Clinical trial results:
An Open-Label, Long-Term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia

Summary

EudraCT number	2014-001891-73
Trial protocol	CZ PL SK HU
Global end of trial date	

Results information

Result version number	v1
This version publication date	27 March 2021
First version publication date	27 March 2021

Trial information

Trial identification

Sponsor protocol code	SD-809-C-20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02198794
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)	
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	04 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the long-term safety, tolerability, and efficacy of SD-809 in reducing the severity of abnormal involuntary movements of moderate to severe tardive dyskinesia. The purpose of part B is to establish the durability of effect of SD-809 following 1-week period of randomized withdrawal (SD-809 and placebo), followed by 12 weeks of maintenance with SD-809.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (for example, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; EU Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2014
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	Czechia: 26
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Poland: 89
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	United States: 195
Worldwide total number of subjects	337
EEA total number of subjects	142

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)	258
From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

343 participants who completed previous SD-809 studies, including study SD-809-C-18 (NCT02195700) or SD-809-C-23 (NCT02291861) were enrolled and 337 participants were eligible for analysis. 6 participants were not evaluable and were excluded from the analysis due to site data integrity issues as reported to the US FDA.

Pre-assignment

Screening details:

This study included 2 parts: Part A and Part B. Participants in Part A who were on a stable dose for a minimum of 4 weeks after a 6-week titration period, were invited to participate in Part B. Participants who are noted as "Completed" for Part A: completed the study in Part A (Week 158) plus continued in Part B.

Period 1

Period 1 title	Part A: Open-Label (158 Weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SD-809

Arm description:

Participants received SD-809 orally BID starting at 12 mg/day, which was titrated based on dyskinesia control and tolerability up to a maximum total dose of 48 mg/day. Participants who declined to participate in Part B, continued at their stable dose of SD-809 BID up to Week 158.

Arm type	Experimental
Investigational medicinal product name	SD-809
Investigational medicinal product code	TEV-50717
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SD-809 was administered per dose and schedule specified in the arm.

Number of subjects in period 1	SD-809
Started	337
Received at least 1 dose of study drug	337
Intent-to-Treat (ITT) Population	337
Participants participated in Part A only	195
Completed	32
Not completed	305
Adverse event, serious fatal	8
Study terminated	1
Consent withdrawn by subject	79
Agreed to continue in Part B	142

Adverse event, non-fatal	33
Protocol deviation	1
Noncompliance with study drug	3
Other than specified	5
Lost to follow-up	24
Lack of efficacy	9

Period 2

Period 2 title	Part B: Randomized (13 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part B: Placebo

Arm description:

Participants received placebo matched to SD-809 for 1 week in randomized withdrawal period and thereafter received SD-809 (stable dose) for 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 SD-809 was administered per schedule specified in the arm.

Arm title	Part B: SD-809

Arm description:

Participants received SD-809 (stable dose) for 1 week in randomized withdrawal period and continued to receive the same dose of SD-809 for an additional 12 weeks.

Arm type	Experimental
Investigational medicinal product name	SD-809
Investigational medicinal product code	TEV-50717
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SD-809 was administered per dose and schedule specified in the arm.

Number of subjects in period 2	Part B: Placebo	Part B: SD-809
Started	16	16
Completed	66	68
Not completed	5	3
Consent withdrawn by subject	3	1
Lost to follow-up	2	2
Joined	55	55
142 participants from Part A were randomized	55	55

Baseline characteristics

Reporting groups	
Reporting group title	SD-809
Reporting group description:	
Participants received SD-809 orally BID starting at 12 mg/day, which was titrated based on dyskinesia control and tolerability up to a maximum total dose of 48 mg/day. Participants who declined to participate in Part B, continued at their stable dose of SD-809 BID up to Week 158.	

Reporting group values	SD-809	Total	
Number of subjects	337	337	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.9		
standard deviation	± 10.65	-	
Sex: Female, Male Units: participants			
Female	188	188	
Male	149	149	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaskan Native	1	1	
Asian	2	2	
Black	69	69	
White	264	264	
Other	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	28	
Not Hispanic or Latino	300	300	
Unknown or Not Reported	9	9	
Total Motor Abnormal Involuntary Movement Scale (AIMS) Score			
AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia.			
Units: units on a scale			
arithmetic mean	10.7		
standard deviation	± 4.68	-	
AIMS Individual Items (8-10) Scores: Severity of abnormal movements (Item 8) Score			
AIMS is composed of 12 clinician-administered and -scored items. Item 8 (used as an overall severity index indicating severity of abnormal movements) was rated on a 5-point anchored scale ranging from 0 (no dyskinetic movements) to 4 (severe dyskinetic movements). Items 9 and 10 (provide additional information with regard to participant's incapacitation due to abnormal movements and participant's awareness of abnormal movements) were rated on a 5-point anchored scale ranging from 0 (none or no			

awareness) to 4 (severe or aware, severe distress). Higher scores indicated more severe disease.			
Units: units on a scale arithmetic mean standard deviation	 2.6 ± 0.78	 -	
AIMS Individual Items (8-10) Scores: Incapacitation due to abnormal movements (Item 9) Score			
AIMS is composed of 12 clinician-administered and -scored items. Item 8 (used as an overall severity index indicating severity of abnormal movements) was rated on a 5-point anchored scale ranging from 0 (no dyskinetic movements) to 4 (severe dyskinetic movements). Items 9 and 10 (provide additional information with regard to participant's incapacitation due to abnormal movements and participant's awareness of abnormal movements) were rated on a 5-point anchored scale ranging from 0 (none or no awareness) to 4 (severe or aware, severe distress). Higher scores indicated more severe disease.			
Units: units on a scale arithmetic mean standard deviation	 2.0 ± 1.07	 -	
AIMS Individual Items (8-10) Scores: Participant's awareness of abnormal movements (Item 10) Score			
AIMS is composed of 12 clinician-administered and -scored items. Item 8 (used as an overall severity index indicating severity of abnormal movements) was rated on a 5-point anchored scale ranging from 0 (no dyskinetic movements) to 4 (severe dyskinetic movements). Items 9 and 10 (provide additional information with regard to participant's incapacitation due to abnormal movements and participant's awareness of abnormal movements) were rated on a 5-point anchored scale ranging from 0 (none or no awareness) to 4 (severe or aware, severe distress). Higher scores indicated more severe disease.			
Units: units on a scale arithmetic mean standard deviation	 2.2 ± 1.08	 -	
Modified Craniocervical Dystonia Questionnaire 24 (CDQ-24) Score			
CDQ-24 is a disease-specific quality of life questionnaire developed for use in participants with craniocervical dystonia. CDQ-24 was modified such that the questions focus more directly on the impact of TD on quality of life. The following domains were evaluated in mCDQ-24: stigma, emotional well-being, pain, activities of daily living, and social/family life. Each of the 24 questions were rated by participants on a scale of 0 = never or no impairment to 4 = always or very severe impairment. Total score ranged from 0 – 96, with higher score indicative of severe impairment.			
Units: units on a scale arithmetic mean standard deviation	 29.2 ± 18.96	 -	

End points

End points reporting groups

Reporting group title	SD-809
Reporting group description:	
Participants received SD-809 orally BID starting at 12 mg/day, which was titrated based on dyskinesia control and tolerability up to a maximum total dose of 48 mg/day. Participants who declined to participate in Part B, continued at their stable dose of SD-809 BID up to Week 158.	
Reporting group title	Part B: Placebo
Reporting group description:	
Participants received placebo matched to SD-809 for 1 week in randomized withdrawal period and thereafter received SD-809 (stable dose) for 12 weeks.	
Reporting group title	Part B: SD-809
Reporting group description:	
Participants received SD-809 (stable dose) for 1 week in randomized withdrawal period and continued to receive the same dose of SD-809 for an additional 12 weeks.	
Subject analysis set title	Part B: Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received placebo matched to SD-809 for 1 week in randomized withdrawal period and thereafter received SD-809 (stable dose) for 12 weeks.	
Subject analysis set title	Part B: SD-809
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received SD-809 (stable dose) for 1 week in randomized withdrawal period and continued to receive the same dose of SD-809 for an additional 12 weeks.	

Primary: Part A and B: Number of Participants With Treatment-Emergent AEs (TEAEs), Serious TEAEs, Severe TEAEs, Drug-Related TEAEs, and TEAEs Leading to Withdrawal

End point title	Part A and B: Number of Participants With Treatment-Emergent AEs (TEAEs), Serious TEAEs, Severe TEAEs, Drug-Related TEAEs, and TEAEs Leading to Withdrawal[1]
End point description:	
AEs were analyzed as 1 group combined for parts A and B per planned analysis. An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severe AE=prevents normal daily activities. Drug-related TEAEs=TEAEs with possible, probable, or definite relationship to study drug. Serious AEs=death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, significant disability or incapacity, congenital anomaly or birth defect, or an important medical event that jeopardized participant and required medical intervention to prevent 1 of the outcomes listed in the definition. TEAE=an AE that began after the first administration of study drug or existing AEs that worsened after first dose of study drug. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received any study drug.	
End point type	Primary
End point timeframe:	
Baseline up to the end of follow-up (4 weeks after the last dose of study drug; up to approximately 1371 days)	

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: Safety analyses were descriptive in nature.

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	337			
Units: participants				
Any TEAEs	269			
Serious TEAEs	68			
Severe TEAEs	57			
Drug-Related TEAEs	154			
TEAEs Leading to Withdrawal From Study	42			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Change From Day 1 Visit in Total Motor AIMS Score at Day 7 Visit, as Assessed by Blinded Central Video Rating

End point title	Part B: Change From Day 1 Visit in Total Motor AIMS Score at Day 7 Visit, as Assessed by Blinded Central Video Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The randomized withdrawal modified intent-to-treat (mITT) population included all participants enrolled in Part B who received study drug during the randomized withdrawal period and had a total motor AIMS score as assessed by blinded central video rating at both the pre-withdrawal visit and the post-withdrawal visit.

End point type	Primary

End point timeframe:

Day 1 of Part B, Day 7 of Part B

End point values	Part B: Placebo	Part B: SD-809		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	65		
Units: units on a scale				
arithmetic mean (standard error)				
Pre-withdrawal	5.7 (± 0.55)	5.0 (± 0.49)		
Change at Post-withdrawal	0.6 (± 0.28)	0 (± 0.29)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The statistical model was an analysis of covariance (ANCOVA) with treatment group and dopamine

receptor antagonist status at the pre-withdrawal visit as fixed effects and the pre-withdrawal visit value as a covariate.

Comparison groups	Part B: Placebo v Part B: SD-809
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.121 [2]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	0.17

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Part A: Change From Baseline in Total Motor AIMS Score at Week 145, as Assessed by the Site Rating

End point title	Part A: Change From Baseline in Total Motor AIMS Score at Week 145, as Assessed by the Site Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of tardive dyskinesia (TD) over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: units on a scale				
arithmetic mean (standard error)	-6.6 (± 0.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in Total Motor AIMS Score at Week 158, as Assessed by the Site Rating

End point title	Part A: Change From Baseline in Total Motor AIMS Score at

	Week 158, as Assessed by the Site Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 158

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard error)	-6.3 (± 0.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in Total Motor AIMS Score at Week 145, as Assessed by the Site Rating

End point title	Part A: Percent Change From Baseline in Total Motor AIMS Score at Week 145, as Assessed by the Site Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: percent change				
arithmetic mean (standard error)	-57.0 (± 2.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in Total Motor AIMS Score at Week 158, as Assessed by the Site Rating

End point title	Part A: Percent Change From Baseline in Total Motor AIMS Score at Week 158, as Assessed by the Site Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 158

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percent change				
arithmetic mean (standard error)	-54.9 (± 6.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Participants who had a 50% or Greater Reduction From Baseline in Total Motor AIMS Score, as Assessed by the Site Rating

End point title	Part A: Percentage of Participants who had a 50% or Greater Reduction From Baseline in Total Motor AIMS Score, as Assessed by the Site Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral

movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline to Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: percentage of participants	67			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Participants who had a 70% or Greater Reduction From Baseline in Total Motor AIMS Score, as Assessed by the Site Rating

End point title	Part A: Percentage of Participants who had a 70% or Greater Reduction From Baseline in Total Motor AIMS Score, as Assessed by the Site Rating

End point description:

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS is composed of 12 clinician-administered and -scored items. A total motor score from Items 1 to 7 (orofacial, extremity, and truncal movements) was calculated. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 5-point anchored scale ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). Total motor AIMS score for Items 1-7 ranged from 0 to 28, with higher scores indicative of more severe dyskinesia. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline to Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: percentage of participants	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in AIMS Items 8, 9, and 10 Score at Week 145, as Assessed by the Site Rating

End point title	Part A: Change From Baseline in AIMS Items 8, 9, and 10 Score at Week 145, as Assessed by the Site Rating

End point description:

AIMS is composed of 12 clinician-administered and -scored items. Items 8 to 10 deal with global severity as judged by the examiner, and the participant's awareness of the movements and distress associated with them. Item 8 (used as an overall severity index indicating severity of abnormal movements) was rated on a 5-point anchored scale ranging from 0 (no dyskinetic movements) to 4 (severe dyskinetic movements). Items 9 and 10 (provide additional information with regard to participant's incapacitation due to abnormal movements and participant's awareness of abnormal movements) were rated on a 5-point anchored scale ranging from 0 (none or no awareness) to 4 (severe or aware, severe distress). Higher scores indicated more severe disease. ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: units on a scale				
arithmetic mean (standard error)				
Severity of abnormal movements	-1.3 (± 0.07)			
Incapacitation due to abnormal movements	-1.3 (± 0.08)			
Participant's awareness of abnormal movements	-1.3 (± 0.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Participants who Were a Treatment Success, Based on the Clinical Global Impression of Change (CGIC)

End point title	Part A: Percentage of Participants who Were a Treatment Success, Based on the Clinical Global Impression of Change (CGIC)

End point description:

A treatment success was defined as much or very much improved on the CGIC from baseline of this study. The CGIC is a single-item questionnaire that asks the investigator to assess a participant's TD symptoms at specific visits/weeks after initiating therapy. The CGIC uses a 7-point Likert scale, ranging from -3 to +3 (-3 = very much worse, -2 = much worse, -1 = minimally worse, 0 = not changed, 1 = minimally improved, 2 = much improved, 3 = very much improved), to assess overall response to therapy. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: percentage of participants	73			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Participants who Were a Treatment Success, Based on the Patient Global Impression of Change (PGIC)

End point title	Part A: Percentage of Participants who Were a Treatment Success, Based on the Patient Global Impression of Change (PGIC)

End point description:

A treatment success was defined as much or very much improved on the PGIC from baseline of this study. The PGIC is single-item questionnaire that asks the participant to assess their TD symptoms at specific visits/weeks after initiating therapy. The PGIC uses a 7-point Likert scale, ranging from -3 to +3 (-3 = very much worse, -2 = much worse, -1 = minimally worse, 0 = not changed, 1 = minimally improved, 2 = much improved, 3 = very much improved), to assess overall response to therapy. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 145

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: percentage of participants	63			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in Modified CDQ-24 Score at Week 158

End point title	Part A: Change From Baseline in Modified CDQ-24 Score at Week 158

End point description:

The CDQ-24 is a disease-specific quality of life questionnaire developed for use in participants with craniocervical dystonia, including both cervical dystonia (CD) and blepharospasm (BPS). The CDQ-24 was modified such that the questions focus more directly on the impact of TD (as opposed to CD/BPS) on quality of life. The following domains were evaluated in the mCDQ-24: stigma, emotional well-being, pain, activities of daily living, and social/family life. Each of the 24 questions were rated by participants on a scale of 0 = never or no impairment to 4 = always or very severe impairment. Total score ranged from 0 – 96, with higher score indicative of severe impairment. The ITT population included all participants who were enrolled in the study, regardless of whether or not a participant received a dose of study drug. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 158

End point values	SD-809			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: units on a scale				
arithmetic mean (standard error)	-6.3 (± 2.61)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to the end of follow-up (4 weeks after the last dose of study drug; up to approximately 1371 days)

Adverse event reporting additional description:

Adverse events were analyzed as one group combined for parts A and B per planned analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Part A and Part B Participants

Reporting group description:

Participants received SD-809 orally BID starting at 12 mg/day, which was titrated based on dyskinesia control and tolerability up to a maximum total dose of 48 mg/day. Participants who declined to participate in Part B, continued at their stable dose of SD-809 BID up to Week 158. Participants who agreed to participate in Part B, received SD-809 or placebo matched to SD-809 for 1 week in randomized withdrawal period and thereafter received SD-809 (stable dose) for 12 weeks.

Serious adverse events	Part A and Part B Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 337 (20.18%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign breast neoplasm			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the tongue				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Iliac artery occlusion				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Non-cardiac chest pain				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			

subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Depressive symptom				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Homicidal ideation				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomania				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Schizoaffective disorder				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				

subjects affected / exposed	5 / 337 (1.48%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	3 / 337 (0.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Burns second degree				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carbon monoxide poisoning				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				

subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Traumatic haemothorax				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				

subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiopulmonary failure				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiovascular insufficiency				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ventricular tachycardia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised non-convulsive epilepsy			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic duct stenosis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholelithiasis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cyst				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver disorder				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure acute				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Stress urinary incontinence				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteoarthritis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				

subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colonic abscess				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mycobacterium avium complex infection				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 337 (1.19%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				

subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	1 / 337 (0.30%)		
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	Part A and Part B Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	171 / 337 (50.74%)		
Investigations			
Weight decreased			
subjects affected / exposed	32 / 337 (9.50%)		
occurrences (all)	34		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	18 / 337 (5.34%)		
occurrences (all)	23		
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 337 (6.53%)		
occurrences (all)	24		
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	22 / 337 (6.53%)		
occurrences (all)	29		
Headache			
subjects affected / exposed	24 / 337 (7.12%)		
occurrences (all)	31		
Somnolence			
subjects affected / exposed	34 / 337 (10.09%)		
occurrences (all)	41		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 337 (8.01%)		
occurrences (all)	32		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 41 / 337 (12.17%) 51 35 / 337 (10.39%) 45		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 20 / 337 (5.93%) 28 31 / 337 (9.20%) 56		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2015	The following major procedural changes (not all-inclusive) were made to the protocol: - Participants who previously participated in another study of TEV-50717 for the treatment of moderate to severe TD, including Study C-23, were allowed to participate in Study C-20. - The long-term treatment period was extended from 1 year to 2 years, and clinic visits were added at Weeks 67, 80, 93, and 106/end of treatment (ET). The follow-up clinic visit was changed to Week 107, and telephone contact was changed to Week 110. - Hepatic or renal impairment at screening of the parent study was considered exclusionary.
27 September 2016	The following major procedural changes (not all-inclusive) were made to the protocol: - The long-term treatment period was extended from 2 years to 3 years, and clinic visits were added at Weeks 119, 132, 145, and 158/ET. The follow-up clinic visit was changed to Week 159, and telephone contact was changed to Week 162. - Treatment modification instructions regarding maximum dosage were expanded with greater detail for weight-based dosing and strong CYP2D6 inhibitor use, allowing doses up to 42 mg for participants ≥100 kg and doses up to 36 for participants <100 mg. - It was added that participants who have not achieved adequate control of dyskinesia during the study may have up to 2 blood samples collected for future pharmacokinetic assessment of α- and β- dihydrotetrabenazine (HTBZ).
08 February 2017	The following major procedural changes (not all-inclusive) were made to the protocol: - As hypokalemia and hypomagnesaemia may contribute to QT prolongation, criteria for suspending treatment were added in case a participant's potassium or magnesium levels fall below the lower limit of normal. - If the participant met either of the following criteria, study treatment was discontinued and an ET visit was conducted: a mean QTcF value >500 msec or a mean change in QTcF of >60 msec from baseline. - Given the potential for many antipsychotics to prolong the QT interval, additional electrocardiogram (ECG) monitoring was added if participants increased antipsychotic dose, switched to a new antipsychotic, or had a new antipsychotic treatment added to their regimen.
23 January 2018	The following major procedural changes (not all-inclusive) were made to the protocol: - The optional double-blind, placebo-controlled randomization withdrawal period (Part B) was added to the study with the objective to evaluate the persistence of the therapeutic effect of TEV-50717. The previous study design was labeled Part A for differentiation. - The time period was updated from 3 to 4 weeks after EOT/ET visit. - The requirement for participants to discuss reasons for study withdrawal with medical monitor or sponsor clinician was removed. - Dose reduction instructions to include CYP2D were added. - The AIMS video recording measure was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported