the assigned total daily dose of 225 mg. Doses were titrated during the first 4 weeks, starting at a total daily dose of 45 mg, up to the assigned total daily dose of 225 mg which was taken from Day 28 to Week 52.

Primary: Change From Baseline in Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) at Week 26

End point title	Change From Baseline in Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) at Week 26
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End point description:

TMS was defined as the sum of all UHDRS motor domains ratings. The motor section of the UHDRS assesses Motor features of Huntington's Disease (HD) with standardized ratings of oculo-motor function, dysarthria, chorea, dystonia, gait, and postural stability. Each of 15 assessments is rated on a scale of 0

(normal) to 4 (marked impairment) for a TMS range of 0-124. Negative change from baseline values indicate improvement.

End point type	Primary
End point timeframe:	
26 weeks	

End point values	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid	Pridopidine 90 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81 ^[1]	75 ^[2]	79 ^[3]	81 ^[4]
Units: units on a scale				
least squares mean (standard error)	-4.79 (± 0.99)	-3.37 (± 1.05)	-3.09 (± 1.02)	-4.13 (± 1.00)

Notes:

[1] - Full analysis set, i.e. randomised and treated patients with at least 1 post-baseline assessment

[2] - Full analysis set, i.e. randomised and treated patients with at least 1 post-baseline assessment

[3] - Full analysis set, i.e. randomised and treated patients with at least 1 post-baseline assessment

[4] - Full analysis set, i.e. randomised and treated patients with at least 1 post-baseline assessment

End point values	Pridopidine 112.5 mg bid			
Subject group type	Reporting group			
Number of subjects analysed	81 ^[5]			
Units: units on a scale				
least squares mean (standard error)	-2.74 (± 1.01)			

Notes:

[5] - Full analysis set, i.e. randomised and treated patients with at least 1 post-baseline assessment

Statistical analyses

Statistical analysis title	TMS: Pridopidine 45 mg - Placebo
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Statistical analysis description:

The change from baseline in TMS was analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model included the following fixed effects: categorical week in study by treatment interaction, country, neuroleptic use or no use, baseline TMS score, and categorical week in study by baseline TMS interaction.

Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3202
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	4.23

Statistical analysis title	TMS: Pridopidine 67.5 mg - Placebo
Statistical analysis description:	
The change from baseline in TMS was analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model included the following fixed effects: categorical week in study by treatment interaction, country, neuroleptic use or no use, baseline TMS score, and categorical week in study by baseline TMS interaction.	
Comparison groups	Pridopidine 67.5 mg bid v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2266
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	4.46

Statistical analysis title	TMS: Pridopidine 90 mg - Placebo
Statistical analysis description:	
The change from baseline in TMS was analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model included the following fixed effects: categorical week in study by treatment interaction, country, neuroleptic use or no use, baseline TMS score, and categorical week in study by baseline TMS interaction.	
Comparison groups	Pridopidine 90 mg bid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6348
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	3.39

Statistical analysis title	TMS: Pridopidine 112.5 mg - Placebo
Statistical analysis description:	
The change from baseline in TMS was analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model included the following fixed effects: categorical week in study by treatment interaction, country, neuroleptic use or no use,	

baseline TMS score, and categorical week in study by baseline TMS interaction.

Comparison groups	Pridopidine 112.5 mg bid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1447
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	4.8

Secondary: Number of patients with Adverse Events

End point title	Number of patients with Adverse Events
End point description:	
Number of patients with Adverse Events	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid	Pridopidine 90 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	82	81	82	81
Units: participants	62	63	69	71

End point values	Pridopidine 112.5 mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: participants	67			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Total Functional Capacity (TFC) at Week 52

End point title	Change From Baseline in Total Functional Capacity (TFC) at
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End point description:

End point type Other pre-specified

End point timeframe:

52 weeks

End point values	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid	Pridopidine 90 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	75	78	81
Units: score on a scale				
least squares mean (standard error)	-0.83 (\pm 0.20)	0.04 (\pm 0.22)	-0.72 (\pm 0.21)	-0.65 (\pm 0.20)

End point values	Pridopidine 112.5 mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: score on a scale				
least squares mean (standard error)	-0.59 (\pm 0.22)			

Statistical analyses

Statistical analysis title	TFC: Pridopidine 45 mg - Placebo
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.45

Statistical analysis title	TFC: Pridopidine 67.5 mg - Placebo
Comparison groups	Placebo v Pridopidine 67.5 mg bid

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7042
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.68

Statistical analysis title	TFC: Pridopidine 90 mg - Placebo
Comparison groups	Placebo v Pridopidine 90 mg bid
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5099
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.75

Statistical analysis title	TFC: Pridopidine 112.5 mg - Placebo
Comparison groups	Placebo v Pridopidine 112.5 mg bid
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4061
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.82

Other pre-specified: Change in Total Functional Capacity (TFC) From Baseline in

Patients With Early HD (Defined as Patients With TFC≥7)

End point title	Change in Total Functional Capacity (TFC) From Baseline in Patients With Early HD (Defined as Patients With TFC≥7)
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End point description:

The TFC is one subscale of the Unified Huntington's Disease Rating Scale (UHDRS), comprising 5 functional Domains associated with disability (occupation, finances, domestic chores, activities of daily living, and care level), with scores on each item ranging from 0 to either 2 or 3. The TFC total score is the sum of the 5 TFC items and can range from 0 to 13, with greater scores indicating higher functioning.

End point type	Other pre-specified
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End point timeframe:

52 weeks

End point values	Placebo	Pridopidine 45 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	59		
Units: score on a scale				
least squares mean (standard error)	-1.17 (± 0.22)	-0.01 (± 0.23)		

Statistical analyses

Statistical analysis title	TFC, early HD responders
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	121
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.78

Other pre-specified: Change From Baseline in Quantitative Motor (Q-motor) Measurements, Pro-Sup-Inter-Tap-interval-MN-Hand

End point title	Change From Baseline in Quantitative Motor (Q-motor) Measurements, Pro-Sup-Inter-Tap-interval-MN-Hand
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End point description:

Q-motor assessments were based on the application of force transducers and 3-dimensional position sensors. The reported parameter is the Pro-Sup-Inter-Tap-interval-MN-Hand, measured in seconds.

End point type	Other pre-specified
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End point timeframe:

26 and 52 weeks

End point values	Placebo	Pridopidine 45 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	54		
Units: second				
least squares mean (standard error)				
Change from baseline to Week 26	0.0247 (\pm 0.0118)	-0.0096 (\pm 0.0110)		
Change from baseline to Week 52	0.0447 (\pm 0.0142)	0.0003 (\pm 0.0150)		

Statistical analyses

Statistical analysis title	Week 26
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	109
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0346
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-0.0341
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0658
upper limit	-0.0026

Statistical analysis title	Week 52
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	109
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0305
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-0.0444
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0847
upper limit	-0.0042

Other pre-specified: Total Functional Capacity Responder Rate

End point title	Total Functional Capacity Responder Rate
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End point description:

The TFC is one subscale of the Unified Huntington's Disease Rating Scale (UHDRS), comprising 5 functional domains associated with disability (occupation, finances, domestic chores, activities of daily living, and care level), with scores on each item ranging from 0 to either 2 or 3. The TFC total score is the sum of the 5 TFC items and can range from 0 to 13, with greater scores indicating higher functioning.

Responder was defined as a TFC change to Week 52 of TFC \geq 0.

End point type	Other pre-specified
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End point timeframe:

52 weeks

End point values	Placebo	Pridopidine 45 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	37		
Units: Patients	20	30		

Statistical analyses

Statistical analysis title	Pridopidine 45 mg bid - placebo
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	78
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.003
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

52 weeks

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Pridopidine matching placebo (hard capsules)

Patients received a starting dose of placebo matching pridopidine 22.5 mg and were during the first 4 weeks of treatment titrated to the randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Reporting group title	Pridopidine 45 mg bid
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Reporting group description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Reporting group title	Pridopidine 67.5 mg bid
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Reporting group description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Reporting group title	Pridopidine 90 mg bid
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Reporting group description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Reporting group title	Pridopidine 112.5 mg bid
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Reporting group description:

Pridopidine given as hard capsules, twice daily

Patients received a starting dose of pridopidine 22.5 mg and were during the first 4 weeks of Treatment titrated to their randomized dose level. The randomized dose level was then to be maintained for the remainder of the treatment period through Week 52.

Serious adverse events	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	8 / 81 (9.88%)	9 / 82 (10.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Laceration			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	4 / 81 (4.94%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	2 / 81 (2.47%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Face injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Grand mal convulsion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Akathisia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor hyperactivity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic ischaemic neuropathy			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer perforation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine prolapse			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mood disorder due to a general medical condition			
alternative assessment type:			

Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritonitis			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pridopidine 90 mg bid	Pridopidine 112.5 mg bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 81 (11.11%)	9 / 82 (10.98%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Laceration			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Head injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Grand mal convulsion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Akathisia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic ischaemic neuropathy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Duodenal ulcer perforation alternative assessment type: Systematic				
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Duodenitis alternative assessment type: Systematic				
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dysphagia alternative assessment type: Systematic				
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vomiting alternative assessment type: Systematic				
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain alternative assessment type: Systematic				
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diarrhoea alternative assessment type: Systematic				
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain upper alternative assessment type: Systematic				

subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine prolapse			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Mood disorder due to a general medical condition			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
alternative assessment type:			

Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Peritonitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 81 (1.23%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Pridopidine 45 mg bid	Pridopidine 67.5 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 82 (54.88%)	49 / 81 (60.49%)	63 / 82 (76.83%)
Investigations			
Weight decreased			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 82 (3.66%)	4 / 81 (4.94%)	3 / 82 (3.66%)
occurrences (all)	3	4	3
Creatinine renal clearance decreased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 82 (1.22%)	5 / 81 (6.17%)	2 / 82 (2.44%)
occurrences (all)	1	6	2
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 82 (20.73%)	16 / 81 (19.75%)	21 / 82 (25.61%)
occurrences (all)	31	44	31
Contusion			

alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 3	6 / 81 (7.41%) 7	6 / 82 (7.32%) 8
Vascular disorders Hypertension alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 82 (1.22%) 1	0 / 81 (0.00%) 0	1 / 82 (1.22%) 1
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all) Chorea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dizziness alternative assessment type: Systematic subjects affected / exposed occurrences (all) Balance disorder alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 82 (9.76%) 8 1 / 82 (1.22%) 1 2 / 82 (2.44%) 2 3 / 82 (3.66%) 3	7 / 81 (8.64%) 18 4 / 81 (4.94%) 4 2 / 81 (2.47%) 2 2 / 81 (2.47%) 3	7 / 82 (8.54%) 11 13 / 82 (15.85%) 15 6 / 82 (7.32%) 12 5 / 82 (6.10%) 6
General disorders and administration site conditions Fatigue alternative assessment type: Systematic subjects affected / exposed occurrences (all)	7 / 82 (8.54%) 10	3 / 81 (3.70%) 3	6 / 82 (7.32%) 6
Gastrointestinal disorders Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	9 / 82 (10.98%) 14	9 / 81 (11.11%) 11	11 / 82 (13.41%) 14

Vomiting alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 82 (4.88%) 6	5 / 81 (6.17%) 7	6 / 82 (7.32%) 7
Nausea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 82 (4.88%) 4	4 / 81 (4.94%) 6	7 / 82 (8.54%) 10
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 82 (2.44%) 2	5 / 81 (6.17%) 5	2 / 82 (2.44%) 2
Psychiatric disorders Anxiety alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 82 (2.44%) 2	6 / 81 (7.41%) 6	6 / 82 (7.32%) 6
Suicidal ideation alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 82 (0.00%) 0	2 / 81 (2.47%) 2	7 / 82 (8.54%) 8
Insomnia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 5	5 / 81 (6.17%) 6	11 / 82 (13.41%) 11
Irritability alternative assessment type: Systematic subjects affected / exposed occurrences (all)	7 / 82 (8.54%) 8	4 / 81 (4.94%) 4	6 / 82 (7.32%) 7
Musculoskeletal and connective tissue disorders Back pain alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 3	4 / 81 (4.94%) 4	3 / 82 (3.66%) 3
Infections and infestations Nasopharyngitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	7 / 82 (8.54%) 8	14 / 81 (17.28%) 21	12 / 82 (14.63%) 16
Urinary tract infection alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 82 (4.88%) 4	3 / 81 (3.70%) 3	6 / 82 (7.32%) 6

Non-serious adverse events	Pridopidine 90 mg bid	Pridopidine 112.5 mg bid	
Total subjects affected by non-serious adverse events subjects affected / exposed	57 / 81 (70.37%)	53 / 82 (64.63%)	
Investigations Weight decreased alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	7 / 82 (8.54%) 7	
Creatinine renal clearance decreased alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 4	5 / 82 (6.10%) 8	
Injury, poisoning and procedural complications Fall alternative assessment type: Systematic subjects affected / exposed occurrences (all)	13 / 81 (16.05%) 19	16 / 82 (19.51%) 42	
Contusion alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	3 / 82 (3.66%) 4	
Vascular disorders			

Hypertension alternative assessment type: Systematic subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 6	2 / 82 (2.44%) 2	
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all) Chorea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dizziness alternative assessment type: Systematic subjects affected / exposed occurrences (all) Balance disorder alternative assessment type: Systematic subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 19 3 / 81 (3.70%) 3 5 / 81 (6.17%) 5 1 / 81 (1.23%) 1	8 / 82 (9.76%) 10 7 / 82 (8.54%) 8 6 / 82 (7.32%) 8 3 / 82 (3.66%) 3	
General disorders and administration site conditions Fatigue alternative assessment type: Systematic subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 7	1 / 82 (1.22%) 1	
Gastrointestinal disorders Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Vomiting alternative assessment type: Systematic subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 17 5 / 81 (6.17%) 5	10 / 82 (12.20%) 15 4 / 82 (4.88%) 4	

Nausea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 6	3 / 82 (3.66%) 3	
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	5 / 82 (6.10%) 5	
Psychiatric disorders Anxiety alternative assessment type: Systematic subjects affected / exposed occurrences (all) Suicidal ideation alternative assessment type: Systematic subjects affected / exposed occurrences (all) Insomnia alternative assessment type: Systematic subjects affected / exposed occurrences (all) Irritability alternative assessment type: Systematic subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 8 1 / 81 (1.23%) 1 9 / 81 (11.11%) 10 5 / 81 (6.17%) 5	5 / 82 (6.10%) 5 0 / 82 (0.00%) 0 9 / 82 (10.98%) 11 2 / 82 (2.44%) 2	
Musculoskeletal and connective tissue disorders Back pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 9	5 / 82 (6.10%) 6	
Infections and infestations Nasopharyngitis alternative assessment type: Systematic			

subjects affected / exposed	13 / 81 (16.05%)	15 / 82 (18.29%)	
occurrences (all)	15	23	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 81 (4.94%)	5 / 82 (6.10%)	
occurrences (all)	5	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2013	<p>Amendment 1 to the protocol (dated 24 September 2013) was issued before any patients were enrolled in the study.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none">- The duration of treatment with study drug was increased from 12 weeks to 26 weeks- The 45 mg dose was removed from the efficacy analyses- The timing of the DSMB meetings was changed- The opportunity to enter the open-label extension study was introduced- Rules for discontinuation of treatment groups were modified
03 February 2014	<p>Amendment 2 to the protocol (dated 03 February 2014) was issued before any patients were enrolled in the study.</p> <p>Clarification that the mPPT will be used as the secondary efficacy endpoint</p> <ul style="list-style-type: none">- Increased frequency of DSMB meetings until 100 patients (20 from each treatment group) have completed two weeks of treatment on full dose- Clarification that Patients with a legal guardian should be consented according to local requirements- The EQ-5D-5L scale was added as an assessment- The possibility for patients to continue in the study after study drug discontinuation, due to safety or tolerability reasons, was introduced- Clarification regarding the number of capsules in the dispensed bottles- Change to time points at which exploratory efficacy endpoints (PBA-s, CIBIC-Plus, PDS, CGI-C, Walk-12, and TUG test) are assessed to reduce patient burden
16 September 2014	<p>Amendment 3 to the protocol (dated 16 September 2014) was issued after 24 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none">- Extension of the period between screening and baseline visit to 12 weeks, to allow a switch in concomitant drugs if deemed medically justified and for the benefit of the patient by the investigator- Revised text to reflect that the investigator can unblind the treatment code in an emergency situation without prior approval of the sponsor- The ECG on Day 56 would be optional, unless required by local regulations- Clarification regarding the ECG at Week 2 (ie, that it will be performed in triplicate before the afternoon dose of that visit)- Prolonged QTcF deleted from baseline visit as an eligibility criterion. Prolonged QT at baseline will be handled according to the discontinuation rules specified in the protocol- Inclusion criterion was revised to read "IS equal to or less than 90% at the screening visit", to include also patients with a IS of 90%- The protocol was updated to require that all serious adverse events be reported within 24 hours of when the investigator learns of the event, regardless of whether it's a non-working day- Instructions on how to resume study drug after temporary interruption- Prohibited medications timing also changed from 6 weeks prior to screening to 6 weeks prior to baseline (eg, QT-interval prolonging meds, CYP2D6 metabolized meds, and tetrabenazine)- Rescreening of selected patients now permitted if not originally eligible for enrollment- Clarification regarding the time frame for suicide attempts prior to screening (ie, if the attempt or acts were performed within 1 year of screening)- New text regarding required reporting of suicidality as an adverse event

12 January 2015	<p>Amendment 4 to the protocol (dated 12 January 2015) was issued after 133 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The study was extended from 26 to 52 weeks, to allow the assessment of pridopidine on TFC. A minimum of 52 weeks are needed for placebo to decline in TFC to allow a window to detect a potential therapeutic effect of a drug on this endpoint.</p> <p>In addition, the following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"> - endpoints modified and/or added to reflect the study extension - days of assessments and procedures modified to reflect changes in time points - clarification to allow only 1 titration during the entire study period - new text added to define the population sets that will be used to analyze the data from the second study period
31 March 2016	<p>Amendment 5 to the protocol (dated 31 March 2016) was issued after 408 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study.</p> <ul style="list-style-type: none"> - Addition of 2 telephone calls for safety evaluation (at Weeks 40 to 44 and Weeks 46 to 51) including C-SSRS and an abbreviated PBA-s assessment - Addition of suicidal ideations and suicide attempts as protocol-defined adverse events for expedited reporting - Addition of discontinuation criteria for individual patients and stopping rules for treatment groups - Clarification of study conduct - Revision of the Study Procedures and Assessments and Overall Study Schema to reflect the amended study design

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33164941>