# 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<br>Change of sponsor name and additional information |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | TV7820-CNS-20002 |

**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., clinicaltrialseu@prilenia.com |
| Scientific contact | Michal Geva, Prilenia Neurotherapeutics Ltd., clinicaltrialseu@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 |

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 |

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 |

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 |

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 |

| | |
|---|---|
| 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 |

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 |

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 |

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 |
|---|---|

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)<br>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<br>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<br>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<br>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<br>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<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 50.3 | 51.9 | 51.0 |
| standard deviation | ± 11.34 | ± 11.75 | ± 11.83 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 40 | 40 | 41 |
| Male | 42 | 41 | 41 |
| Race<br>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 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 |
|---|---|

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 |
|---|---|

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 |

| | |
|---|---|
| | Week 52 |

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: scoreon a scale | | | | |
| least squares mean (standard error) | -0.83 (± 0.20) | 0.04 (± 0.22) | -0.72 (± 0.21) | -0.65 (± 0.20) |

| **End point values** | Pridopidine 112.5 mg bid | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 81 | | | |
| Units: scoreon a scale | | | | |
| least squares mean (standard error) | -0.59 (± 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) |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 (± 0.0118) | -0.0096 (± 0.0110) | | |
| Change from baseline to Week 52 | 0.0447 (± 0.0142) | 0.0003 (± 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 |
|---|---|

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>=0.

| End point type | Other pre-specified |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### 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.

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

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 82 (3.66%) | 4 / 81 (4.94%) | 3 / 82 (3.66%) |
| occurrences (all) | 3 | 4 | 3 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 7 / 82 (8.54%) | 14 / 81 (17.28%) | 12 / 82 (14.63%) |
| occurrences (all) | 8 | 21 | 16 |
| Urinary tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 82 (4.88%) | 3 / 81 (3.70%) | 6 / 82 (7.32%) |
| occurrences (all) | 4 | 3 | 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 | 3 / 81 (3.70%) | 7 / 82 (8.54%) | |
| occurrences (all) | 3 | 7 | |
| Creatinine renal clearance decreased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 3 / 81 (3.70%) | 5 / 82 (6.10%) | |
| occurrences (all) | 4 | 8 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 13 / 81 (16.05%) | 16 / 82 (19.51%) | |
| occurrences (all) | 19 | 42 | |
| Contusion | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 3 / 82 (3.66%) | |
| occurrences (all) | 0 | 4 | |
| Vascular disorders | | | |

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

| | | | |
|---|---|---|---|
| Nausea<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all) | <br><br>4 / 81 (4.94%)<br>6 | <br><br>3 / 82 (3.66%)<br>3 | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all) | <br><br><br>1 / 81 (1.23%)<br>1 | <br><br><br>5 / 82 (6.10%)<br>5 | |
| Psychiatric disorders<br>Anxiety<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Suicidal ideation<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Irritability<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all) | <br><br><br>7 / 81 (8.64%)<br>8<br><br><br><br>1 / 81 (1.23%)<br>1<br><br><br><br>9 / 81 (11.11%)<br>10<br><br><br><br>5 / 81 (6.17%)<br>5 | <br><br><br>5 / 82 (6.10%)<br>5<br><br><br><br>0 / 82 (0.00%)<br>0<br><br><br><br>9 / 82 (10.98%)<br>11<br><br><br><br>2 / 82 (2.44%)<br>2 | |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all) | <br><br><br>6 / 81 (7.41%)<br>9 | <br><br><br>5 / 82 (6.10%)<br>6 | |
| Infections and infestations<br>Nasopharyngitis<br>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 | Amendment 1 to the protocol (dated 24 September 2013) was issued before any patients were enrolled in the study.<br><br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- The duration of treatment with study drug was increased from 12 weeks to 26 weeks<br>- The 45 mg dose was removed from the efficacy analyses<br>- The timing of the DSMB meetings was changed<br>- The opportunity to enter the open-label extension study was introduced<br>- Rules for discontinuation of treatment groups were modified |
| 03 February 2014 | Amendment 2 to the protocol (dated 03 February 2014) was issued before any patients were enrolled in the study.<br><br>Clarification that the mPPT will be used as the secondary efficacy endpoint<br>- Increased frequency of DSMB meetings until 100 patients (20 from each treatment group) have completed two weeks of treatment on full dose<br>- Clarification that Patients with a legal guardian should be consented according to local requirements<br>- The EQ-5D-5L scale was added as an assessment<br>- The possibility for patients to continue in the study after study drug discontinuation, due to safety or tolerability reasons, was introduced<br>- Clarification regarding the number of capsules in the dispensed bottles<br>- 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 | 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.<br><br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- 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<br>- Revised text to reflect that the investigator can unblind the treatment code in an emergency situation without prior approval of the sponsor<br>- The ECG on Day 56 would be optional, unless required by local regulations<br>- Clarification regarding the ECG at Week 2 (ie, that it will be performed in triplicate before the afternoon dose of that visit)<br>- 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<br>- 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%<br>- 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<br>- Instructions on how to resume study drug after temporary interruption<br>-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)<br>- Rescreening of selected patients now permitted if not originally eligible for enrollment<br>- Clarification regarding the time frame for suicide attempts prior to screening (ie, if the attempt or acts were performed within 1 year of screening)<br>- New text regarding required reporting of suicidality as an adverse event |

| | |
|---|---|
| 12 January 2015 | 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.<br>In addition, the following major procedural changes (not all-inclusive) were made to the protocol:<br>- endpoints modified and/or added to reflect the study extension<br>- days of assessments and procedures modified to reflect changes in time points<br>- clarification to allow only 1 titration during the entire study period<br>- new text added to define the population sets that will be used to analyze the data from the second study period |
| 31 March 2016 | 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.<br><br>- 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<br>- Addition of suicidal ideations and suicide attempts as protocol-defined adverse events for expedited reporting<br>- Addition of discontinuation criteria for individual patients and stopping rules for treatment groups<br>- Clarification of study conduct<br>- 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