



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease

Summary

EudraCT number	2020-002822-10
Trial protocol	DE AT FR CZ NL IT
Global end of trial date	21 March 2024

Results information

Result version number	v1 (current)
This version publication date	30 May 2024
First version publication date	30 May 2024

Trial information

Trial identification

Sponsor protocol code	PL101-HD301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04556656
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Prilenia Therapeutics B.V.
Sponsor organisation address	Gooimeer 2, DC Naarden, Netherlands, 1411
Public contact	Prilenia medical information, Prilenia Therapeutics B.V., medinfo@prilenia.com
Scientific contact	Prilenia medical information, Prilenia Therapeutics B.V., medinfo@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	Interim
Date of interim/final analysis	25 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2023
Global end of trial reached?	Yes
Global end of trial date	21 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of pridopidine on functional capacity in participants with stage 1-2 HD.

Note: The primary and key secondary endpoints showed no beneficial effect of pridopidine compared to placebo in the full study population. Importantly, however, this population consisted of both patients on ADMs and patients off ADMs. Concomitant use of these drugs may have masked or interfered with clinically meaningful effects of pridopidine. Indeed, in the group of patients who did not use ADMs at any point in the study, pridopidine demonstrated robust benefits over placebo. The observed benefit are considered clinically meaningful.

Protection of trial subjects:

This study was conducted in accordance with the protocol and according to the ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and applicable laws and regulations.

Participants were informed that their participation is voluntary. Participants were required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

During the double-blind treatment period of the Main Study, an independent, unblinded Safety Monitoring Committee assessed the safety and if requested efficacy.

Background therapy:

For allowed antipsychotic, antidepressant, antiarrhythmic, or other medication, the dosing had to be stable for at least 4 weeks before the baseline visit (Amiodarone was not allowed within 6 weeks of baseline visit) and had to be kept constant during the study.

Prohibited medication included medications that prolong QT interval such as non-allowed antipsychotic medications, tricyclic antidepressants, and/or Class I antiarrhythmics, use of pridopidine within 12 months before the baseline visit, gene therapy at any time, and prior participation in studies with tominersen at any time.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	16 October 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United States: 201

Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Italy: 58
Worldwide total number of subjects	499
EEA total number of subjects	254

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)	420
From 65 to 84 years	78
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Approximately 480 participants were planned to be enrolled (240 per arm) at approximately 60 sites in North America and Europe.

A total of 499 patients with Huntington Disease were randomized and received at least one dose of study treatment.

Pre-assignment

Screening details:

Screening period of up to 6 weeks.

Period 1

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

Blinding implementation details:

All participants, site staff, Sponsor, contract research organization (CRO) and vendors involved with the study remained blinded to treatment assignments until the database was locked and the study unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pridopidine 45 mg bid

Arm description:

During the titration period, all participants self-administered 1 capsule of study drug orally (PO), once daily, in the morning for 2 weeks. Thereafter, the study drug was taken PO, bid in the morning and in the afternoon (7-10 hours apart).

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:

Administered orally at a dose of 45 mg bid

Arm title	Placebo
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Arm description: -

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

Dosage and administration details:

Administered orally bid

Number of subjects in period 1	Pridopidine 45 mg bid	Placebo
Started	250	249
Completed	222	227
Not completed	28	22
Consent withdrawn by subject	14	12
Physician decision	1	-
Adverse event, non-fatal	4	7
Death	4	-
Other	2	1
Lost to follow-up	3	2

Baseline characteristics

Reporting groups

Reporting group title	Pridopidine 45 mg bid
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Reporting group description:

During the titration period, all participants self-administered 1 capsule of study drug orally (PO), once daily, in the morning for 2 weeks. Thereafter, the study drug was taken PO, bid in the morning and in the afternoon (7-10 hours apart).

Reporting group title	Placebo
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Reporting group description: -

Reporting group values	Pridopidine 45 mg bid	Placebo	Total
Number of subjects	250	249	499
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	207	213	420
From 65-84 years	42	36	78
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	52.2	52.7	
standard deviation	± 11.93	± 11.39	-
Gender categorical			
Units: Subjects			
Female	132	127	259
Male	118	122	240

Subject analysis sets

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population included all randomized participants. Treatment was assigned based on the treatment to which participants were randomized.

The ITT population was the main analysis population of the primary endpoint for EMA region.

Subject analysis set title	mITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The modified intent to treat (mITT) population was a subset of the ITT population and included all participants in the ITT population who received at least one dose of study drug and had valid in-clinic TFC scores both at baseline and at least one post-baseline timepoint. The mITT population was analyzed according to the treatment to which the participant was randomized.

The mITT population was the main analysis population for the primary endpoint in non-EMA regions. For

all other efficacy analyses, the mITT population was the main analysis population in both EMA and non-EMA regions.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SP) included all randomized participants who received at least one dose of study drug. Treatment was assigned based upon the treatment participants actually received.

Reporting group values	ITT	mITT	Safety
Number of subjects	499	490	499
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	420	414	420
From 65-84 years	78	75	78
85 years and over	1	1	1
Age continuous Units: years			
arithmetic mean	52.5	52.5	52.5
standard deviation	± 11.66	± 11.63	± 11.66
Gender categorical Units: Subjects			
Female	259	256	259
Male	240	234	240

End points

End points reporting groups

Reporting group title	Pridopidine 45 mg bid
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Reporting group description:

During the titration period, all participants self-administered 1 capsule of study drug orally (PO), once daily, in the morning for 2 weeks. Thereafter, the study drug was taken PO, bid in the morning and in the afternoon (7-10 hours apart).

Reporting group title	Placebo
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Reporting group description: -

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population included all randomized participants. Treatment was assigned based on the treatment to which participants were randomized.

The ITT population was the main analysis population of the primary endpoint for EMA region.

Subject analysis set title	mITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The modified intent to treat (mITT) population was a subset of the ITT population and included all participants in the ITT population who received at least one dose of study drug and had valid in-clinic TFC scores both at baseline and at least one post-baseline timepoint. The mITT population was analyzed according to the treatment to which the participant was randomized.

The mITT population was the main analysis population for the primary endpoint in non-EMA regions. For all other efficacy analyses, the mITT population was the main analysis population in both EMA and non-EMA regions.

Subject analysis set title	Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety population (SP) included all randomized participants who received at least one dose of study drug. Treatment was assigned based upon the treatment participants actually received.

Primary: Change from baseline to Week 65 in the Unified Huntington Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) score (ITT)

End point title	Change from baseline to Week 65 in the Unified Huntington Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) score (ITT)
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End point description:

The primary efficacy endpoint for this study was the change from baseline to Week 65 in the TFC (defined as the sum of all TFC 5-items ratings [domestic chores, activities of daily living, finances, care level, and occupation]). The TFC is the standard and well-accepted clinical scale for staging and tracking the progression of HD using functional capacity. Scores range from 0 to 13, with 13 as the least affected and 0 as complete incapacity. In Europe, the ITT set was used for the primary endpoint analysis.

End point type	Primary
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End point timeframe:

From baseline to Week 65

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Score on a scale				
least squares mean (standard error)	-1.17 (± 0.120)	-0.94 (± 0.120)		

Statistical analyses

Statistical analysis title	Mixed model for repeated measures (MMRM)
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Statistical analysis description:

In the MMRM, change from baseline in TFC score is the dependent variable, and independent variables include treatment arm, baseline TFC, region, neuroleptic use or no use, baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. The unstructured covariance matrix is used for repeated measurements at patient level.

Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1598
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.162

Primary: Change from baseline to Week 65 in the UHDRS TFC score (mITT)

End point title	Change from baseline to Week 65 in the UHDRS TFC score (mITT)
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End point description:

The primary efficacy endpoint for this study was the change from baseline to Week 65 in the TFC (defined as the sum of all TFC 5-items ratings [domestic chores, activities of daily living, finances, care level, and occupation]). The TFC is the standard and well-accepted clinical scale for staging and tracking the progression of HD using functional capacity. Scores range from 0 to 13, with 13 as the least affected and 0 as complete incapacity. In non-EMA regions, the mITT set was used for the primary endpoint analysis.

End point type	Primary
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End point timeframe:

From baseline to Week 65.

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	247		
Units: Score on a scale				
least squares mean (standard error)	-1.18 (\pm 0.119)	-0.95 (\pm 0.119)		

Statistical analyses

Statistical analysis title	Mxed model for repeated measures (MMRM)
Statistical analysis description:	
In the MMRM, change in TFC score from baseline was the dependent variable, and independent variables included treatment arm, baseline TFC, region, neuroleptic use or no use, baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.	
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.162

Secondary: Change from baseline to Week 65 in composite UHDRS (cUHDRS) total score (mITT)

End point title	Change from baseline to Week 65 in composite UHDRS (cUHDRS) total score (mITT)
End point description:	
The composite Unified Huntington Disease Rating Scale (cUHDRS) is a composite measure of motor (Total Motor Score [TMS]), cognitive (Stroop Word Reading [SWR] and Symbol Digit Modalities Test [SDMT]), and global functional decline (Total Functional Capacity [TFC]).	
End point type	Secondary
End point timeframe:	
From baseline to Week 65.	

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	247		
Units: Score on a scale				
least squares mean (standard error)	-0.99 (± 0.109)	-0.88 (± 0.108)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In the MMRM, change in cUHDRS score from baseline was the dependent variable, while independent variables included treatment arm, baseline cUHDRS, region, neuroleptic use or no use, baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. The unstructured covariance matrix was used for repeated measurements at patient level. No imputation was performed on missing data.

Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4544
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.148

Other pre-specified: Change from baseline in cUHDRS total score - Patients Off ADMs (mITT)

End point title	Change from baseline in cUHDRS total score - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.

End point type	Other pre-specified
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End point timeframe:

Time course from baseline to Week 78

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: Score on a scale				
least squares mean (standard error)				
Week 26	0.15 (± 0.114)	-0.31 (± 0.108)		
Week 39	0.10 (± 0.130)	-0.34 (± 0.125)		
Week 52	-0.07 (± 0.140)	-0.48 (± 0.135)		
Week 65	-0.26 (± 0.143)	-0.53 (± 0.137)		
Week 78	-0.40 (± 0.159)	-0.54 (± 0.158)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In the MMRM model, change in cUHDRS score from baseline was the dependent variable and independent variables included treatment group, baseline cUHDRS, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, concomitant use of select medications and Treatment x Concomitant use of select medications, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.76
Variability estimate	Standard error of the mean
Dispersion value	0.156

Notes:

[1] - P-value for Week 26.

Statistical analysis title	Week 39 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.179

Notes:

[2] - P-value for Week 39.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0351 ^[3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.79
Variability estimate	Standard error of the mean
Dispersion value	0.193

Notes:

[3] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1683 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.66

Variability estimate	Standard error of the mean
Dispersion value	0.197

Notes:

[4] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5315 ^[5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.223

Notes:

[5] - P-value for Week 78.

Other pre-specified: Change from baseline in Q-Motor Finger Tapping Inter-Onset Interval (IOI) Mean - Patients Off ADMs (mITT)

End point title	Change from baseline in Q-Motor Finger Tapping Inter-Onset Interval (IOI) Mean - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes. Note that negative changes represent improvements.

End point type	Other pre-specified
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End point timeframe:

Time course from baseline to Week 78.

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: milliseconds				
least squares mean (standard error)				
Week 26	-14.85 (± 6.846)	6.30 (± 6.449)		
Week 52	-2.37 (± 7.135)	11.95 (± 6.792)		
Week 65	-0.79 (± 7.365)	23.93 (± 7.028)		

Week 78	1.46 (\pm 7.444)	24.36 (\pm 7.230)		
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Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
Statistical analysis description:	
In thMMRM model, change in Q-Motor Finger Tapping IOI Mean from baseline was the dependent variable and independent variables included treatment group, baseline Q-Motor Finger Tapping IOI Mean, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, concomitant use of select medications and Treatment x Concomitant use of select medications, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.	
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0253 ^[6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-21.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.66
upper limit	-2.64
Variability estimate	Standard error of the mean
Dispersion value	9.406
Notes:	
[6] - P-value for Week 26.	

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1474 ^[7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-14.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.71
upper limit	5.08
Variability estimate	Standard error of the mean
Dispersion value	9.853

Notes:

[7] - P-value for Week 52

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0159 ^[8]
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-24.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.76
upper limit	-4.67
Variability estimate	Standard error of the mean
Dispersion value	10.185

Notes:

[8] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0283 ^[9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.34
upper limit	-2.45
Variability estimate	Standard error of the mean
Dispersion value	10.38

Notes:

[9] - P-value for Week 78.

Other pre-specified: Change from baseline in Q-Motor Pronation/Supination Inter-Tap Interval Mean - Patients Off ADMs (mITT)

End point title	Change from baseline in Q-Motor Pronation/Supination Inter-Tap Interval Mean - Patients Off ADMs (mITT)
End point description:	
In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.	
End point type	Other pre-specified

End point timeframe:

Time course from baseline to Week 78.

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: milliseconds				
least squares mean (standard error)				
Week 26	-17.63 (± 8.029)	20.43 (± 7.448)		
Week 52	-0.15 (± 9.124)	20.07 (± 8.555)		
Week 65	4.64 (± 8.380)	28.55 (± 7.867)		
Week 78	12.73 (± 9.740)	34.97 (± 9.412)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In the MMRM model, change in Q-Motor Pronation/Supination ITI Mean from baseline was the dependent variable and independent variables included treatment group, baseline Q-Motor Pronation/Supination ITI Mean, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 ^[10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-38.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.74
upper limit	-16.37
Variability estimate	Standard error of the mean
Dispersion value	10.999

Notes:

[10] - P-value at Week 26.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v Pridopidine 45 mg bid

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1087 ^[11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.95
upper limit	4.53
Variability estimate	Standard error of the mean
Dispersion value	12.547

Notes:

[11] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0395 ^[12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-23.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.68
upper limit	-1.16
Variability estimate	Standard error of the mean
Dispersion value	11.541

Notes:

[12] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1038 ^[13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.08
upper limit	4.61

Variability estimate	Standard error of the mean
Dispersion value	13.587

Notes:

[13] - P-value for Week 78.

Other pre-specified: Change from baseline in Q-Motor Pronation/Supination IOI Mean - Patients Off ADMs (mITT)

End point title	Change from baseline in Q-Motor Pronation/Supination IOI Mean - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.

End point type	Other pre-specified
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End point timeframe:

Time course from baseline to Week 78.

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: milliseconds				
least squares mean (standard error)				
Week 26	-16.70 (± 9.399)	13.68 (± 8.829)		
Week 52	7.40 (± 10.978)	24.23 (± 10.467)		
Week 65	7.34 (± 10.730)	30.13 (± 10.232)		
Week 78	19.21 (± 12.702)	41.93 (± 12.435)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In MMRM model, change in Q-Motor Pronation/Supination IOI Mean from baseline was the dependent variable and independent variables included treatment group, baseline Q-Motor Pronation/Supination IOI Mean, region, categorical week, baseline HD stage (HD1 and HD2), treatment by categorical week interaction, concomitant use of select medications and Treatment x Concomitant use of select medications, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Placebo v Pridopidine 45 mg bid
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Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0193 ^[14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-30.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.78
upper limit	-4.98
Variability estimate	Standard error of the mean
Dispersion value	12.902

Notes:

[14] - P-value for Week 26.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.268 ^[15]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-16.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.69
upper limit	13.02
Variability estimate	Standard error of the mean
Dispersion value	15.17

Notes:

[15] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1255 ^[16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.97
upper limit	6.4

Variability estimate	Standard error of the mean
Dispersion value	14.829

Notes:

[16] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2024 ^[17]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.72
upper limit	12.28
Variability estimate	Standard error of the mean
Dispersion value	17.777

Notes:

[17] - P-value for Week 78.

Other pre-specified: Change from baseline in the UHDRS TFC score - Patients Off ADMs (mITT)

End point title	Change from baseline in the UHDRS TFC score - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.

End point type	Other pre-specified
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End point timeframe:

Timecourse from baseline to Week 78.

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: Score on a scale				
least squares mean (standard error)				
Week 26	-0.01 (± 0.131)	-0.23 (± 0.124)		
Week 39	-0.11 (± 0.137)	-0.31 (± 0.131)		
Week 52	-0.19 (± 0.149)	-0.45 (± 0.143)		

Week 65	-0.49 (± 0.156)	-0.54 (± 0.150)		
Week 78	-0.42 (± 0.166)	-0.54 (± 0.163)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In the MMRM model, change in UHDRS-TFC score from baseline was the dependent variable and independent variables included treatment group, baseline UHDRS-TFC, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, concomitant use of select medications and Treatment x Concomitant use of select medications, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2088 ^[18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.179

Notes:

[18] - P-value for Week 26.

Statistical analysis title	Week 39 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2991 ^[19]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.57
Variability estimate	Standard error of the mean
Dispersion value	0.188

Notes:

[19] - P-value for Week 39.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2116 ^[20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.66
Variability estimate	Standard error of the mean
Dispersion value	0.205

Notes:

[20] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8242 ^[21]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.215

Notes:

[21] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5918 ^[22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.231

Notes:

[22] - P-value for Week 78.

Other pre-specified: Change from baseline in Stroop Word Reading (SWR) - Patients Off ADMs (mITT)

End point title	Change from baseline in Stroop Word Reading (SWR) - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.

End point type	Other pre-specified
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End point timeframe:

Timecourse from baseline to Week 78

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: Score on a scale				
least squares mean (standard error)				
Week 26	2.34 (± 0.964)	-0.82 (± 0.916)		
Week 39	2.85 (± 1.100)	-0.04 (± 1.051)		
Week 52	2.73 (± 1.078)	-0.32 (± 1.039)		
Week 65	1.39 (± 1.243)	-0.94 (± 1.193)		
Week 78	0.91 (± 1.261)	-1.08 (± 1.249)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In MMRM model, change in SWR score from baseline was the dependent variable and independent variables included treatment group, baseline SWR, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, concomitant use of select medications and Treatment x Concomitant use of select medications, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Placebo v Pridopidine 45 mg bid
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Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0178 ^[23]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	5.77
Variability estimate	Standard error of the mean
Dispersion value	1.326

Notes:

[23] - P-value for Week 26.

Statistical analysis title	Week 39 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0576 ^[24]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	5.88
Variability estimate	Standard error of the mean
Dispersion value	1.518

Notes:

[24] - P-value for Week 39.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0418 ^[25]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	5.99

Variability estimate	Standard error of the mean
Dispersion value	1.493

Notes:

[25] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1775 ^[26]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	5.71
Variability estimate	Standard error of the mean
Dispersion value	1.719

Notes:

[26] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2627 ^[27]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	5.48
Variability estimate	Standard error of the mean
Dispersion value	1.772

Notes:

[27] - P-value for Week 78.

Other pre-specified: Change from baseline in Symbol Digit Modalities Test (SDMT) - Patients Off ADMs (mITT)

End point title	Change from baseline in Symbol Digit Modalities Test (SDMT) - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"),

pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.

End point type	Other pre-specified
End point timeframe:	
Timecourse from baseline to Week 78.	

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: Score on a scale				
least squares mean (standard error)				
Week 26	0.54 (± 0.521)	-0.47 (± 0.484)		
Week 39	0.82 (± 0.512)	-0.06 (± 0.478)		
Week 52	-0.42 (± 0.578)	-0.33 (± 0.543)		
Week 65	0.35 (± 0.616)	0.07 (± 0.576)		
Week 78	0.07 (± 0.617)	-0.36 (± 0.598)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In the MMRM model, change in SDMT score from baseline was the dependent variable and independent variables included treatment group, baseline SDMT, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1586 [28]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.41
Variability estimate	Standard error of the mean
Dispersion value	0.712

Notes:

[28] - P-value for Week 26.

Statistical analysis title	Week 39 - Mixed Model for Repeated Measures (MMRM)
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Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2144 ^[29]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	2.25
Variability estimate	Standard error of the mean
Dispersion value	0.701

Notes:

[29] - P-value for Week 39.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9119 ^[30]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	1.48
Variability estimate	Standard error of the mean
Dispersion value	0.793

Notes:

[30] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7339 ^[31]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	1.95
Variability estimate	Standard error of the mean
Dispersion value	0.844

Notes:

[31] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6213 ^[32]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	2.12
Variability estimate	Standard error of the mean
Dispersion value	0.859

Notes:

[32] - P-value for Week 78.

Other pre-specified: Change from baseline in Total Motor Score (TMS) - Patients Off ADMs (mITT)

End point title	Change from baseline in Total Motor Score (TMS) - Patients Off ADMs (mITT)
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End point description:

In addition to the main efficacy analyses, sensitivity analyses were performed in a sub-group of patients who were off neuroleptics AND off vesicular monoamine transporter-2 (VMAT2) inhibitors (together called antidopaminergics, or ADMs) at any time during the study. In this population ("off ADMs"), pridopidine demonstrated robust benefits, with consistent and clinically meaningful effect sizes.

End point type	Other pre-specified
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End point timeframe:

Timecourse from baseline to Week 78.

End point values	Pridopidine 45 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	112		
Units: Score on a scale				
least squares mean (standard error)				

Week 26	-0.21 (± 0.568)	-0.03 (± 0.530)		
Week 39	0.06 (± 0.780)	0.96 (± 0.729)		
Week 52	0.47 (± 0.766)	0.80 (± 0.720)		
Week 65	0.92 (± 0.847)	1.28 (± 0.790)		
Week 78	2.19 (± 0.954)	1.63 (± 0.916)		

Statistical analyses

Statistical analysis title	Week 26 - Mixed Model for Repeated Measures (MMRM)
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Statistical analysis description:

In the MMRM model, change in TMS score from baseline was the dependent variable and independent variables included treatment group, baseline TMS, region, categorical week, baseline HD stage (HD1 and HD2), and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. No imputation was performed on missing data.

Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8205 ^[33]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	1.36
Variability estimate	Standard error of the mean
Dispersion value	0.777

Notes:

[33] - P-value for Week 26.

Statistical analysis title	Week 39 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4028 ^[34]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	1.067

Notes:

[34] - P-value for Week 39.

Statistical analysis title	Week 52 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7577 ^[35]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1.75
Variability estimate	Standard error of the mean
Dispersion value	1.051

Notes:

[35] - P-value for Week 52.

Statistical analysis title	Week 65 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Pridopidine 45 mg bid v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7605 ^[36]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.64
upper limit	1.93
Variability estimate	Standard error of the mean
Dispersion value	1.158

Notes:

[36] - P-value for Week 65.

Statistical analysis title	Week 78 - Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v Pridopidine 45 mg bid
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6694 ^[37]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	3.18
Variability estimate	Standard error of the mean
Dispersion value	1.323

Notes:

[37] - P-value for Week 78.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening until 2 weeks after End of Study/End of Treatment visit (unless a patient continued in the open-label extension part of the study).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Pridopidine 45 mg bid
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Reporting group description:

During the titration period, all participants self-administered 1 capsule of study drug orally (PO), once daily, in the morning for 2 weeks. Thereafter, the study drug was taken PO, bid in the morning and in the afternoon (7-10 hours apart).

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Pridopidine 45 mg bid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 250 (13.60%)	21 / 249 (8.43%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	3	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	2 / 250 (0.80%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord neoplasm			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (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			
Epistaxis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	2 / 250 (0.80%)	2 / 249 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	1 / 250 (0.40%)	2 / 249 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	3 / 250 (1.20%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritability			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			

subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 250 (0.00%)	2 / 249 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial bones fracture			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Head injury			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Limb injury			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal cord injury cervical			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 250 (0.00%)	3 / 249 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 250 (0.00%)	2 / 249 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			

subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chorea			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 250 (0.80%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pridopidine 45 mg bid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	204 / 250 (81.60%)	212 / 249 (85.14%)	
Investigations			
Weight decreased			
subjects affected / exposed	13 / 250 (5.20%)	7 / 249 (2.81%)	
occurrences (all)	13	7	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	55 / 250 (22.00%)	57 / 249 (22.89%)	
occurrences (all)	114	111	
Contusion			
subjects affected / exposed	12 / 250 (4.80%)	14 / 249 (5.62%)	
occurrences (all)	20	15	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	16 / 250 (6.40%) 18	25 / 249 (10.04%) 34	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	21 / 250 (8.40%) 27	22 / 249 (8.84%) 32	
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	26 / 250 (10.40%) 27 19 / 250 (7.60%) 22	12 / 249 (4.82%) 12 16 / 249 (6.43%) 20	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	12 / 250 (4.80%) 13	14 / 249 (5.62%) 16	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	59 / 250 (23.60%) 62 19 / 250 (7.60%) 22 11 / 250 (4.40%) 12	57 / 249 (22.89%) 66 18 / 249 (7.23%) 20 17 / 249 (6.83%) 20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2020	Updated secondary and exploratory endpoints, clarified OLE duration, removed blood draws for coagulation test.
29 September 2020	Updated exclusion criteria, specified OLE duration, updated frequencies of assessments, added exploratory endpoints.
25 October 2020	Added text for handling of intercurrent events, added that separate analyses of the primary endpoint would be performed for EMA and Non EMA regions
13 May 2021	Added objectives and endpoints for OLE, updated inclusion and exclusion criteria, expanded post Week 4 (V3) in-clinic visit windows, updated permitted medications.
27 January 2022	Added Q-Motor to efficacy endpoints, updated assessments and visits during OLE, clarified virtual phone visits vs in-clinic visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported