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 of Two Fixed Doses of Tavapadon in Early Parkinson's Disease (TEMPO-1 TRIAL)

Summary

EudraCT number	2019-002949-38
Trial protocol	HU CZ DE FR PL ES BG IT
Global end of trial date	28 June 2024

Results information

Result version number	v1 (current)
This version publication date	26 June 2025
First version publication date	26 June 2025

Trial information

Trial identification

Sponsor protocol code	CVL-751-PD-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04201093
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, 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	28 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 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 evaluate the clinical efficacy, safety and pharmacokinetics (PK) of 2 fixed doses of tavapadon and placebo in participants with early PD.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2019
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: 37
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	United States: 158
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Bulgaria: 93
Country: Number of subjects enrolled	Czechia: 32
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Italy: 21
Worldwide total number of subjects	529
EEA total number of subjects	278

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)	254
From 65 to 84 years	275
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this Phase 3, Double-Blind study, a total of 529 subjects with Parkinson’s Disease (PD) were be randomized in a 1:1:1 ratio to 3 treatment groups: Tavapadon 5 mg, Tavapadon 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

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 will be 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 serious adverse events (SAEs)

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:

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

Arm title	Tavapadon 5 mg

Arm description:

Subjects will receive tavapadon tablet titrated up to 5 milligram (mg) once daily (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:

Subjects will receive tavapadon tablet titrated up to either 5 milligram (mg) or 15 mg (based on Arm) once daily (QD) orally for 27 weeks.

Arm title	Tavapadon 15 mg

Arm description:

Subjects will receive tavapadon tablet titrated up to 15 milligram (mg) 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:

Subjects will receive tavapadon tablet titrated up to either 5 milligram (mg) or 15 mg (based on Arm) once daily (QD) orally for 27 weeks.

Number of subjects in period 1	Placebo	Tavapadon 5 mg	Tavapadon 15 mg
Started	175	177	177
Completed	148	134	118
Not completed	27	43	59
Treatment with Prohibited Concomitant Medications	-	-	1
Consent withdrawn by subject	7	8	15
Physician decision	1	-	-
Failure to Meet Continuation Criteria	-	-	1
Adverse event, non-fatal	6	29	35
Death	2	1	-
Other	-	1	2
Non- Compliance with Study Schedule	-	-	1
Site Terminated by Sponsor	5	3	1
Lost to follow-up	-	-	1
Lack of efficacy	5	1	2
Protocol deviation	1	-	-

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 5 mg
Reporting group description:	
Subjects will receive tavapadon tablet titrated up to 5 milligram (mg) once daily (QD) orally for 27 weeks.	
Reporting group title	Tavapadon 15 mg
Reporting group description:	
Subjects will receive tavapadon tablet titrated up to 15 milligram (mg) QD orally for 27 weeks.	

Reporting group values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg
Number of subjects	175	177	177
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.5	63.7	63.8
standard deviation	± 9.62	± 9.80	± 9.40
Gender categorical Units: Subjects			
Female	63	66	58
Male	112	111	119
Ethnicity (NIH/ OMB) Units: Subjects			
Hispanic or Latino	9	13	10
Not Hispanic or Latino	154	153	158
Unknown or Not Reported	12	11	9
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	3	0	2
White	168	174	172
More than one race	0	1	0
Unknown or Not Reported	2	1	2
MDS-UPDRS Score at Baseline (Parts II and III Combined)			
The MDS-UPDRS rating tool was used to follow longitudinal course of Parkinson's Disease. It was made up of 4 parts: Part 1: Non-motor aspects of experiences of daily living (13 items. Score range: 0-52); Part 2: Motor aspects of experiences of daily living (13 items. Score range: 0-52); Part 3: Motor examination (18 items. Score range: 0-132); Part 4: Motor complications (6 items. Score range: 0-24. Part 4 was not collected in this trial). Each item has 0-4 rating on scale from 0 (normal) to 4 (severe). Higher values represent a worse outcome.			
Units: units on a scale			

arithmetic mean	32.0	31.3	32.1
standard deviation	± 9.96	± 10.87	± 11.55

Reporting group values	Total		
Number of subjects	529		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	187		
Male	342		
Ethnicity (NIH/ OMB) Units: Subjects			
Hispanic or Latino	32		
Not Hispanic or Latino	465		
Unknown or Not Reported	32		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	2		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	5		
White	514		
More than one race	1		
Unknown or Not Reported	5		
MDS-UPDRS Score at Baseline (Parts II and III Combined)			
The MDS-UPDRS rating tool was used to follow longitudinal course of Parkinson's Disease. It was made up of 4 parts: Part 1: Non-motor aspects of experiences of daily living (13 items. Score range: 0-52); Part 2: Motor aspects of experiences of daily living (13 items. Score range: 0-52); Part 3: Motor examination (18 items. Score range: 0-132); Part 4: Motor complications (6 items. Score range: 0-24. Part 4 was not collected in this trial). Each item has 0-4 rating on scale from 0 (normal) to 4 (severe). Higher values represent a worse outcome.			
Units: units on a scale arithmetic mean standard deviation	 -		

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 5 mg
Reporting group description:	
Subjects will receive tavapadon tablet titrated up to 5 milligram (mg) once daily (QD) orally for 27 weeks.	
Reporting group title	Tavapadon 15 mg
Reporting group description:	
Subjects will receive tavapadon tablet titrated up to 15 milligram (mg) QD orally for 27 weeks.	

Primary: Change From Baseline in the MDS-UPDRS Parts II and III Combined Score

End point title	Change From Baseline in the MDS-UPDRS Parts II and III Combined Score
End point description:	
The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) rating tool was used to follow longitudinal course of Parkinson's Disease. It was made up of 4 parts: Part 1: Non-motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 2: Motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 3: Motor examination (18 items. Score range: 0–132); Part 4: Motor complications (6 items. Score range: 0–24. Part 4 was not collected in this trial). Each item has 0–4 rating on scale from 0 (normal) to 4 (severe). Higher values represent a worse outcome. A negative change from baseline represents an improvement in motor function.	
End point type	Primary
End point timeframe:	
Week 26	

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	132	116	
Units: score on a scale				
least squares mean (standard error)	1.8 (± 0.82)	-9.7 (± 0.86)	-10.2 (± 0.88)	

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg

Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	-9.2
Variability estimate	Standard error of the mean
Dispersion value	1.16

Notes:

[1] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	-9.8
Variability estimate	Standard error of the mean
Dispersion value	1.17

Notes:

[2] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the MDS-UPDRS Part II Score

End point title	Change From Baseline in the MDS-UPDRS Part II Score

End point description:

The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) rating tool was used to follow longitudinal course of Parkinson's Disease. It was made up of 4 parts: Part 1: Non-motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 2: Motor aspects of experiences of daily living
(13 items. Score range: 0–52); Part 3: Motor examination (18 items. Score range: 0–132); Part 4: Motor complications (6 items. Score range: 0–24. Part 4 was not collected in this trial). Each item has 0–4 rating on scale from 0 (normal) to 4 (severe). Higher values represent a worse outcome. A negative change from baseline represents an improvement in motor function.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	132	116	
Units: score on a scale				
least squares mean (standard error)	0.9 (± 0.30)	-1.6 (± 0.31)	-1.7 (± 0.32)	

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

Notes:

[3] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

Notes:

[4] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Percentage of Responders With a Score of "Much Improved" or "Very Much Improved" on PGIC

End point title	Percentage of Responders With a Score of "Much Improved" or "Very Much Improved" on PGIC

End point description:

The Patient Global Impression of Change (PGIC) is a 7-point response scale. The participant response to the question, "Compared to your condition at the beginning of treatment, how much has your condition changed?" was assessed. Scores ranged from 1–7 on a scale of 1 (very much improved) to 7 (very much worse). Higher values represent a worse outcome.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	132	117	
Units: Count of Participants	18	60	52	

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	6.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.339
upper limit	11.321

Statistical analysis title	Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	5.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.22
upper limit	11.062

Secondary: Change From Baseline in the MDS-UPDRS Parts II and III Combined Score

End point title	Change From Baseline in the MDS-UPDRS Parts II and III Combined Score

End point description:

The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) rating tool was used to follow longitudinal course of Parkinson's Disease. It was made up of 4 parts: Part 1: Non-motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 2: Motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 3: Motor examination (18 items. Score range: 0–132); Part 4: Motor complications (6 items. Score range: 0–24. Part 4 was not collected in this trial). Each item has 0–4 rating on scale from 0 (normal) to 4 (severe). Higher values represent a worse outcome. A negative change from baseline represents an improvement in motor function.

End point type	Secondary

End point timeframe:

Week 5, 8, 11, 14, 18, 22, 26, and 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[5]	174[6]	172[7]	
Units: score on a scale				
least squares mean (standard error)				
Week 5	-1.2 (± 0.57)	-4.4 (± 0.59)	-4.7 (± 0.59)	
Week 8	-2.2 (± 0.62)	-6.9 (± 0.65)	-6.7 (± 0.65)	
Week 11	-0.9 (± 0.72)	-8.1 (± 0.75)	-9.1 (± 0.75)	
Week 14	-1.2 (± 0.74)	-8.8 (± 0.78)	-9.4 (± 0.78)	
Week 18	0.4 (± 0.78)	-9.1 (± 0.82)	-9.7 (± 0.83)	
Week 22	0.4 (± 0.81)	-9.6 (± 0.84)	-10.9 (± 0.86)	
Week 26	1.8 (± 0.82)	-9.7 (± 0.86)	-10.2 (± 0.88)	
Week 27	2.2 (± 0.92)	-8.6 (± 0.96)	-10.0 (± 0.99)	

Notes:

[5] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 171, 168, 160, 158, 153, 150, 148, and 148, respectively.
[6] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 154, 147, 138, 142, 138, 137, 132, and 134, respectively.

[7] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 159, 150, 135, 134, 129, 126, 116, and 119, respectively.

Statistical analyses

Statistical analysis title	Week 26: Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	-9.2
Variability estimate	Standard error of the mean
Dispersion value	1.16

Notes:

[8] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Week 26: Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	-9.8
Variability estimate	Standard error of the mean
Dispersion value	1.17

Notes:

[9] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the MDS-UPDRS Parts I, II and III Combined Score

End point title	Change From Baseline in the MDS-UPDRS Parts I, II and III

	Combined Score

End point description:

End point type	Secondary

End point timeframe:

Week 5, 8, 11, 14, 18, 22, 26, and 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[10]	174[11]	172[12]	
Units: score on a scale				
least squares mean (standard error)				
Week 5	-1.2 (± 0.67)	-3.9 (± 0.69)	-4.0 (± 0.69)	
Week 8	-2.6 (± 0.72)	-6.4 (± 0.76)	-6.2 (± 0.75)	
Week 11	-1.2 (± 0.81)	-7.7 (± 0.86)	-8.6 (± 0.86)	
Week 14	-1.5 (± 0.85)	-8.8 (± 0.89)	-8.7 (± 0.90)	
Week 18	0.3 (± 0.91)	-9.3 (± 0.95)	-9.1 (± 0.96)	
Week 22	0.2 (± 0.94)	-9.5 (± 0.98)	-10.3 (± 1.00)	
Week 26	2.3 (± 0.95)	-9.4 (± 1.00)	-9.7 (± 1.02)	
Week 27	2.4 (± 1.06)	-8.5 (± 1.11)	-9.4 (± 1.14)	

Notes:

[10] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 171, 168, 160, 158, 153, 150, 148, and 148, respectively.
[11] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 154, 147, 138, 142, 138, 137, 132, and 134, respectively.
[12] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 159, 150, 135, 134, 129, 126, 116, and 119, respectively.

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	-9.1
Variability estimate	Standard error of the mean
Dispersion value	1.35

Notes:

[13] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	-9.3
Variability estimate	Standard error of the mean
Dispersion value	1.37

Notes:

[14] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the MDS-UPDRS Parts I, II and III Individual Score

End point title	Change From Baseline in the MDS-UPDRS Parts I, II and III Individual Score

End point description:

The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) rating tool was used to follow longitudinal course of Parkinson's Disease. It was made up of 4 parts: Part 1: Non-motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 2: Motor aspects of experiences of daily living (13 items. Score range: 0–52); Part 3: Motor examination (18 items. Score range: 0–132); Part 4: Motor complications (6 items. Score range: 0–24. Part 4 was not collected in this trial). Each item has 0–4 rating on scale from 0 (normal) to 4 (severe). Higher values represent a worse outcome. A negative change from baseline represents an improvement in motor function.
For Weeks 5, 8, 11, 14, 18, 22, 26, and 27:
Part I: N = 171, 168, 161, 158, 153, 150, 148, and 148, respectively.
Part II: N = 171, 168, 161, 159, 153, 150, 148, and 148, respectively.
Part III: N = 171, 168, 160, 158, 153, 150, 148, and 148, respectively.

End point type	Secondary

End point timeframe:

Week 5, 8, 11, 14, 18, 22, 26, and 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[15]	174[16]	172[17]	
Units: score on a scale				
least squares mean (standard error)				
Part I: Week 5	0.0 (± 0.23)	0.6 (± 0.24)	0.7 (± 0.24)	
Part I: Week 8	-0.4 (± 0.23)	0.5 (± 0.24)	0.4 (± 0.24)	
Part I: Week 11	-0.3 (± 0.23)	0.4 (± 0.24)	0.4 (± 0.25)	
Part I: Week 14	-0.2 (± 0.25)	0.0 (± 0.27)	0.6 (± 0.27)	
Part I: Week 18	-0.1 (± 0.25)	-0.2 (± 0.26)	0.5 (± 0.27)	
Part I: Week 22	-0.2 (± 0.26)	0.2 (± 0.27)	0.4 (± 0.28)	
Part I: Week 26	0.5 (± 0.27)	0.2 (± 0.28)	0.4 (± 0.29)	
Part I: Week 27	0.2 (± 0.27)	0.2 (± 0.28)	0.3 (± 0.29)	
Part II: Week 5	-0.2 (± 0.22)	-0.8 (± 0.23)	-1.0 (± 0.22)	
Part II: Week 8	-0.5 (± 0.23)	-1.0 (± 0.25)	-1.6 (± 0.24)	
Part II: Week 11	0.0 (± 0.26)	-1.7 (± 0.27)	-2.0 (± 0.27)	
Part II: Week 14	-0.1 (± 0.27)	-1.6 (± 0.28)	-2.0 (± 0.28)	
Part II: Week 18	0.4 (± 0.29)	-1.9 (± 0.31)	-1.8 (± 0.31)	
Part II: Week 22	0.3 (± 0.28)	-1.7 (± 0.29)	-2.1 (± 0.29)	
Part II: Week 26	0.9 (± 0.30)	-1.6 (± 0.31)	-1.7 (± 0.32)	
Part II: Week 27	0.9 (± 0.31)	-1.7 (± 0.32)	-1.8 (± 0.33)	
Part III: Week 5	-1.0 (± 0.44)	-3.7 (± 0.46)	-3.7 (± 0.45)	
Part III: Week 8	-1.7 (± 0.50)	-6.0 (± 0.52)	-5.1 (± 0.52)	
Part III: Week 11	-1.0 (± 0.55)	-6.5 (± 0.58)	-7.1 (± 0.59)	
Part III: Week 14	-1.1 (± 0.58)	-7.2 (± 0.61)	-7.4 (± 0.61)	
Part III: Week 18	0.0 (± 0.60)	-7.3 (± 0.63)	-7.9 (± 0.64)	
Part III: Week 22	0.0 (± 0.64)	-8.0 (± 0.67)	-8.8 (± 0.68)	
Part III: Week 26	0.9 (± 0.63)	-8.1 (± 0.66)	-8.5 (± 0.68)	
Part III: Week 27	1.1 (± 0.71)	-7.1 (± 0.75)	-8.3 (± 0.77)	

Notes:

[15] - N values vary per part and week, see End Point description for each specific N.

[16] - N values vary per part and week, see End Point description for each specific N.

[17] - N values vary per part and week, see End Point description for each specific N.

Statistical analyses

Statistical analysis title	Part I: Week 26 - Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4822 [18]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.5

Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[18] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Part I: Week 26 - Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7742 [19]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[19] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Part II: Week 26 - Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

Notes:

[20] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Part II: Week 26 - Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg

Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

Notes:

[21] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Part III: Week 26 - Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	-7.3
Variability estimate	Standard error of the mean
Dispersion value	0.89

Notes:

[22] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Part III: Week 26 - Placebo, Tavapadon 15 mg
Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-9.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	-7.6
Variability estimate	Standard error of the mean
Dispersion value	0.9

Notes:

[23] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the CGI-S Score

End point title	Change From Baseline in the CGI-S Score

End point description:

The Global Impression – Severity of Illness (CGI-S) Score is a clinician's impression of a participant's severity of illness on a 7-point scale. Scores ranged from 1-7 on a scale of 1 (normal) to 7 (among the most extremely ill participants). Higher values represent a worse outcome.

End point type	Secondary

End point timeframe:

Week 5, 8, 11, 14, 18, 22, 26, and 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[24]	174[25]	172[26]	
Units: score on a scale				
least squares mean (standard error)				
Week 5	0.0 (± 0.04)	-0.1 (± 0.05)	0.0 (± 0.05)	
Week 8	0.0 (± 0.05)	-0.1 (± 0.05)	-0.1 (± 0.05)	
Week 11	0.0 (± 0.05)	-0.2 (± 0.05)	-0.3 (± 0.05)	
Week 14	0.1 (± 0.05)	-0.2 (± 0.05)	-0.3 (± 0.05)	
Week 18	0.1 (± 0.05)	-0.3 (± 0.06)	-0.3 (± 0.06)	
Week 22	0.1 (± 0.05)	-0.2 (± 0.06)	-0.3 (± 0.06)	
Week 26	0.2 (± 0.05)	-0.3 (± 0.05)	-0.2 (± 0.06)	
Week 27	0.1 (± 0.05)	-0.2 (± 0.06)	-0.2 (± 0.06)	

Notes:

[24] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 171, 168, 161, 158, 153, 150, 148, and 147, respectively.
[25] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 155, 148, 141, 141, 138, 137, 132, and 134, respectively.
[26] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 160, 151, 135, 133, 129, 126, 117, and 119, respectively.

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg

Statistical analysis description:

Week 26

Comparison groups	Tavapadon 5 mg v Placebo

Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[27] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[28] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the CGI-I Score

End point title	Change From Baseline in the CGI-I Score

End point description:

The Clinical Global Impression – Improvement (CGI-I) Score is a clinician's impression of how much the participant's illness has improved or worsened relative to the baseline on a 7-point scale. Scores ranged from 1-7 on a scale of 1 (very much improved) to 7 (very much worse). Higher values represent a worse outcome.

End point type	Secondary

End point timeframe:

Week 5, 8, 11, 14, 18, 22, 26, and 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[29]	174[30]	172[31]	
Units: score on a scale				
least squares mean (standard error)				
Week 5	3.8 (± 0.06)	3.4 (± 0.06)	3.4 (± 0.06)	
Week 8	3.8 (± 0.06)	3.2 (± 0.07)	3.3 (± 0.07)	
Week 11	3.8 (± 0.07)	3.0 (± 0.08)	3.1 (± 0.08)	
Week 14	3.8 (± 0.07)	3.0 (± 0.08)	3.0 (± 0.08)	
Week 18	3.9 (± 0.08)	2.8 (± 0.08)	2.9 (± 0.08)	
Week 22	3.9 (± 0.08)	2.9 (± 0.09)	3.0 (± 0.09)	
Week 26	3.9 (± 0.09)	2.8 (± 0.09)	3.0 (± 0.09)	
Week 27	4.0 (± 0.09)	2.8 (± 0.09)	2.9 (± 0.09)	

Notes:

[29] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 171, 167, 160, 158, 153, 150, 148, and 147, respectively.
[30] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 154, 148, 141, 142, 138, 136, 132, and 134, respectively.
[31] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 160, 150, 134, 134, 128, 126, 117, and 119, respectively.

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg
Statistical analysis description:	
Week 26	
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[32] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg
Statistical analysis description:	
Week 26	
Comparison groups	Placebo v Tavapadon 15 mg

Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[33] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the PGIC Score

End point title	Change From Baseline in the PGIC Score

End point description:

The Patient Global Impression of Change (PGIC) is a 7-point response scale. The participant response to the question, "Compared to your condition at the beginning of treatment, how much has your condition changed?" was assessed. Scores ranged from 1-7 on a scale of 1 (very much improved) to 7 (very much worse). Higher values represent a worse outcome.

End point type	Secondary

End point timeframe:

Week 5, 8, 11, 14, 18, 22, 26, and 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[34]	174[35]	172[36]	
Units: score on a scale				
least squares mean (standard error)				
Week 5	3.7 (± 0.07)	3.5 (± 0.07)	3.4 (± 0.07)	
Week 8	3.8 (± 0.08)	3.2 (± 0.08)	3.2 (± 0.08)	
Week 11	3.8 (± 0.08)	3.0 (± 0.08)	3.1 (± 0.08)	
Week 14	3.8 (± 0.08)	2.8 (± 0.09)	3.0 (± 0.09)	
Week 18	3.9 (± 0.09)	2.8 (± 0.10)	2.9 (± 0.10)	
Week 22	3.8 (± 0.09)	2.9 (± 0.10)	2.9 (± 0.10)	
Week 26	4.0 (± 0.10)	2.8 (± 0.10)	2.8 (± 0.11)	
Week 27	4.0 (± 0.10)	2.8 (± 0.11)	2.9 (± 0.11)	

Notes:

[34] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 171, 168, 161, 159, 154, 151, 147, and 147, respectively.
[35] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 155, 148, 141, 142, 137, 137, 132, and 134, respectively.
[36] - Wk 5, 8, 11, 14, 18, 22, 26, and 27, N = 160, 151, 135, 134, 129, 126, 117, and 119, respectively.

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg

Statistical analysis description:

Week 26

Comparison groups	Tavapadon 5 mg v Placebo
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [37]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[37] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [38]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[38] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the Epworth Sleepiness Scale (ESS)

End point title	Change From Baseline in the Epworth Sleepiness Scale (ESS)

End point description:

The ESS is an 8-question, participant questionnaire that is intended to measure daytime sleepiness. It assesses the likelihood of dozing off or falling asleep in the following common situations: sitting and reading, sitting inactive in a public place as a passenger in a car for an hour or more without stopping

for a break, lying down to rest when circumstances permit, sitting and talking to someone, sitting quietly after a meal without alcohol, and in a car while stopped for a few minutes in traffic or at a light. Each situation is rated on a 4-point (0-3) scale with scores ranging from 0 (would never nod off) to 3 (high chance of
nodding off). Higher values represent a worse outcome.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	134	118	
Units: score on a scale				
least squares mean (standard error)	-0.2 (± 0.23)	-0.3 (± 0.24)	-0.5 (± 0.24)	

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg
Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6047 [39]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[39] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 15 mg

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.257 [40]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[40] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Change From Baseline in the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS)

End point title	Change From Baseline in the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS)

End point description:

QUIP-RS is a global screening instrument that assesses impulse control disorders (ICDs) and related disorders (punding, hobbyism, and dopamine dysregulation syndrome) in participants with PD. The QUIP-RS has 4 primary questions that pertain to commonly reported thoughts, urges/desires, and behaviors associated with ICDs, each of
which is applied to 4 ICDs (compulsive gambling, buying, eating, sexual behavior) and 3 related disorders (medication use, punding, and hobbyism). The QUIP-RS uses a 5-point Likert scale (score 0–4 [0 means "never" and 4 means "very often"] for each question) to gauge the frequency of behaviors. Scores for each ICD and related disorder range from 0 to 16, with a higher score indicating greater severity (frequency) of symptoms. The total QUIP-RS score for all ICDs and related disorders combined ranges from 0 to 112.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	134	118	
Units: score on a scale				
least squares mean (standard error)	-2.1 (± 0.46)	-2.2 (± 0.47)	-2.4 (± 0.48)	

Statistical analyses

Statistical analysis title	Placebo, Tavapadon 5 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 5 mg
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8516 [41]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.63

Notes:

[41] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Statistical analysis title	Placebo, Tavapadon 15 mg

Statistical analysis description:

Week 26

Comparison groups	Placebo v Tavapadon 15 mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6421 [42]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.64

Notes:

[42] - LS Means, SE, difference from placebo, and CI's are estimated using a mixed effects repeated measures model with fixed effects for treatment group, visits, treatment by visit interaction and MAO-B inhibitor use with the baseline value as a covariate.

Secondary: Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Suicidal ideation (SI) categories include the following: wish to be dead; nonspecific active suicidal thoughts; active suicidal ideation without intent to act; active suicidal ideation with some intent to act but no plan; active suicidal ideation with plan and intent. Suicidal behavior categories include the following: actual attempt; interrupted attempt; aborted attempt; preparatory acts or behavior; suicidal behavior; completed suicide.

End point type	Secondary

End point timeframe:

Week 27

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	177	177	
Units: Count of Participants				
Participants With Any Suicidal Ideations	3	3	3	
Participants With Any Suicidal Behaviors	0	0	0	
Participants With Any Suicidal Behaviors or Ideati	3	3	3	
Participants With Non-Suicidal Self-Injurious Beha	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. The investigator assesses the relationship of each event to the use of study drug. A serious adverse event (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above. Treatment emergent adverse events/treatment-emergent serious adverse events (TEAEs/TESAEs) are defined as any event that began or worsened in severity on or after the first dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug until 190 days following last dose of study drug.

End point values	Placebo	Tavapadon 5 mg	Tavapadon 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	177	177	
Units: Participants	100	142	139	

Statistical analyses

No statistical analyses for this end point

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 190,190, and 189 days for Placebo, Tavapadon 5 mg, and Tavapadon 15 mg, 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 for all Arms; mean duration on study drug was 27 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tavapadon_15_mg_QD
Reporting group description: -	
Reporting group title	Tavapadon_5_mg_QD

Reporting group description: -

Serious adverse events	Placebo	Tavapadon_15_mg_QD	Tavapadon_5_mg_QD
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 175 (6.29%)	10 / 177 (5.65%)	4 / 177 (2.26%)
number of deaths (all causes)	2	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATE CANCER			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CELL CARCINOMA			

subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAD INJURY			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
THROMBOSIS			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ANGINA UNSTABLE			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY STENOSIS			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 175 (0.00%)	0 / 177 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 175 (0.00%)	0 / 177 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
subjects affected / exposed	1 / 175 (0.57%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
PROSTATOMEGALY			

subjects affected / exposed	0 / 175 (0.00%)	0 / 177 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
HALLUCINATION, TACTILE			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	1 / 175 (0.57%)	2 / 177 (1.13%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	2 / 175 (1.14%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	3 / 175 (1.71%)	0 / 177 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
TRACHEOBRONCHITIS			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Tavapadon_15_mg_QD	Tavapadon_5_mg_QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 175 (41.14%)	125 / 177 (70.62%)	125 / 177 (70.62%)
Investigations			
SARS-COV-2 TEST POSITIVE			

subjects affected / exposed	2 / 175 (1.14%)	0 / 177 (0.00%)	4 / 177 (2.26%)
occurrences (all)	2	0	4
WEIGHT DECREASED			
subjects affected / exposed	2 / 175 (1.14%)	4 / 177 (2.26%)	3 / 177 (1.69%)
occurrences (all)	2	4	4
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	6 / 175 (3.43%)	7 / 177 (3.95%)	4 / 177 (2.26%)
occurrences (all)	6	8	4
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	4 / 175 (2.29%)	8 / 177 (4.52%)	7 / 177 (3.95%)
occurrences (all)	4	9	9
HYPERTENSION			
subjects affected / exposed	8 / 175 (4.57%)	2 / 177 (1.13%)	1 / 177 (0.56%)
occurrences (all)	8	2	1
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 175 (0.00%)	4 / 177 (2.26%)	11 / 177 (6.21%)
occurrences (all)	0	4	11
Nervous system disorders			
PAROSMIA			
subjects affected / exposed	0 / 175 (0.00%)	4 / 177 (2.26%)	4 / 177 (2.26%)
occurrences (all)	0	4	4
PARAESTHESIA			
subjects affected / exposed	1 / 175 (0.57%)	8 / 177 (4.52%)	3 / 177 (1.69%)
occurrences (all)	1	11	5
HYPOAESTHESIA			
subjects affected / exposed	2 / 175 (1.14%)	6 / 177 (3.39%)	3 / 177 (1.69%)
occurrences (all)	2	9	4
HEADACHE			
subjects affected / exposed	9 / 175 (5.14%)	37 / 177 (20.90%)	22 / 177 (12.43%)
occurrences (all)	16	39	25
DYSGEUSIA			
subjects affected / exposed	0 / 175 (0.00%)	14 / 177 (7.91%)	14 / 177 (7.91%)
occurrences (all)	0	17	14
DIZZINESS			

subjects affected / exposed	8 / 175 (4.57%)	21 / 177 (11.86%)	24 / 177 (13.56%)
occurrences (all)	9	23	32
AGEUSIA			
subjects affected / exposed	0 / 175 (0.00%)	5 / 177 (2.82%)	1 / 177 (0.56%)
occurrences (all)	0	6	1
TREMOR			
subjects affected / exposed	2 / 175 (1.14%)	3 / 177 (1.69%)	4 / 177 (2.26%)
occurrences (all)	3	3	4
SOMNOLENCE			
subjects affected / exposed	6 / 175 (3.43%)	5 / 177 (2.82%)	6 / 177 (3.39%)
occurrences (all)	6	5	6
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 175 (0.00%)	1 / 177 (0.56%)	4 / 177 (2.26%)
occurrences (all)	0	1	5
FATIGUE			
subjects affected / exposed	6 / 175 (3.43%)	16 / 177 (9.04%)	10 / 177 (5.65%)
occurrences (all)	6	17	11
ASTHENIA			
subjects affected / exposed	0 / 175 (0.00%)	2 / 177 (1.13%)	5 / 177 (2.82%)
occurrences (all)	0	2	5
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	1 / 175 (0.57%)	3 / 177 (1.69%)	6 / 177 (3.39%)
occurrences (all)	1	3	6
VERTIGO			
subjects affected / exposed	2 / 175 (1.14%)	3 / 177 (1.69%)	5 / 177 (2.82%)
occurrences (all)	2	3	6
Gastrointestinal disorders			
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 175 (0.57%)	4 / 177 (2.26%)	7 / 177 (3.95%)
occurrences (all)	1	4	7
DYSPEPSIA			
subjects affected / exposed	2 / 175 (1.14%)	10 / 177 (5.65%)	5 / 177 (2.82%)
occurrences (all)	3	10	6
ABDOMINAL PAIN			

subjects affected / exposed	2 / 175 (1.14%)	4 / 177 (2.26%)	3 / 177 (1.69%)
occurrences (all)	2	4	3
DIARRHOEA			
subjects affected / exposed	2 / 175 (1.14%)	2 / 177 (1.13%)	4 / 177 (2.26%)
occurrences (all)	2	3	4
CONSTIPATION			
subjects affected / exposed	1 / 175 (0.57%)	5 / 177 (2.82%)	4 / 177 (2.26%)
occurrences (all)	1	5	4
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 175 (0.00%)	6 / 177 (3.39%)	1 / 177 (0.56%)
occurrences (all)	0	8	1
DRY MOUTH			
subjects affected / exposed	0 / 175 (0.00%)	9 / 177 (5.08%)	11 / 177 (6.21%)
occurrences (all)	0	9	12
VOMITING			
subjects affected / exposed	1 / 175 (0.57%)	9 / 177 (5.08%)	12 / 177 (6.78%)
occurrences (all)	2	11	13
NAUSEA			
subjects affected / exposed	3 / 175 (1.71%)	48 / 177 (27.12%)	42 / 177 (23.73%)
occurrences (all)	5	56	44
SALIVARY HYPERSECRETION			
subjects affected / exposed	0 / 175 (0.00%)	4 / 177 (2.26%)	2 / 177 (1.13%)
occurrences (all)	0	4	2
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	1 / 175 (0.57%)	6 / 177 (3.39%)	2 / 177 (1.13%)
occurrences (all)	1	6	2
Psychiatric disorders			
SLEEP DISORDER			
subjects affected / exposed	1 / 175 (0.57%)	3 / 177 (1.69%)	4 / 177 (2.26%)
occurrences (all)	1	3	4
INSOMNIA			
subjects affected / exposed	4 / 175 (2.29%)	7 / 177 (3.95%)	5 / 177 (2.82%)
occurrences (all)	4	8	5
DEPRESSION			

subjects affected / exposed	4 / 175 (2.29%)	4 / 177 (2.26%)	2 / 177 (1.13%)
occurrences (all)	4	4	2
ANXIETY			
subjects affected / exposed	5 / 175 (2.86%)	9 / 177 (5.08%)	10 / 177 (5.65%)
occurrences (all)	5	10	11
ABNORMAL DREAMS			
subjects affected / exposed	1 / 175 (0.57%)	6 / 177 (3.39%)	10 / 177 (5.65%)
occurrences (all)	1	6	10
HALLUCINATION, VISUAL			
subjects affected / exposed	0 / 175 (0.00%)	5 / 177 (2.82%)	0 / 177 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	5 / 175 (2.86%)	4 / 177 (2.26%)	4 / 177 (2.26%)
occurrences (all)	5	4	5
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 175 (0.00%)	5 / 177 (2.82%)	6 / 177 (3.39%)
occurrences (all)	0	5	7
NECK PAIN			
subjects affected / exposed	3 / 175 (1.71%)	4 / 177 (2.26%)	4 / 177 (2.26%)
occurrences (all)	4	4	4
MUSCLE SPASMS			
subjects affected / exposed	1 / 175 (0.57%)	3 / 177 (1.69%)	4 / 177 (2.26%)
occurrences (all)	1	3	4
BACK PAIN			
subjects affected / exposed	6 / 175 (3.43%)	4 / 177 (2.26%)	7 / 177 (3.95%)
occurrences (all)	6	4	8
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	9 / 175 (5.14%)	3 / 177 (1.69%)	6 / 177 (3.39%)
occurrences (all)	10	4	7
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 175 (1.71%)	4 / 177 (2.26%)	0 / 177 (0.00%)
occurrences (all)	3	4	0
NASOPHARYNGITIS			

subjects affected / exposed	4 / 175 (2.29%)	6 / 177 (3.39%)	2 / 177 (1.13%)
occurrences (all)	5	6	2
COVID-19			
subjects affected / exposed	4 / 175 (2.29%)	6 / 177 (3.39%)	9 / 177 (5.08%)
occurrences (all)	4	6	9
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 175 (0.57%)	5 / 177 (2.82%)	3 / 177 (1.69%)
occurrences (all)	1	5	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2020	Incorporate measures into the protocol to ensure the safety of the trial subjects and the validity of the trial data in the environment of the COVID-19 pandemic and to clarify other aspects of trial conduct unrelated to the COVID-19 pandemic.
03 September 2021	Correct errors and to harmonize similar content across the Phase 3 tavapadon protocols via modification and clarification of eligibility criteria, procedural aspects, and statistical considerations.
06 July 2023	Add eye examinations as an additional trial assessment to monitor for the new potential risk of increased intraocular pressure across the Phase 3 tavapadon protocols.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported