Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Summary

EudraCT number	2016-000622-19
Trial protocol	ES DK
Global end of trial date	12 November 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	TV50717-CNS-30046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03452943
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2019
Global end of trial reached?	Yes
Global end of trial date	12 November 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 the efficacy 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 (eg, Code of Federal Regulations [CFR] 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	05 February 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	Canada: 21
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	United States: 66
Worldwide total number of subjects	119
EEA total number of subjects	15

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)	62
Adolescents (12-17 years)	57
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 119 participants were randomized in a 1:1 ratio to either TEV-50717 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

Arm description:

TEV-50717 tablets twice daily (BID) up to 48 milligrams (mg)/day orally for a total of 12 weeks

Arm type	Experimental
Investigational medicinal product name	TEV-50717
Investigational medicinal product code	
Other name	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 specified in the arm.

Arm title	Placebo

Arm description:

Placebo matched to TEV-50717 BID for a total of 12 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 per schedule specified in the arm.

Number of subjects in period 1	TEV-50717	Placebo
Started	59	60
Received at least 1 dose of study drug	58	59
Modified ITT (mITT) Analysis Set	58	59
Completed	51	56
Not completed	8	4

Consent withdrawn by subject	5	2
Adverse event, non-fatal	2	1
Lost to follow-up	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TEV-50717
Reporting group description:	
TEV-50717 tablets twice daily (BID) up to 48 milligrams (mg)/day orally for a total of 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to TEV-50717 BID for a total of 12 weeks	

Reporting group values	TEV-50717	Placebo	Total
Number of subjects	59	60	119
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	11.5	11.5	
standard deviation	± 2.52	± 2.59	-
Sex: Female, Male Units: participants			
Female	6	9	15
Male	53	51	104
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	8	13
Not Hispanic or Latino	51	50	101
Unknown or Not Reported	3	2	5
Race/Ethnicity, Customized Units: Subjects			
White	49	53	102
Black	3	3	6
Asian	1	1	2
Native American	1	0	1
Multiple	3	1	4
Other	2	2	4
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	31.7	33.0	
standard deviation	± 5.81	± 5.96	-

End points

End points reporting groups	
Reporting group title	TEV-50717
Reporting group description:	
TEV-50717 tablets twice daily (BID) up to 48 milligrams (mg)/day orally for a total of 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to TEV-50717 BID for a total of 12 weeks	

Primary: Change From Baseline in the TTS of the YGTSS at Week 12	
End point title	Change From Baseline in the TTS of the YGTSS at Week 12
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 = none to 5 = severe). MTSS = sum of the 5 items for motor tic severity and VTSS is sum of the 5 items for vocal tic severity. TTS = 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 (5 levels: weeks 2, 4, 6, 9, and 12), and 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 12	

End point values	TEV-50717	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: units on a scale				
least squares mean (standard error)	-9.1 (± 1.28)	-8.4 (± 1.25)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TEV-50717 v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.692 [1]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	2.8

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in the Tourette Syndrome-Clinical Global Impression (TS-CGI) Score at Week 12

End point title	Change From Baseline in the Tourette Syndrome-Clinical Global Impression (TS-CGI) Score at Week 12

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 (5 levels: weeks 2, 4, 6, 9, and 12), 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 12

End point values	TEV-50717	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: units on a scale				
least squares mean (standard error)	-0.7 (± 0.13)	-0.7 (± 0.12)		

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 12

End point title	Change From Baseline in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) Score at Week 12

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 12

End point values	TEV-50717	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: units on a scale				
arithmetic mean (standard error)	-0.7 (± 0.18)	-0.4 (± 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 at Week 12

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 12

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 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 (5 levels: weeks 2,4,6,9, and 12), 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 12

End point values	TEV-50717	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: units on a scale				
least squares mean (standard error)	-9.9 (± 2.37)	-8.8 (± 2.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)

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. 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. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to follow-up (Week 14)

End point values	TEV-50717	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: percentage of participants				
number (not applicable)				
Any AEs	65.5	55.9		
Treatment-related AEs	50.0	20.3		
Serious AEs	0	0		
AEs leading to discontinuation	1.7	1.7		

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 14)	
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
Reporting group description:	
TEV-50717 tablets BID up to 48 mg/day orally for a total of 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to TEV-50717 BID for a total of 12 weeks	

Serious adverse events	TEV-50717	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 58 (0.00%)	0 / 59 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	TEV-50717	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 58 (37.93%)	23 / 59 (38.98%)	
Investigations			
Weight increased			
subjects affected / exposed	7 / 58 (12.07%)	1 / 59 (1.69%)	
occurrences (all)	7	1	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 58 (10.34%)	6 / 59 (10.17%)	
occurrences (all)	6	12	
Somnolence			

subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)	
occurrences (all)	8	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 58 (12.07%)	3 / 59 (5.08%)	
occurrences (all)	8	4	
Pyrexia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	
occurrences (all)	4	1	
Nausea			
subjects affected / exposed	4 / 58 (6.90%)	5 / 59 (8.47%)	
occurrences (all)	5	11	
Vomiting			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Depressed mood			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Enuresis			
subjects affected / exposed	4 / 58 (6.90%)	0 / 59 (0.00%)	
occurrences (all)	6	0	
Suicidal ideation			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	7 / 59 (11.86%) 9	
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	1 / 59 (1.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2018	The primary reason for this amendment was to include additional nonclinical data observed in rat toxicology studies; further clarify procedures to be carried out during the screening and enrollment periods (for example, informed consent/assent stipulations); update requirements on drug storage and security; update/clarify participant inclusion criteria, exclusion criteria, and withdrawal criteria; provide updates on allowed and prohibited medications; include additional guidance for evaluation and handling of suicidal ideation, suicidal behavior, and depression; and streamline birth control methods language for females of childbearing potential.
25 March 2019	The primary reason for this amendment was to update the anticipated participant enrollment numbers and related statistical considerations, update requirements on drug storage and security, update/clarify participant inclusion criteria and withdrawal criteria, update administrative details with regard to clinical study personnel contact information and vendor selection, and provide additional guidance on dose suspension.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported