Clinical trial results:
A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Flexible-Dose, 27-Week Trial to Evaluate the Efficacy, Safety, and Tolerability of Tavapadon as Adjunctive Therapy for Parkinson's Disease in Levodopa-Treated Adults With Motor Fluctuations (TEMPO-3 Trial)

Summary

EudraCT number	2019-002951-40
Trial protocol	DE CZ ES FR HU BG IT
Global end of trial date	15 February 2024
Results information	
Result version number	v1 (current)
This version publication date	23 February 2025
First version publication date	23 February 2025

Trial information

Trial identification	
Sponsor protocol code	CVL-751-PD-003
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 118,647

Notes:

Sponsors	
Sponsor organisation name	Cerevel Therapeutics, LLC
Sponsor organisation address	222 Jacobs Street, Suite 200, Cambridge, United States, 02141
Public contact	AbbVie, Global Medical Services, +1 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	AbbVie, Global Medical Services, +1 800-633-9110, abbvieclinicaltrials@abbvie.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	15 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the effect of tavapadon on the change from baseline in total daily hours of "on" time
without troublesome dyskinesia in L-Dopa-treated participants with Parkinson's Disease (PD) who are experiencing motor
fluctuations.

Protection of trial subjects:

The investigator or his/her representative explained the nature of the trial to the participant or his/her legally authorized representative and answered all questions regarding the trial. Participants were informed that their participation was voluntary. Participants were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or trial center. A copy of the ICF was provided to the participant or the participant’s legally authorized representative.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	United States: 139
Country: Number of subjects enrolled	Poland: 104
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Bulgaria: 39
Country: Number of subjects enrolled	Czechia: 24
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 22
Worldwide total number of subjects	507
EEA total number of subjects	265

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)	223
From 65 to 84 years	284
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this Phase 3, Double-Blind study, a total of 507 subjects with Parkinson’s Disease(PD) were randomized in a 1:1 ratio to receive Tavapadon (5 mg to 15 mg) or Placebo once daily (QD) for 27 Weeks.

Period 1

Period 1 title	Overall 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:

Treatment assignments were blinded to the investigators and other trial site personnel, the subjects, and all sponsor personnel who are involved in the conduct of the trial (including trial monitoring, data management, and data analysis).Access to the treatment codes were restricted to personnel who are responsible for generating and maintaining the randomization code, packaging the IMPs, operating the IVRS/IWRS, analyzing the PK blood samples, or reporting SAEs or AESI to regulatory agency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants will receive placebo matching to tavapadon tablet QD orally for 27 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will receive placebo matching to tavapadon QD orally for 27 weeks.

Arm title	Tavapadon

Arm description:

Participants will be randomized to receive tavapadon 5 to 15 mg tablet QD orally for 27 weeks.

Arm type	Experimental
Investigational medicinal product name	Tavapadon
Investigational medicinal product code	
Other name	PF-06649751, CVL-751
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will be randomized to receive tavapadon 5 to 15 mg tablet QD orally for 27 weeks.

Number of subjects in period 1	Placebo	Tavapadon
Started	255	252
Completed	206	159
Not completed	49	93
Treatment with Prohibited Concomitant Medications	1	-
Consent withdrawn by subject	12	33
Non- Compliance with Study Drug	-	2
Physician decision	-	1
Failure to Meet Continuation Criteria	-	1
Adverse event, non-fatal	23	43
Not specified	2	2
Site Terminated by Sponsor	3	5
Lost to follow-up	3	4
Lack of efficacy	5	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants will receive placebo matching to tavapadon tablet QD orally for 27 weeks.	
Reporting group title	Tavapadon
Reporting group description:	
Participants will be randomized to receive tavapadon 5 to 15 mg tablet QD orally for 27 weeks.	

Reporting group values	Placebo	Tavapadon	Total
Number of subjects	255	252	507
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.1	65.6	
standard deviation	± 8.52	± 8.42	-
Gender categorical Units: Subjects			
Female	85	101	186
Male	170	151	321
ON Time (hours) Without Troublesome Dyskinesia at Baseline Units: hours			
arithmetic mean	10.148	9.884	
standard deviation	± 2.637	± 2.569	-
OFF Time (hours) at Baseline Units: hours			
arithmetic mean	5.408	5.638	
standard deviation	± 2.484	± 2.246	-
MDS-UPDRS Score at Baseline (Part I)			
The MDS-UPDRS is a multidimensional scale that assesses the motor and non-motor impacts of PD across 4 parts. Each item of all the parts will be rated on a scale from 0 to 4 on which 0 = normal, 1=slight, 2=mild, 3=moderate, and 4=severe.			
Units: units on a scale			
arithmetic mean	7.5	8.0	
standard deviation	± 4.93	± 5.13	-
MDS-UPDRS Score at Baseline (Part II)			
The MDS-UPDRS is a multidimensional scale that assesses the motor and non-motor impacts of PD across 4 parts. Each item of all the parts will be rated on a scale from 0 to 4 on which 0 = normal, 1=slight, 2=mild, 3=moderate, and 4=severe.			
Units: units on a scale			
arithmetic mean	12.5	13.3	
standard deviation	± 7.05	± 6.54	-
MDS-UPDRS Score at Baseline (Part III)			
The MDS-UPDRS is a multidimensional scale that assesses the motor and non-motor impacts of PD across 4 parts. Each item of all the parts will be rated on a scale from 0 to 4 on which 0 = normal, 1=slight, 2=mild, 3=moderate, and 4=severe.			
Units: units on a scale			

arithmetic mean	32.4	32.6	
standard deviation	± 14.26	± 14.34	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants will receive placebo matching to tavapadon tablet QD orally for 27 weeks.	
Reporting group title	Tavapadon
Reporting group description:	
Participants will be randomized to receive tavapadon 5 to 15 mg tablet QD orally for 27 weeks.	

Primary: Change From Baseline in the Total "On" Time Without Troublesome Dyskinesia Based on the 2-day Average of the Self-completed Home Diary for Motor Function Status (Hauser Diary)

End point title	Change From Baseline in the Total "On" Time Without Troublesome Dyskinesia Based on the 2-day Average of the Self-completed Home Diary for Motor Function Status (Hauser Diary)

End point description:

The Hauser diary assesses participant-defined clinical status over a period of time and provides a tool for assessment of the change in "off" time and "on" time with troublesome dyskinesia (which is a more accurate reflection of clinical response than "off" time alone). The Hauser diary asks participants to rate their mobility for each 30-minute period and to record their status for the majority of the period in 1 of 5 categories as: "on" time without dyskinesia, "on" time with nontroublesome dyskinesia, "on" time with troublesome dyskinesia, "off" time, or asleep. The total "on" time without troublesome dyskinesia will be assessed and reported at endpoint.

End point type	Primary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	153		
Units: Hours				
least squares mean (standard error)	0.619 (± 0.188)	1.721 (± 0.207)		

Statistical analyses

Statistical analysis title	Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon

Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	1.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.553
upper limit	1.653
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[1] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Secondary: Change From Baseline in Total Daily "Off" Time Based on the 2-Day Average of the Self-Completed Home Diary for Motor Function Status (Hauser Diary)

End point title	Change From Baseline in Total Daily "Off" Time Based on the 2-Day Average of the Self-Completed Home Diary for Motor Function Status (Hauser Diary)

End point description:

The Hauser diary assesses participant-defined clinical status over a period of time and provides a tool for assessment
of the change in "off" time and "on" time with troublesome dyskinesia (which is a more accurate reflection of clinical
response than "off" time alone). The Hauser diary asks participants to rate their mobility for each 30-minute period and to record their status for the majority of the period in 1 of 5 categories as: "on" time without dyskinesia, "on" time with nontroublesome dyskinesia, "on" time with troublesome dyskinesia, "off" time, or asleep. The total daily "Off" time will be assessed and reported at endpoint.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	153		
Units: hours				
least squares mean (standard error)	-0.933 (± 0.182)	-1.876 (± 0.200)		

Statistical analyses

Statistical analysis title	Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon

Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [2]
Method	Mixed-effect Model Repeated Measureme
Parameter estimate	LS Mean of Difference
Point estimate	-0.943
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.475
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.271

Notes:

[2] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Secondary: Change From Baseline in the Total "On" Time Without Troublesome Dyskinesia Based on the 2-day Average of the Self-completed Home Diary for Motor Function Status (Hauser Diary)

End point title	Change From Baseline in the Total "On" Time Without Troublesome Dyskinesia Based on the 2-day Average of the Self-completed Home Diary for Motor Function Status (Hauser Diary)

End point description:

The Hauser diary assesses participant-defined clinical status over a period of time and provides a tool for assessment
of the change in "off" time and "on" time with troublesome dyskinesia (which is a more accurate reflection of clinical
response than "off" time alone). The Hauser diary asks participants to rate their mobility for each 30-minute period and to record their status for the majority of the period in 1 of 5 categories as: "on" time without dyskinesia, "on" time with nontroublesome dyskinesia, "on" time with troublesome dyskinesia, "off" time, or asleep. The total "on" time without troublesome dyskinesia will be assessed and reported at different time points.

End point type	Secondary

End point timeframe:

Week 2, 5, 8, 11, 14, 18, 22, and 26

End point values	Placebo	Tavapadon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: Hours				
least squares mean (standard error)				
Week 2	0.535 (± 0.133)	0.305 (± 0.133)		
Week 5	0.516 (± 0.148)	0.616 (± 0.151)		
Week 8	0.470 (± 0.162)	1.052 (± 0.168)		
Week 11	0.705 (± 0.163)	1.063 (± 0.171)		

Week 14	0.584 (± 0.175)	1.282 (± 0.187)		
Week 18	0.623 (± 0.174)	1.592 (± 0.185)		
Week 22	0.870 (± 0.177)	1.749 (± 0.190)		
Week 26	0.619 (± 0.188)	1.721 (± 0.207)		

Statistical analyses

Statistical analysis title	Week 2: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2216 [3]
Method	Mixed-effect Model Repeated Measureme
Parameter estimate	LS Mean of Difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.188

Notes:

[3] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 5: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6379 [4]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.316
upper limit	0.515
Variability estimate	Standard error of the mean
Dispersion value	0.211

Notes:

[4] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 8: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0132 [5]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.122
upper limit	1.042
Variability estimate	Standard error of the mean
Dispersion value	0.234

Notes:

[5] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 11: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1299 [6]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.358
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.106
upper limit	0.821
Variability estimate	Standard error of the mean
Dispersion value	0.236

Notes:

[6] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 14: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068 [7]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.698
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.194
upper limit	1.202
Variability estimate	Standard error of the mean
Dispersion value	0.257

Notes:

[7] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 18: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [8]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.969
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.469
upper limit	1.469
Variability estimate	Standard error of the mean
Dispersion value	0.254

Notes:

[8] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 22: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [9]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.879

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.369
upper limit	1.389
Variability estimate	Standard error of the mean
Dispersion value	0.259

Notes:

[9] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 26: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	1.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.553
upper limit	1.653
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[10] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Secondary: Change From Baseline in Total Daily "Off" Time Based on the 2-Day Average of the Self-Completed Home Diary for Motor Function Status (Hauser Diary)

End point title	Change From Baseline in Total Daily "Off" Time Based on the 2-Day Average of the Self-Completed Home Diary for Motor Function Status (Hauser Diary)

End point description:

The Hauser diary assesses participant-defined clinical status over a period of time and provides a tool for assessment
of the change in "off" time and "on" time with troublesome dyskinesia (which is a more accurate reflection of clinical
response than "off" time alone). The Hauser diary asks participants to rate their mobility for each 30-minute period and to record their status for the majority of the period in 1 of 5 categories as: "on" time without dyskinesia, "on" time with nontroublesome dyskinesia, "on" time with troublesome dyskinesia, "off" time, or asleep. The total daily "Off" time will be assessed and reported at different time points.

End point type	Secondary

End point timeframe:

Week 2, 5, 8, 11, 14, 18, 22, and 26

End point values	Placebo	Tavapadon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: Hours				
least squares mean (standard error)				
Week 2	-0.598 (± 0.127)	-0.490 (± 0.127)		
Week 5	-0.612 (± 0.144)	-0.849 (± 0.146)		
Week 8	-0.549 (± 0.153)	-1.367 (± 0.159)		
Week 11	-0.876 (± 0.156)	-1.629 (± 0.164)		
Week 14	-0.779 (± 0.173)	-1.682 (± 0.185)		
Week 18	-0.786 (± 0.176)	-1.810 (± 0.187)		
Week 22	-1.014 (± 0.179)	-1.993 (± 0.191)		
Week 26	-0.933 (± 0.182)	-1.876 (± 0.200)		

Statistical analyses

Statistical analysis title	Week 2: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5471 [11]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.245
upper limit	0.461
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

[11] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 5: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2488 [12]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-0.237
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.205

Notes:

[12] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 8: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [13]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-0.818
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.252
upper limit	-0.384
Variability estimate	Standard error of the mean
Dispersion value	0.221

Notes:

[13] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 11: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [14]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-0.753

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.199
upper limit	-0.307
Variability estimate	Standard error of the mean
Dispersion value	0.227

Notes:

[14] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 14: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [15]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-0.904
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.403
upper limit	-0.405
Variability estimate	Standard error of the mean
Dispersion value	0.254

Notes:

[15] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 18: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.528
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.256

Notes:

[16] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 22: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [17]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-0.979
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.493
upper limit	-0.465
Variability estimate	Standard error of the mean
Dispersion value	0.261

Notes:

[17] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Week 26: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [18]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-0.943
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.475
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.271

Notes:

[18] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Secondary: Change From Baseline in the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I, II and III Individual Score

End point title	Change From Baseline in the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I, II and III Individual Score

End point description:

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: units on a scale				
least squares mean (standard error)				
Part I	0.0 (± 0.27)	0.4 (± 0.30)		
Part II	-0.1 (± 0.35)	-1.4 (± 0.39)		
Part III	-4.6 (± 0.65)	-7.0 (± 0.71)		

Statistical analyses

Statistical analysis title	Part I: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3265 [19]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[19] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Part II: Placebo, Tavapadon
Comparison groups	Placebo v Tavapadon
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203 [20]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.2

Variability estimate	Standard error of the mean
Dispersion value	0.52

Notes:

[20] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Statistical analysis title	Part III: Placebo, Tavapadon
Comparison groups	Tavapadon v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118 [21]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean of Difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.96

Notes:

[21] - LS Means, SE, difference from placebo, and confidence intervals are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, and treatment by visit interaction and baseline as a covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality were reported from enrollment to the end of study, median time on follow up (median time subjects were followed) was 190 and 189 days for Placebo and Tavapadon, respectively.

Adverse event reporting additional description:

Treatment-emergent adverse events and serious adverse events were collected from first dose of study drug until 4 weeks after the last dose of study drug; mean duration on study drug was 169.6 and 151.7 days for Placebo and Tavapadon, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants will receive placebo matching to tavapadon tablet QD orally for 27 weeks.

Reporting group title	Tavapadon

Reporting group description:

Participants will be randomized to receive tavapadon 5 to 15 mg tablet QD orally for 27 weeks.

Serious adverse events	Placebo	Tavapadon	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 254 (5.51%)	17 / 251 (6.77%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-CELL SMALL LYMPHOCYTIC LYMPHOMA			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATIC CARCINOMA METASTATIC			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
LYME DISEASE			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	0 / 254 (0.00%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THERMAL BURN			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CARDIAC FAILURE CHRONIC			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
COLLOID BRAIN CYST			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MIDDLE CEREBRAL ARTERY STROKE			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ON AND OFF PHENOMENON			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (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			
ANAEMIA			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
GLAUCOMA			

subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 254 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIATUS HERNIA			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ANXIETY DISORDER			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION, VISUAL			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDAL IDEATION			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC DISORDER			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

RHEUMATIC DISORDER			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (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			
BRONCHITIS BACTERIAL			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 254 (0.79%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EYE INFECTION			
subjects affected / exposed	1 / 254 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE ANEURYSM			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBACUTE ENDOCARDITIS			
subjects affected / exposed	0 / 254 (0.00%)	1 / 251 (0.40%)	
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: 2 %

Non-serious adverse events	Placebo	Tavapadon	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 254 (35.43%)	130 / 251 (51.79%)	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	1 / 254 (0.39%)	7 / 251 (2.79%)	
occurrences (all)	1	7	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	6 / 254 (2.36%)	4 / 251 (1.59%)	
occurrences (all)	7	4	
FALL			
subjects affected / exposed	13 / 254 (5.12%)	13 / 251 (5.18%)	
occurrences (all)	20	18	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	1 / 254 (0.39%)	9 / 251 (3.59%)	
occurrences (all)	1	9	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	3 / 254 (1.18%)	15 / 251 (5.98%)	
occurrences (all)	3	15	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	8 / 254 (3.15%)	18 / 251 (7.17%)	
occurrences (all)	8	20	
DYSGEUSIA			
subjects affected / exposed	0 / 254 (0.00%)	7 / 251 (2.79%)	
occurrences (all)	0	7	
DYSKINESIA			
subjects affected / exposed	4 / 254 (1.57%)	25 / 251 (9.96%)	
occurrences (all)	7	32	
DYSTONIA			
subjects affected / exposed	0 / 254 (0.00%)	7 / 251 (2.79%)	
occurrences (all)	0	9	

HEADACHE			
subjects affected / exposed	7 / 254 (2.76%)	17 / 251 (6.77%)	
occurrences (all)	7	23	
SOMNOLENCE			
subjects affected / exposed	11 / 254 (4.33%)	13 / 251 (5.18%)	
occurrences (all)	11	13	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 254 (0.00%)	8 / 251 (3.19%)	
occurrences (all)	0	8	
FATIGUE			
subjects affected / exposed	11 / 254 (4.33%)	10 / 251 (3.98%)	
occurrences (all)	11	10	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 254 (0.39%)	6 / 251 (2.39%)	
occurrences (all)	1	6	
CONSTIPATION			
subjects affected / exposed	8 / 254 (3.15%)	10 / 251 (3.98%)	
occurrences (all)	9	10	
DRY MOUTH			
subjects affected / exposed	2 / 254 (0.79%)	7 / 251 (2.79%)	
occurrences (all)	2	7	
NAUSEA			
subjects affected / exposed	11 / 254 (4.33%)	36 / 251 (14.34%)	
occurrences (all)	14	44	
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	6 / 254 (2.36%)	3 / 251 (1.20%)	
occurrences (all)	6	3	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	7 / 254 (2.76%)	8 / 251 (3.19%)	
occurrences (all)	7	8	
DEPRESSION			

subjects affected / exposed	2 / 254 (0.79%)	6 / 251 (2.39%)	
occurrences (all)	2	7	
HALLUCINATION, VISUAL			
subjects affected / exposed	3 / 254 (1.18%)	13 / 251 (5.18%)	
occurrences (all)	3	14	
INSOMNIA			
subjects affected / exposed	7 / 254 (2.76%)	1 / 251 (0.40%)	
occurrences (all)	7	1	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	7 / 254 (2.76%)	5 / 251 (1.99%)	
occurrences (all)	7	5	
Infections and infestations			
COVID-19			
subjects affected / exposed	7 / 254 (2.76%)	13 / 251 (5.18%)	
occurrences (all)	7	13	
NASOPHARYNGITIS			
subjects affected / exposed	6 / 254 (2.36%)	7 / 251 (2.79%)	
occurrences (all)	6	7	
URINARY TRACT INFECTION			
subjects affected / exposed	7 / 254 (2.76%)	7 / 251 (2.79%)	
occurrences (all)	9	10	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 254 (0.39%)	6 / 251 (2.39%)	
occurrences (all)	1	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2020	Version 2.0
03 September 2021	Version 3.0
06 July 2023	Version 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported