Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SD-809 (DEUTETRABENAZINE) FOR THE TREATMENT OF MODERATE TO SEVERE TARDIVE DYSKINESIA

Summary

EudraCT number	2014-001890-15
Trial protocol	CZ PL SK
Global end of trial date	21 May 2015

Results information

Result version number	v1 (current)
This version publication date	18 March 2017
First version publication date	18 March 2017

Trial information

Trial identification

Sponsor protocol code	SD-809-C-18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02195700
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auspex Pharmaceuticals, Inc
Sponsor organisation address	3333 N. Torrey Pines Court, Ste. 400, La Jolla, CA, United States, 92037
Public contact	Director, Clinical Research, Teva Branded Pharmaceuticals Products, R&D, Inc, 1 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceuticals Products, R&D, Inc, 1 215-591-3000, ustevatrials@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	30 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the efficacy of SD-809 to reduce the severity of abnormal involuntary movements of Tardive Dyskinesia
• To evaluate the safety and tolerability of titration and maintenance therapy with SD-809 in subjects with drug-induced Tardive Dyskinesia

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, 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 GCP in the conduct of clinical trials on medicinal products for human use).
Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	11 June 2014
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	Slovakia: 4
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	United States: 97
Worldwide total number of subjects	117
EEA total number of subjects	20

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)	101
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

202 patients were screened and gave informed consent to enter the study. 85 were either ineligible for entry into the study or declined study participation. The most common reason for ineligibility (49 patients) was insufficient TD severity as assessed with Abnormal Involuntary Movement Scale (AIMS). 117 patients were randomized.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

This was a randomized, double blind, placebo controlled, parallel group study. Patients were randomly assigned to receive treatment with SD 809 or a matching placebo in a 1:1 ratio. Patients were randomly assigned to treatment through an Interactive Technology Response System (ITRS). Using this system ensured a balance across treatment groups; no effort was made to maintain a balance among treatment groups within a study center. No patient's treatment assignment was unblinded during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	SD-809

Arm description:

Patients underwent dose adjustment of SD-809 over the initial 6 weeks of treatment, starting treatment with SD-809 at 6 mg twice daily and titrating to a maximum total daily dose of 48 mg per day. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

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

Dosage and administration details:

A tablet formulation of SD 809 was administered with food twice daily, approximately 10 hours apart during the day.
Starting dose level was 6 mg BID and adjusted over the 6-week titration period. Weekly dose adjustments for insufficient dyskinesia control were limited to increments of 6 mg per day and all dose levels were administered in 2 divided doses. The maximum total daily dose of SD 809 was 48 mg per day, unless the patient was receiving a strong CYP2D6 inhibitor, in which case the maximum total daily dose was 36 mg. Once adequate control of dyskinesia was achieved, the dose of study drug was not to be increased further. The optimal dose was continued for an additional 6 weeks of maintenance therapy.

Arm title	Placebo

Arm description:

Patients underwent 'dose adjustment' of placebo over the initial 6 weeks of treatment. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

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-treated patients received tablets identical in appearance to the SD-809 tablets which were administered with food twice daily, approximately 10 hours apart during the day.
Doses were adjusted over the 6-week titration period. Once adequate control of dyskinesia was achieved, the dose of study drug was not to be increased further. The optimal dose was continued for an additional 6 weeks of maintenance therapy.

Number of subjects in period 1	SD-809	Placebo
Started	58	59
Safety population	58	59
ITT population	58	59
Modified ITT population	56	57
Maintenance period	53	54
Completed	52	52
Not completed	6	7
Consent withdrawn by subject	3	2
Adverse event, non-fatal	1	2
Lost to follow-up	1	1
Noncompliance	1	-
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	SD-809

Reporting group description:

Patients underwent dose adjustment of SD-809 over the initial 6 weeks of treatment, starting treatment with SD-809 at 6 mg twice daily and titrating to a maximum total daily dose of 48 mg per day. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

Reporting group title	Placebo

Reporting group description:

Patients underwent 'dose adjustment' of placebo over the initial 6 weeks of treatment. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

Reporting group values	SD-809	Placebo	Total
Number of subjects	58	59	117
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	55.9	53.3	
standard deviation	± 9.82	± 10.64	-
Gender categorical Units: Subjects			
Female	29	32	61
Male	29	27	56
Race Units: Subjects			
White	37	44	81
Black or African American	19	14	33
Asian	2	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	4	11	15
Not Hispanic or Latino	53	47	100
Not reported	1	1	2
Using a Dopamine Receptor Antagonist (DRA)			
The randomization was stratified by baseline use of DRA (currently taking versus not currently taking a DRA).			
Units: Subjects			
Yes	45	49	94
No	13	10	23
Education level Units: Subjects			

= 12 years of fewer of formal education	30	30	60
> 12 years of education	28	29	57

Weight			
Units: kg			
arithmetic mean	86.94	84.95	
standard deviation	± 24.081	± 20.975	-
Body Mass Index			
Units: kg/m^2			
arithmetic mean	30.35	29.45	
standard deviation	± 7.926	± 6.958	-
Duration of tardive dyskinesia			
Units: months			
arithmetic mean	72.6	76.8	
standard deviation	± 81.65	± 82.05	-
Centrally Read Abnormal Involuntary Movement Scale (AIMS) Score			
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. The AIMS examination was digitally video recorded using a standard protocol and independently reviewed by blinded central raters who were experts in movement disorders. This outcome sums items 1 through 7 which cover orofacial movements, as well as extremity and truncal dyskinesia. Ratings were based on a 5-point scale of severity from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), to 4 (severe) for a total scale of 0-28. n=58, 58			
Units: units on a scale			
arithmetic mean	9.6	9.6	
standard deviation	± 4.07	± 3.77	-
Height			
Units: cm			
arithmetic mean	169.23	169.72	
standard deviation	± 11.462	± 10.098	-
Modified Craniocervical Dystonia Questionnaire (CDQ-24)			
The CDQ-24 is a disease-specific quality of life questionnaire developed for use in patients 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. Each of the 24 questions was rated by patients on a scale of 0=no impairment to 4=severest impairment for a total scale of 0 – 96. n=58, 57			
Units: units on a scale			
arithmetic mean	38.4	39.7	
standard deviation	± 20.41	± 18.17	-

End points

End points reporting groups

Reporting group title	SD-809

Reporting group description:

Patients underwent dose adjustment of SD-809 over the initial 6 weeks of treatment, starting treatment with SD-809 at 6 mg twice daily and titrating to a maximum total daily dose of 48 mg per day. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

Reporting group title	Placebo

Reporting group description:

Patients underwent 'dose adjustment' of placebo over the initial 6 weeks of treatment. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

Subject analysis set title	SD-809 mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients underwent dose adjustment of SD-809 over the initial 6 weeks of treatment, starting treatment with SD-809 at 6 mg twice daily and titrating to a maximum total daily dose of 48 mg per day. The optimal dose was continued by a 6-week maintenance period.

The modified intention-to-treat (mITT) population was defined as all randomized patients who received study drug and had at least 1 centrally read postbaseline assessment of the AIMS from at least 1 scheduled postbaseline time point.

Subject analysis set title	Placebo mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients underwent 'dose adjustment' of placebo over the initial 6 weeks of treatment. The optimal dose was continued by a 6-week maintenance period.

The modified intention-to-treat (mITT) population was defined as all randomized patients who received study drug and had at least 1 centrally read postbaseline assessment of the AIMS from at least 1 scheduled postbaseline time point.

Primary: Change in Centrally Read Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Using Mixed Model Repeated Measures (MMRM) Analysis

End point title	Change in Centrally Read Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Using Mixed Model Repeated Measures (MMRM) Analysis

End point description:

AIMS is an assessment tool used to detect and follow the severity of TD over time. AIMS is composed of 12 clinician-administered and scored items. The exam was digitally video recorded using a standard protocol, and independently reviewed by blinded central raters who were experts in movement disorders.

This outcome sums items 1 through 7 which cover orofacial movements, as well as extremity and truncal dyskinesia. Ratings were based on a 5-point scale of severity from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), to 4 (severe) for a total scale of 0-28. A negative change from baseline score indicates improvement.

A MMRM analysis with change from baseline in AIMS score as dependent variable was used. The model included fixed effects for treatment, time point, treatment-by-time point interaction, DRA status, and baseline AIMS as a covariate. An unstructured covariance model was used.

End point type	Primary

End point timeframe:

Day 0 (Baseline), Weeks 2, 4, 6, 9 and 12

End point values	SD-809 mITT	Placebo mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	51		
Units: units on a scale				
least squares mean (standard error)	-3 (± 0.45)	-1.6 (± 0.46)		

Statistical analyses

Statistical analysis title	Change in AIMS to Week 12

Statistical analysis description:

The linear mixed model for repeated measurements (MMRM) included fixed effects for treatment, each scheduled time point (5 levels: weeks 2, 4, 6, 9, and 12), the treatment-by-time point interaction, and the DRA status. Baseline AIMS score was a covariate. The unstructured covariance model was used, and the primary analysis compared the SD-809 and placebo groups at week 12. This was based on the F-test using the Satterhwaite method to compute the denominator degrees of freedom.

Comparison groups	SD-809 mITT v Placebo mITT
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0188 [1]
Method	unstructured covariance
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[1] - 5% level of significance (2-sided)

Secondary: Percentage of Patients Who Are a Treatment Success at Week 12 as Assessed by the Clinical Global Impression of Change (CGIC)

End point title	Percentage of Patients Who Are a Treatment Success at Week 12 as Assessed by the Clinical Global Impression of Change (CGIC)

End point description:

The CGIC is a single-item questionnaire that asks the investigator to assess a patient's TD symptoms at specific visits after initiating therapy. The CGIC uses a 7 point Likert Scale, ranging from very much worse (–3) to very much improved (+3), to assess overall response to therapy.

A treatment success was defined as "much improved" or "very much improved" at the week 12 visit. Patients whose status at week 12 was not known, as well as patients who were not "much improved" or "very much improved" at the week 12 visit, were considered treatment failures.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	SD-809 mITT	Placebo mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: percentage of participants				
number (not applicable)	48.2	40.4		

Statistical analyses

Statistical analysis title	Trt Success at Week 12

Statistical analysis description:

The secondary efficacy endpoints were analyzed using a hierarchical testing procedure. If the primary analysis was statistically significant ($p<0.05$), then the first key secondary endpoint was to be analyzed. If the first key secondary endpoint was statistically significant, then the second key secondary endpoint was to be similarly analyzed. For any analysis that was not statistically significant, all subsequent analyses of key secondary endpoints were exploratory rather than confirmatory.

Comparison groups	SD-809 mITT v Placebo mITT
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4001 [2]
Method	Pearson's chi-square test
Parameter estimate	Differences in %
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	25.2

Notes:

[2] - 5% level of significance (2-sided)

Secondary: Percentage of Patients Who Are a Treatment Success at Week 12 as Assessed by the Patient Global Impression of Change (PGIC)

End point title	Percentage of Patients Who Are a Treatment Success at Week 12 as Assessed by the Patient Global Impression of Change (PGIC)

End point description:

The PGIC is a single-item questionnaire that asks the patient to assess their TD symptoms at specific visits after initiating therapy. The PGIC uses a 7 point Likert Scale, ranging from very much worse (–3) to very much improved (+3), to assess overall response to therapy.
A treatment success was defined as "much improved" or "very much improved" at the week 12 visit. Patients whose status at week 12 was not known, as well as patients who were not "much improved" or "very much improved" at the week 12 visit, were considered treatment failures.

End point type	Secondary

End point timeframe:

Week 12

End point values	SD-809 mITT	Placebo mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: units on a scale				
number (not applicable)	42.9	29.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in the Modified Craniocervical Dystonia Questionnaire (CDQ-24)

End point title	Change from Baseline to Week 12 in the Modified Craniocervical Dystonia Questionnaire (CDQ-24)

End point description:

The CDQ-24 is a disease-specific quality of life questionnaire developed for use in patients 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 are evaluated in the CDQ-24: stigma, emotional well-being, pain, activities of daily living, and social/family life. Each of the 24 questions were rated by patients on a scale of 0=no impairment to 4=severest impairment for a total scale of 0 – 96. Negative change from baseline scores indicate improvement.

End point type	Secondary

End point timeframe:

Day 0 (Baseline), Week 12 with last observation carried forward

End point values	SD-809 mITT	Placebo mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: units on a scale				
least squares mean (standard error)	-11.1 (± 2.14)	-8.3 (± 2.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Adverse Events for the Overall Treatment Period

End point title	Participants with Adverse Events for the Overall Treatment Period

End point description:

An adverse event 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. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relation of AE to treatment was determined by the investigator and includes possibly, probably and definitely related categories. Serious AEs (SAE) 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 patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	SD-809	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[3]	59[4]		
Units: patients				
Overall Treatment Period: any AE	41	36		
Overall Treatment Period: SAE	3	5		
Overall Treatment Period: Severe AE	3	3		
Overall Treatment Period: treatment-related AE	28	21		
Overall Treatment Period: Deaths	0	0		

Notes:

[3] - Safety population

[4] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	SD-809

Reporting group description:

Patients underwent dose adjustment of SD-809 over the initial 6 weeks of treatment, starting treatment with SD-809 at 6 mg twice daily and titrating to a maximum total daily dose of 48 mg per day. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

Reporting group title	Placebo

Reporting group description:

Patients underwent 'dose adjustment' of placebo over the initial 6 weeks of treatment. The optimal dose was continued by a 6-week maintenance period, which was followed by a 1-week washout. Patients who completed the study had the option to rollover into a long-term safety study (Study SD 809 C 20). For patients who did not enter the long-term safety study, there was an additional 3-week safety follow-up period after treatment.

Serious adverse events	SD-809	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 58 (6.90%)	6 / 59 (10.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Diagnostic procedure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			

subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal hypertrophy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SD-809	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 58 (41.38%)	26 / 59 (44.07%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	8 / 58 (13.79%)	6 / 59 (10.17%)	
occurrences (all)	8	8	
Headache			
subjects affected / exposed	4 / 58 (6.90%)	6 / 59 (10.17%)	
occurrences (all)	4	6	
Dizziness			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Akathisia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 58 (6.90%)	5 / 59 (8.47%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 58 (3.45%)	6 / 59 (10.17%)	
occurrences (all)	2	6	
Diarrhoea			
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	3	4	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	3	4	
Insomnia			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	
occurrences (all)	4	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 58 (3.45%)	4 / 59 (6.78%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2014	• Addition of video recording of AIMS assessment at week 2 • Addition of CGIC at week 2 • CDQ-24 endpoint reclassified as an additional secondary endpoint • Addition of sensitivity analyses • Addition of procedures for handling missing data
08 July 2014	• Title amended to provide a better description of the study • Expansion of the role of the independent monitoring committee to include monitoring of all data, including safety data • Modified excluded medications to better reflect medications likely to have significant interactions with SD-809 and/or directly oppose the effects of SD 809 based on known mechanism of action • Added additional guidance on specific excluded anticholinergics and stimulants • Removed exclusion of patients who previously did not respond to tetrabenazine or who discontinued tetrabenazine due to an AE that was considered related to tetrabenazine and was either moderate/severe in severity, or met criteria for an SAE • Added exclusion for participation in any previous study of SD 809 in which patients received SD-809 • Revised time frame for prior suicidality from 5 years to 6 months • Brief physical examination moved from screening visit to baseline visit • Specified that UPDRS III (motor), BARS, and ESS were to be performed at the investigator's discretion at unscheduled visits

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported