Clinical trial results:
A Well-Controlled, Fixed-Dose Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome

Summary

EudraCT number	2017-002976-24
Trial protocol	HU SE IT PL FR NL RO
Global end of trial date	09 December 2019

Results information

Result version number	v1 (current)
This version publication date	05 June 2020
First version publication date	05 June 2020

Trial information

Trial identification

Sponsor protocol code	TV50717-CNS-30060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03571256
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 8884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 8884838279, info.eraclinical@teva.de

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	24 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2019
Global end of trial reached?	Yes
Global end of trial date	09 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate efficacy of fixed doses of TEV-50717 to reduce motor and phonic tics associated with Tourette Syndrome (TS).

Protection of trial subjects:

This study was conducted in full accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Tripartite Guideline (E6) and any applicable national and local laws and regulations (for example, Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, 312, and 314 and European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical studies on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Ukraine: 34
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	158
EEA total number of subjects	53

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)	69
Adolescents (12-17 years)	89
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 158 participants were randomized in a 1:1:1 ratio to TEV-50717 high-dose, TEV-50717 low-dose or placebo group.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	TEV-50717 High-Dose

Arm description:

TEV-50717 tablets twice daily (BID) up to 48 milligrams (mg)/day orally for a total of 8 weeks

Arm type	Experimental
Investigational medicinal product name	TEV-50717
Investigational medicinal product code	
Other name	AUSTEDO, Deutetrabenazine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6-, 9-, 12-, 15-, and 18 mg oral tablets per dose and schedule as specified in the arm.

Arm title	TEV-50717 Low-Dose

Arm description:

TEV-50717 tablets BID up to 36 mg/day orally for a total of 8 weeks

Arm type	Experimental
Investigational medicinal product name	TEV-50717
Investigational medicinal product code	
Other name	AUSTEDO, Deutetrabenazine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6-, 9-, 12-, 15-, and 18 mg oral tablets per dose and schedule as specified in the arm.

Arm title	Placebo

Arm description:

Placebo matched to TEV-50717 for a total of 8 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:
Placebo matched to TEV-50717 tablets were taken BID.

Number of subjects in period 1	TEV-50717 High-Dose	TEV-50717 Low-Dose	Placebo
Started	52	54	52
Received at least 1 dose of study drug	52	54	51
Modified ITT (mITT) Analysis Set	49	53	51
Completed	46	51	48
Not completed	6	3	4
Consent withdrawn by subject	3	1	1
Adverse event, non-fatal	3	-	1
Other than specified	-	1	1
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	TEV-50717 High-Dose
Reporting group description:	
TEV-50717 tablets twice daily (BID) up to 48 milligrams (mg)/day orally for a total of 8 weeks	
Reporting group title	TEV-50717 Low-Dose
Reporting group description:	
TEV-50717 tablets BID up to 36 mg/day orally for a total of 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to TEV-50717 for a total of 8 weeks	

Reporting group values	TEV-50717 High-Dose	TEV-50717 Low-Dose	Placebo
Number of subjects	52	54	52
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	11.7	11.7	11.8
standard deviation	± 2.63	± 2.70	± 2.62
Sex: Female, Male Units: participants			
Female	15	12	12
Male	37	42	40
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	9	15
Not Hispanic or Latino	43	45	37
Unknown or Not Reported	1	0	0
Race/Ethnicity, Customized Units: Subjects			
White	48	48	39
Black	0	1	0
Asian	0	3	4
Native American	1	1	2
Multiple	0	0	2
Other	3	1	5
Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)			
YGTSS is composed of 11 items: 5 items for motor tic severity, 5 items for vocal tic severity, and 1 item for impairment. Each item for motor tic severity and vocal is rated on a 6-point scale (0 for none to 5 for severe). Motor tic severity score (MTSS) is the sum of 5 items for motor tic severity and vocal tic severity score (VTSS) is the sum of 5 items for vocal tic severity. TTS is the sum of MTSS and VTSS, ranges from 0 (none/absent) to 50 (severe). Higher scores indicate greater severity/worse outcome.			
Units: units on a scale			
arithmetic mean	33.9	32.9	34.7
standard deviation	± 6.17	± 7.20	± 6.29

Reporting group values	Total		
Number of subjects	158		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	39		
Male	119		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	32		
Not Hispanic or Latino	125		
Unknown or Not Reported	1		
Race/Ethnicity, Customized Units: Subjects			
White	135		
Black	1		
Asian	7		
Native American	4		
Multiple	2		
Other	9		
Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)			
YGTSS is composed of 11 items: 5 items for motor tic severity, 5 items for vocal tic severity, and 1 item for impairment. Each item for motor tic severity and vocal is rated on a 6-point scale (0 for none to 5 for severe). Motor tic severity score (MTSS) is the sum of 5 items for motor tic severity and vocal tic severity score (VTSS) is the sum of 5 items for vocal tic severity. TTS is the sum of MTSS and VTSS, ranges from 0 (none/absent) to 50 (severe). Higher scores indicate greater severity/worse outcome.			
Units: units on a scale arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	TEV-50717 High-Dose
Reporting group description:	
TEV-50717 tablets twice daily (BID) up to 48 milligrams (mg)/day orally for a total of 8 weeks	
Reporting group title	TEV-50717 Low-Dose
Reporting group description:	
TEV-50717 tablets BID up to 36 mg/day orally for a total of 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to TEV-50717 for a total of 8 weeks	

Primary: Change From Baseline in the TTS of the YGTSS at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the TTS of the YGTSS at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[1]

End point description:

YGTSS is composed of 11 items: 5 items for motor tic severity, 5 items for vocal tic severity, and 1 item for impairment. Each item for motor tic severity and vocal is rated on a 6-point scale (0 for none to 5 to severe). MTSS is the sum of the 5 items for motor tic severity and VTSS is the sum of the 5 items for vocal tic severity. TTS is the sum of MTSS and VTSS, ranges from 0 (none/absent) to 50 (severe). Higher scores indicate greater severity/worse outcome. Least square (LS) mean and standard error (SE) was calculated using mixed-model repeated-measures (MMRM) with treatment group, week (3 levels: Weeks 2, 4, and 8), and the treatment group by week interaction as fixed effects; and baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) as covariates. mITT analysis set included all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Primary

End point timeframe:

Baseline, Week 8

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 High-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: units on a scale				
least squares mean (standard error)	-7.8 (± 1.24)	-7.0 (± 1.16)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TEV-50717 High-Dose v Placebo

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6 [2]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	2.3

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in the Tourette Syndrome-Clinical Global Impression (TS-CGI) Score at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the Tourette Syndrome-Clinical Global Impression (TS-CGI) Score at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[3]

End point description:

The TS-CGI scale is a 7-point Likert scale that allows the clinician to use all available information to assess the impact of tics on the participant's quality of life. The TS-CGI is rated as follows: 1 (normal or no tics at all), 2 (borderline), 3 (mild), 4 (moderate), 5 (marked), 6 (severe), and 7 (extreme, incapacitating tics). Lower scores indicate better quality of life. LS mean and SE was calculated using MMRM with treatment group, week (3 levels: Weeks 2, 4, and 8), and the treatment group by week interaction as fixed effects; and baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) as covariates. mITT analysis set included all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 High-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: units on a scale				
least squares mean (standard error)	-0.8 (± 0.14)	-0.6 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the TTS of the YGTSS at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the TTS of the YGTSS at Week 8 Between Low-Dose TEV-50717-Treated Participants and

	Placebo-Treated Participants[4]

End point description:

YGTSS is composed of 11 items: 5 items for motor tic severity, 5 items for vocal tic severity, and 1 item for impairment. Each item for motor tic severity and vocal is rated on a 6-point scale (0 for none to 5 to severe). MTSS is the sum of the 5 items for motor tic severity and VTSS is the sum of the 5 items for vocal tic severity. TTS is the sum of MTSS and VTSS, ranges from 0 (none/absent) to 50 (severe). Higher scores indicate greater severity/worse outcome. LS mean and SE was calculated using MMRM with treatment group, week (3 levels: Weeks 2, 4, and 8), and the treatment group by week interaction as fixed effects; and baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) as covariates. mITT analysis set included all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 Low-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: units on a scale				
least squares mean (standard error)	-5.9 (± 1.18)	-7.0 (± 1.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the TS-CGI Score at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the TS-CGI Score at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[5]

End point description:

The TS-CGI scale is a 7-point Likert scale that allows the clinician to use all available information to assess the impact of tics on the participant's quality of life. The TS-CGI is rated as follows: 1 (normal or no tics at all), 2 (borderline), 3 (mild), 4 (moderate), 5 (marked), 6 (severe), and 7 (extreme, incapacitating tics). Lower scores indicate better quality of life. LS mean and SE was calculated using MMRM with treatment group, week (3 levels: Weeks 2, 4, and 8), and the treatment group by week interaction as fixed effects; and baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) as covariates. mITT analysis set included all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 Low-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: units on a scale				
least squares mean (standard error)	-0.6 (± 0.13)	-0.6 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) Score at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) Score at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[6]

End point description:

The TS-PGII is a single-item questionnaire that asks the participant to assess the degree of impact due to current tics (How much do your current tics disrupt things in your life?). The TS-PGII uses a 5-point scale, ranging from not at all (1) to very much (5), to assess overall response to therapy. mITT analysis set included all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 High-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: units on a scale				
arithmetic mean (standard error)	-0.8 (± 0.17)	-0.7 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the TS-PGII Score at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the TS-PGII Score at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[7]

End point description:

The TS-PGII is a single-item questionnaire that asks the participant to assess the degree of impact due to current tics (How much do your current tics disrupt things in your life?). The TS-PGII uses a 5-point

scale, ranging from not at all (1) to very much (5), to assess overall response to therapy. mITT analysis set included all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 Low-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: units on a scale				
arithmetic mean (standard error)	-0.7 (± 0.15)	-0.7 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) Activities of Daily Living (ADL) Subscale Score at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) Activities of Daily Living (ADL) Subscale Score at Week 8 Between High-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[8]

End point description:

C&A-GTS-QOL is a 27-item questionnaire that contains 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Following 3 questions were assessed in ADL C&A-GTS-QOL subscale: Question 2 (Had difficulty with school or sport activities?), 24 (Felt you needed more help from other people?), and 26 (Had difficulty going out with other people?). Total score of ADL subscale ranged from 0 (no problem) to 12 (extreme problem). Lower score = better quality of life. LS mean and SE was calculated using MMRM with treatment group, week (3 levels: Weeks 2, 4, and 8), and treatment group by week interaction as fixed effects; and baseline TTS, region, and age group at baseline (2 levels: 6-11 years, 12-16 years) as covariates. mITT analysis set: all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 High-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: units on a scale				
least squares mean (standard error)	-10.3 (± 2.85)	-9.0 (± 2.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the C&A-GTS-QOL ADL Subscale Score at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants

End point title	Change From Baseline in the C&A-GTS-QOL ADL Subscale Score at Week 8 Between Low-Dose TEV-50717-Treated Participants and Placebo-Treated Participants[9]

End point description:

C&A-GTS-QOL is a 27-item questionnaire that contains 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Following 3 questions were assessed in ADL C&A-GTS-QOL subscale: Question 2 (Had difficulty with school or sport activities?), 24 (Felt you needed more help from other people?), and 26 (Had difficulty going out with other people?). Total score of ADL subscale ranged from 0 (no problem) to 12 (extreme problem). Lower score = better quality of life. LS mean and SE was calculated using MMRM with treatment group, week (3 levels: Weeks 2, 4, and 8), and treatment group by week interaction as fixed effects; and baseline TTS, region, and age group at baseline (2 levels: 6-11 years, 12-16 years) as covariates. mITT analysis set: all randomized participants who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting statistics for specified arms only.

End point values	TEV-50717 Low-Dose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: units on a scale				
least squares mean (standard error)	-10.0 (± 2.68)	-9.0 (± 2.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Children’s Depression Inventory Second Edition (CDI-2; Parent Version and Self-reported version) Total Score at Week 9

End point title	Change From Baseline in the Children’s Depression Inventory Second Edition (CDI-2; Parent Version and Self-reported version) Total Score at Week 9

End point description:

CDI-2 self-report:28-item questionnaire assessing depressive symptoms in children 7 to 17 years of age with basic reading and comprehension skills. Children were asked to choose 1 of 3 statements that most closely aligns with their feelings in past 2 weeks. It contains 6 subscales (emotional problem,negative mood/physical symptoms,negative self-esteem,functional problems,ineffectiveness,interpersonal problems). Total score = 0 to 56, higher score = greater depression severity.CDI-2 parent:17-item questionnaire administered to parents to assess depression-related behaviors observed in children. Parents were asked to rate their child's behaviors on a 4-point Likert scale from "not at all" to "much or most of the time." It contains 2 subscales (emotional and functional problem). Total score = 0 to 51, higher score = more depression-related behaviors. Safety analysis set: all participants who received at least 1 dose of study drug. 'n' = participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 9

End point values	TEV-50717 High-Dose	TEV-50717 Low-Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	54	51	
Units: units on a scale				
arithmetic mean (standard deviation)				
CDI-2 Parent Version (n=45,52,48)	-1.2 (± 6.53)	-3.8 (± 6.34)	-0.8 (± 5.36)	
CDI-2 Self-Reported Version (n=45,49,46)	-2.0 (± 4.13)	-2.6 (± 4.90)	-0.4 (± 4.99)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants at Baseline and Week 9 with Any Suicidal Ideation or Suicidal Behavior According to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants at Baseline and Week 9 with Any Suicidal Ideation or Suicidal Behavior According to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

C-SSRS included responses for Suicidal Ideation or Suicidal Behavior in following 10 categories: 1 = Wish to be dead; 2 = Non-specific active suicidal thoughts; 3 = Active suicidal ideation with any methods (not plan) without intent to act; 4 = Active suicidal ideation with some intent to act, without specific plan; 5 = Active suicidal ideation with specific plan and intent; 6 = Preparatory acts or behavior; 7 = Aborted attempt; 8 = Interrupted attempt; 9 = Non-fatal suicide attempt; and 10 = Completed suicide. Number of participants with any suicidal ideation or suicidal behavior are reported. Any Suicidal ideation or Suicidal Behavior events reported as TEAEs along with all other reported TEAEs are included in the AE module. Safety analysis set included all participants who received at least 1 dose of study drug. Here, 'number analyzed' signifies participants evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 9

End point values	TEV-50717 High-Dose	TEV-50717 Low-Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	54	51	
Units: participants				
Baseline	0	0	2	
Week 9	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline (Day 1) to follow-up (Week 10)	
Adverse event reporting additional description:	
Safety analysis set included all participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	TEV-50717 High-Dose
Reporting group description:	
TEV-50717 tablets BID up to 48 mg/day orally for a total of 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to TEV-50717 for a total of 8 weeks	
Reporting group title	TEV-50717 Low-Dose
Reporting group description:	
TEV-50717 tablets BID up to 36 mg/day orally for a total of 8 weeks	

Serious adverse events	TEV-50717 High-Dose	Placebo	TEV-50717 Low-Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	0 / 54 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	0 / 54 (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
Tic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	0 / 54 (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

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

Non-serious adverse events	TEV-50717 High-Dose	Placebo	TEV-50717 Low-Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 52 (36.54%)	12 / 51 (23.53%)	16 / 54 (29.63%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 52 (11.54%)	4 / 51 (7.84%)	8 / 54 (14.81%)
occurrences (all)	8	4	13
Somnolence			
subjects affected / exposed	8 / 52 (15.38%)	1 / 51 (1.96%)	2 / 54 (3.70%)
occurrences (all)	11	1	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 52 (9.62%)	0 / 51 (0.00%)	1 / 54 (1.85%)
occurrences (all)	6	0	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 52 (3.85%)	0 / 51 (0.00%)	3 / 54 (5.56%)
occurrences (all)	2	0	3
Vomiting			
subjects affected / exposed	3 / 52 (5.77%)	4 / 51 (7.84%)	1 / 54 (1.85%)
occurrences (all)	3	5	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 52 (3.85%)	3 / 51 (5.88%)	0 / 54 (0.00%)
occurrences (all)	2	4	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 52 (11.54%)	3 / 51 (5.88%)	2 / 54 (3.70%)
occurrences (all)	6	4	2
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	4 / 52 (7.69%)	0 / 51 (0.00%)	1 / 54 (1.85%)
occurrences (all)	4	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2019	The following major procedural changes (not all-inclusive) were made to the protocol: The study sample size was increased. Updated corresponding statistical considerations Included additional nonclinical data observed in rat toxicology studies Further clarified procedures carried out during the screening and enrollment periods (for example, informed consent/assent stipulations) Updated the requirements on drug storage, accountability, and security Updated and clarified the participant inclusion criteria, exclusion criteria, and withdrawal criteria Updated the exploratory endpoints Provided updates on allowed and prohibited medications Included additional guidance for evaluation and management of suicidal ideation, suicidal behavior, and depression
05 May 2019	The following major procedural change (not all-inclusive) was made to the protocol: Reverted the study sample size back to the original sample size prior to Amendment 02. This change was justified upon further evaluation of the external data that was used to support the sample size considerations per Amendment 02 (that is, valbenazine Phase 2 study results, efficacy of TEV-50717 in the treatment of Huntington's disease (HD) and tardive dyskinesia (TD), and ABILIFY Phase 3 data), and the decision had been made not to increase the sample size in the ongoing TV50717-CNS-30060 Phase 3 fixed-dose study. There was substantially lower efficacy in the Abilify Phase 3 study (Study 2) in which a titration regimen was utilized, relative to the efficacy seen with Abilify in the fixed-dose Phase 3 study (Study 1; United States Prescribing Information), which supported the above rationale.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported