Clinical trial results:
An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Summary

EudraCT number	2016-000630-22
Trial protocol	HU SE ES DK PL FR NL IT RO
Global end of trial date	15 May 2020

Results information

Result version number	v1 (current)
This version publication date	27 November 2020
First version publication date	27 November 2020

Trial information

Trial identification

Sponsor protocol code	TV50717-CNS-30047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 1-888-483-8279, USMedInfo@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 1-888-483-8279, USMedInfo@tevapharm.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	19 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2020
Global end of trial reached?	Yes
Global end of trial date	15 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of long-term therapy with TEV-50717.

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	15 May 2018
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: 1
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	United States: 79
Worldwide total number of subjects	228
EEA total number of subjects	61

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)	95
Adolescents (12-17 years)	133
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

228 participants with Tourette Syndrome were enrolled after completing one of two eligible parent studies.

Pre-assignment

Screening details:

Period I included an open-label period with titration and maintenance. Period II included randomized drug withdrawal in which participants were administered their current TEV50717 dose or placebo. Participants were re-titrated to TEV-50717. In Period III, participants continued their open-label maintenance dose of TEV50717.

Period 1

Period 1 title	Period I - Part A
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open-label

Arms

Arm title	TEV-50717

Arm description:

All participants underwent TEV-50717 dose titration in this study. They received 6 mg of TEV-50717 with food on the evening of day 1. The titration scheme and maximum dose were determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status from the parent study.

Arm type	Experimental
Investigational medicinal product name	TEV-50717 (Deuterabenazine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All participants underwent TEV-50717 dose titration in this study. Participants received 6 mg of TEV-50717 with food on the evening of day 1. The titration scheme and maximum dose were determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status from the parent study.

Number of subjects in period 1	TEV-50717
Started	228
Completed	137
Not completed	91
Consent withdrawn by subject	23
Adverse event, non-fatal	14
Terminated by sponsor	44
Lost to follow-up	2
Missing or unknown	7

Protocol deviation	1

Period 2

Period 2 title	Period II - Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Double-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomized TEV-50717

Arm description:

Participants were randomized to their current dose of TEV-50717, which was administered during the Part B Randomized Drug Withdrawal (RW) 2-week period.

Arm type	Experimental
Investigational medicinal product name	TEV-50717 (Deuterabenazine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received their current dose of TEV-50717.

Arm title	Randomized Placebo

Arm description:

Participants were randomized to placebo, which was administered during the Part B Randomized Drug Withdrawal (RW) 2-week period only.

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 was administered during Part B Randomized Drug Withdrawal (RW) 2-week period only.

Number of subjects in period 2	Randomized TEV-50717	Randomized Placebo
Started	91	46
Completed	88	45
Not completed	3	1
Adverse event, non-fatal	1	-
Missing or unknown	2	1

Period 3

Period 3 title	Period III - Part A Resumed
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open-label

Arms

Arm title	TEV-50717 Re-titration and Maintenance

Arm description:

Participants who were randomized to placebo during the withdrawal period were re-titrated to their TEV-50717 maintenance dose. Participants who were randomized to TEV-50717 continued their maintenance dose.

Arm type	Experimental
Investigational medicinal product name	TEV-50717 (Deuterabenazine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received their current dose of TEV-50717 or were re-titrated to TEV-50717 if randomized to the placebo in the previous period.

Number of subjects in period 3	TEV-50717 Re-titration and Maintenance
Started	133
Completed	48
Not completed	85
Consent withdrawn by subject	4
Adverse event, non-fatal	4
Terminated by sponsor	68
Lost to follow-up	1
Missing or unknown	8

Baseline characteristics

Reporting groups	
Reporting group title	TEV-50717

Reporting group description:

All participants underwent TEV-50717 dose titration in this study. They received 6 mg of TEV-50717 with food on the evening of day 1. The titration scheme and maximum dose were determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status from the parent study.

Reporting group values	TEV-50717	Total	
Number of subjects	228	228	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	95	95	
Adolescents (12-17 years)	133	133	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	12		
standard deviation	± 2.59	-	
Sex/Gender, Customized Units: Participants			
Female	45	45	
Male	182	182	
Unknown	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	38	38	
Not Hispanic or Latino	186	186	
Unknown or Not Reported	4	4	
Race/Ethnicity, Customized Units: Subjects			
White	197	197	
Black	4	4	
Asian	7	7	
Native American	5	5	
Other	15	15	

End points

End points reporting groups

Reporting group title	TEV-50717
Reporting group description:	
All participants underwent TEV-50717 dose titration in this study. They received 6 mg of TEV-50717 with food on the evening of day 1. The titration scheme and maximum dose were determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status from the parent study.	
Reporting group title	Randomized TEV-50717
Reporting group description:	
Participants were randomized to their current dose of TEV-50717, which was administered during the Part B Randomized Drug Withdrawal (RW) 2-week period.	
Reporting group title	Randomized Placebo
Reporting group description:	
Participants were randomized to placebo, which was administered during the Part B Randomized Drug Withdrawal (RW) 2-week period only.	
Reporting group title	TEV-50717 Re-titration and Maintenance
Reporting group description:	
Participants who were randomized to placebo during the withdrawal period were re-titrated to their TEV-50717 maintenance dose. Participants who were randomized to TEV-50717 continued their maintenance dose.	

Primary: Number of participants reporting treatment emergent adverse events (AEs) for Parts A & B

End point title	Number of participants reporting treatment emergent adverse events (AEs) for Parts A & B[1]
End point description:	
An AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Incudes clinically significant changes such as changes in vital signs or lab values. Relationship of AE to treatment was determined by the Investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent the previously listed serious outcomes. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section.	
End point type	Primary
End point timeframe:	
Day 1 to Week 55	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: Participants				
At least one adverse event	161			
At least one serious adverse event	2			
At least one severe adverse event	6			
At least one AE related to investigational product	95			

At least one adverse event leading to withdrawal	14			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants reporting treatment emergent adverse events (AEs) in Part B (Period II)

End point title	Number of participants reporting treatment emergent adverse events (AEs) in Part B (Period II)[2]

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Incudes clinically significant changes such as changes in vital signs or lab values. Relationship of AE to treatment was determined by the Investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent the previously listed serious outcomes. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section.

End point type	Primary

End point timeframe:

Weeks 28 to 30

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	Randomized TEV-50717	Randomized Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	42		
Units: Participants				
At least one adverse event	16	6		
At least one serious adverse event	0	0		
At least one severe adverse event	0	0		
At least one AE related to investigational product	6	1		
At least one adverse event leading to withdrawal	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Change From baseline in the Children's Depression Inventory Second Edition (CDI-2; Parent Version) Total Score

End point title	Change From baseline in the Children's Depression Inventory Second Edition (CDI-2; Parent Version) Total Score[3]

End point description:

Parents were asked to rate their child's behaviors in past 2 weeks on a 4-point Likert scale from "not at all" to "much or most of the time." It contains 2 subscales (emotional problems and functional problem). Total score: sum of 2 subscales, ranging from 0 to 51, with higher score indicating more depression-related behaviors.

End point type	Primary

End point timeframe:

Baseline, Weeks 2, 4, 8, 15, 28, 34, 41, 54, 55

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: Units On A Scale				
arithmetic mean (standard deviation)				
CDI-2 Parent Version Week 2	-0.7 (± 4.26)			
CDI-2 Parent Version Week 4	-1.5 (± 4.39)			
CDI-2 Parent Version Week 8	-1.5 (± 5.0)			
CDI-2 Parent Version Week 15	-1.2 (± 5.79)			
CDI-2 Parent Version Week 28	-1.1 (± 5.52)			
CDI-2 Parent Version Week 34	-1.0 (± 6.08)			
CDI-2 Parent Version Week 41	-1.1 (± 5.92)			
CDI-2 Parent Version Week 54	-0.3 (± 5.83)			
CDI-2 Parent Version Week 55	-0.9 (± 4.34)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From baseline in the Children's Depression Inventory Second Edition (CDI-2; Self-reported Version) Total Score

End point title	Change From baseline in the Children's Depression Inventory Second Edition (CDI-2; Self-reported Version) Total Score[4]

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: sum of all subscales scores, ranging from 0 to 56, with higher score indicating greater depression severity.CDI-2 parent: 17-item questionnaire administered to parents to assess depression-related behaviors observed in their children.

End point type	Primary

End point timeframe:

Baseline, Weeks 2, 4, 8, 15, 28, 34, 41, 54, 55

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: Units On A Scale				
arithmetic mean (standard deviation)				
CDI-2 Self-reported Version Week 2	-0.3 (± 3.41)			
CDI-2 Self-reported Version Week 4	-0.5 (± 3.57)			
CDI-2 Self-reported Version Week 8	-0.3 (± 4.35)			
CDI-2 Self-reported Version Week 15	-0.3 (± 4.83)			
CDI-2 Self-reported Version Week 28	0.0 (± 4.65)			
CDI-2 Self-reported Version Week 34	-0.5 (± 4.61)			
CDI-2 Self-reported Version Week 41	-0.7 (± 4.74)			
CDI-2 Self-reported Version Week 54	-0.5 (± 4.01)			
CDI-2 Self-reported Version Week 55	-0.3 (± 4.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From randomized withdrawal baseline (Week 28) in the Children's Depression Inventory Second Edition (CDI-2; Parent Version) Total Score at Week 30

End point title	Change From randomized withdrawal baseline (Week 28) in the Children's Depression Inventory Second Edition (CDI-2; Parent Version) Total Score at Week 30[5]

End point description:

Parents were asked to rate their child's behaviors in past 2 weeks on a 4-point Likert scale from "not at all" to "much or most of the time." It contains 2 subscales (emotional problems and functional problem). Total score: sum of 2 subscales, ranging from 0 to 51, with higher score indicating more depression-related behaviors.

End point type	Primary

End point timeframe:

Week 28, Week 30

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	Randomized TEV-50717	Randomized Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	41		
Units: Units On A Scale				
arithmetic mean (standard deviation)	-0.2 (± 4.68)	0.6 (± 3.62)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From randomized withdrawal baseline (Week 28) in the Children's Depression Inventory Second Edition (CDI-2; Self-reported Version) Total Score at Week 30

End point title	Change From randomized withdrawal baseline (Week 28) in the Children's Depression Inventory Second Edition (CDI-2; Self-reported Version) Total Score at Week 30[6]

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: sum of all subscales scores, ranging from 0 to 56, with higher score indicating greater depression severity.CDI-2 parent: 17-item questionnaire administered to parents to assess depression-related behaviors observed in their children.

End point type	Primary

End point timeframe:

Week 28, Week 30

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	Randomized TEV-50717	Randomized Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	39		
Units: Units On A Scale				
arithmetic mean (standard deviation)	-0.4 (± 3.3)	-0.6 (± 3.08)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants reporting any suicidal ideation or suicidal behavior according to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of participants reporting any suicidal ideation or suicidal behavior according to the Columbia Suicide Severity Rating Scale (C-SSRS)[7]

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.

End point type	Primary

End point timeframe:

Baseline, Weeks 2, 4, 8, 15, 28, 34, 41, 54, 55

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: Participants				
Baseline	0			
Week 2	0			
Week 4	2			
Week 8	0			
Week 15	1			
Week 28	0			
Week 34	0			
Week 41	1			
Week 54	0			
Week 55	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants reporting any suicidal ideation or suicidal behavior according to the Columbia Suicide Severity Rating Scale (C-SSRS) at randomized withdrawal baseline visit (Week 28) and Week 30

End point title	Number of participants reporting any suicidal ideation or suicidal behavior according to the Columbia Suicide Severity Rating Scale (C-SSRS) at randomized withdrawal baseline visit (Week 28) and Week 30[8]

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.

End point type	Primary

End point timeframe:

Week 28, Week 30

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The assessment for this endpoint was descriptive and no statistical analyses were performed for this endpoint.

End point values	Randomized TEV-50717	Randomized Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	42		
Units: Participants				
Week 28	0	0		
Week 30	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)

End point title	Change from baseline in the Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)

End point description:

YGTSS rating scale is a semi-structured clinician rating instrument that provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic tics. 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. Baseline is defined as the last measurement on or prior to the first dose of the open-label study medication.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 15, 28, 41, 54, and 55

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Units on a scale				
arithmetic mean (standard error)				
Week 8	-6.9 (± 0.58)			
Week 15	-7.8 (± 0.58)			
Week 28	-6.2 (± 0.83)			
Week 41	-8.3 (± 0.97)			
Week 54	-6.5 (± 1.47)			
Week 55	-4.3 (± 1.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score

End point title	Change from baseline in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score

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. Baseline is defined as the last measurement on or prior to the first dose of the open-label study medication.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 15, 28, 41, 54, and 55

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Units on a scale				
arithmetic mean (standard error)				
Week 8	-0.7 (± 0.06)			
Week 15	-0.7 (± 0.06)			
Week 28	-0.6 (± 0.08)			
Week 41	-0.6 (± 0.1)			
Week 54	-0.8 (± 0.16)			
Week 55	-0.4 (± 0.15)			

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

End point title	Change from baseline in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score

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. Baseline is defined as the last measurement on or prior to the first dose of the open-label study medication.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 15, 28, 41, 54, and 55

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Units on a scale				
arithmetic mean (standard error)				
Week 8	-0.5 (± 0.07)			

Week 15	-0.5 (± 0.08)			
Week 28	-0.5 (± 0.09)			
Week 41	-0.6 (± 0.12)			
Week 54	-0.5 (± 0.16)			
Week 55	-0.1 (± 0.14)			

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

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

End point description:

C&A-GTS-QOL is a 27-item questionnaire that asks participant to assess the extent to which their quality of life is impacted by their symptoms. C&A-GTS-QOL 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 from 27-item questionnaire were assessed in ADL C&A-GTS-QOL subscale: Question 2 (Had difficulty with school or sport activities?), 24 (Felt you needed more help or support 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 indicated better quality of life. Baseline is defined as the last measurement on or prior to the first dose of the open-label study medication.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6, 28, 34, 54

End point values	TEV-50717			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Units on a scale				
arithmetic mean (standard error)				
Week 6	-4.9 (± 1.12)			
Week 28	-4.4 (± 1.48)			
Week 34	-5.9 (± 1.82)			
Week 54	-2.7 (± 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomized withdrawal baseline (Week 28) in the Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS) to Week 30

End point title	Change from randomized withdrawal baseline (Week 28) in the

	Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS) to Week 30

End point description:

YGTSS rating scale is a semi-structured clinician rating instrument that provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic tics. 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. The model is an ANCOVA model that includes fixed effects for treatment group. The randomized withdrawal baseline TTS and age group at baseline (2 levels: 6-11 years, 12-18 years) are included as covariates.

End point type	Secondary

End point timeframe:

Week 28, Week 30

End point values	Randomized TEV-50717	Randomized Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	26		
Units: Units on a scale				
least squares mean (standard error)	1.6 (± 0.86)	2.0 (± 1.24)		

Statistical analyses

Statistical analysis title	Least Squares Mean
Comparison groups	Randomized TEV-50717 v Randomized Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	2.6

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Week 55	
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	Total
Reporting group description:	
All participants underwent TEV-50717 dose titration in this study. They received 6 mg of TEV-50717 with food on the evening of day 1. The titration scheme and maximum dose were determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status from the parent study.	

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 227 (0.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Self-injurious ideation			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 227 (47.58%)		
Investigations			
Weight increased			
subjects affected / exposed	22 / 227 (9.69%)		
occurrences (all)	22		
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 227 (13.22%)		
occurrences (all)	55		
Somnolence			
subjects affected / exposed	28 / 227 (12.33%)		
occurrences (all)	33		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	13 / 227 (5.73%)		
occurrences (all)	13		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	15 / 227 (6.61%)		
occurrences (all)	30		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	17 / 227 (7.49%)		
occurrences (all)	18		
Tic			
subjects affected / exposed	15 / 227 (6.61%)		
occurrences (all)	29		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 227 (10.13%)		
occurrences (all)	33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2017	To change study conduct including number of participants randomized and clinical study personnel.
15 November 2017	To incorporate randomized drug withdrawal period and update prohibited medications.
01 February 2018	To correct the re-titration regiment in Part II.
22 May 2019	To address regulatory requirements such as updated number of participants, an interim analysis, and clarify screening procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: