Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia

Summary

EudraCT number	2014-003135-19
Trial protocol	SK PL CZ HU DE
Global end of trial date	19 August 2016

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	SD-809-C-23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02291861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auspex Pharmaceuticals, Inc.
Sponsor organisation address	3333 N. Torrey Pines Court, Suite 400, La Jolla, California, United States, 92037
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.era-clinical@teva.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were:
- To evaluate the efficacy of fixed doses of SD-809 to reduce the severity of abnormal involuntary movements of TD
- To evaluate the safety and tolerability of fixed doses of SD-809 in patients with TD

Protection of trial subjects:

This study was conducted in full accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations 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).

Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP, and for collecting, recording, and reporting the data accurately and properly.

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	29 October 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	Czech Republic: 24
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Poland: 84
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	United States: 161

Worldwide total number of subjects	298
EEA total number of subjects	137

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)	226
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was performed at 75 study centers (38 in the US, 19 in Poland, 7 in Hungary, 6 in the Czech Republic, 3 in Slovakia, and 2 in Germany) by 75 investigators; 298 patients were enrolled.

Pre-assignment

Screening details:

Participants were randomly assigned in a 1:1:1:1 ratio to receive 1 of 3 fixed-dose regimens of SD-809 (deutetrabenazine) or placebo following a screening period.

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, Monitor

Blinding implementation details:

During the treatment period the sponsor, patients, as well as the investigators and their site personnel were blinded to treatment assignment.
Active and placebo study drug were identical in appearance and packaged in study drug kits according to the randomization code

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo tablets taken twice daily 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 tablets taken twice daily for 12 weeks. Tablets were swallowed whole with water and taken with food.

Arm title	SD-809 12 mg/day

Arm description:

SD-809 tablets 6 mg taken twice a day (BID) for 12 weeks.

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

Dosage and administration details:

SD-809 tablets dose titrated for 4 weeks until target randomized dose is reached. The dose is maintained for an additional 8 weeks. Tablets were swallowed whole with water and taken with food.

Arm title	SD-809 24 mg/day

Arm description:

SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 12 mg BID. The total daily dose of 24 mg was maintained for an additional 8 weeks.

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

Dosage and administration details:

SD-809 tablets dose titrated for 4 weeks until target randomized dose is reached. The dose is maintained for an additional 8 weeks. Tablets were swallowed whole with water and taken with food.

Arm title	SD-809 36 mg/day

Arm description:

SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 18 mg BID. The total daily dose of 36 mg was maintained for an additional 8 weeks.

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

Dosage and administration details:

SD-809 tablets dose titrated for 4 weeks until target randomized dose is reached. The dose is maintained for an additional 8 weeks. Tablets were swallowed whole with water and taken with food.

Number of subjects in period 1	Placebo	SD-809 12 mg/day	SD-809 24 mg/day
Started	74	75	74
Safety population	72	74	73
Completed	67	67	65
Not completed	7	8	9
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	1	2	1
Adverse event, non-fatal	2	4	1
Not specified	-	-	-
Lost to follow-up	2	1	4
Protocol deviation	1	-	-
Noncompliance	1	1	2

Number of subjects in period 1	SD-809 36 mg/day
Started	75
Safety population	74
Completed	65
Not completed	10
Adverse event, serious fatal	1
Consent withdrawn by subject	4
Adverse event, non-fatal	2

Not specified	1
Lost to follow-up	-
Protocol deviation	1
Noncompliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets taken twice daily for 12 weeks.	
Reporting group title	SD-809 12 mg/day
Reporting group description:	
SD-809 tablets 6 mg taken twice a day (BID) for 12 weeks.	
Reporting group title	SD-809 24 mg/day
Reporting group description:	
SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 12 mg BID. The total daily dose of 24 mg was maintained for an additional 8 weeks.	
Reporting group title	SD-809 36 mg/day
Reporting group description:	
SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 18 mg BID. The total daily dose of 36 mg was maintained for an additional 8 weeks.	

Reporting group values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day
Number of subjects	74	75	74
Age categorical Units: Subjects			
< 21 years	0	0	0
21 - 81 years	74	75	74
Age Continuous Units: years			
arithmetic mean	54.6	57.0	55.5
standard deviation	± 11.92	± 9.89	± 11.29
Sex: Female, Male Units: Subjects			
Female	37	42	42
Male	37	33	32
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	0	0	0
Black or African American	14	16	20
Native Hawaiian or Pacific Islander	0	0	0
White	59	58	54
Other	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or latino	7	6	3
Not hispanic or latino	66	65	70
Not reported	0	3	1
Unknown	1	1	0
Education Level Units: Subjects			
<= 12 years	41	45	44

> 12 years	33	30	30
Use of a Dopamine Receptor Antagonist			
The randomization was stratified by baseline use of DRA (currently taking versus not currently taking a DRA).			
Units: Subjects			
Yes - Use of DRA	58	57	58
No Use of DRA	16	18	16
Weight			
Units: kg			
arithmetic mean	82.5	80.9	86.8
standard deviation	± 18.52	± 20.87	± 18.66
Height			
Units: cm			
arithmetic mean	168.5	168.0	168.5
standard deviation	± 9.18	± 10.93	± 9.43
Body Mass Index			
Units: kg/m^2			
arithmetic mean	29.04	28.63	30.71
standard deviation	± 6.158	± 6.791	± 6.992
Time Since Tardive Dyskinesia (TD) Diagnosis			
Units: years			
arithmetic mean	5.98	5.49	4.93
standard deviation	± 5.291	± 5.389	± 6.012
Total Motor 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. Total Motor assessment 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.			
Units: units on a scale			
arithmetic mean	8.6	8.5	7.6
standard deviation	± 3.24	± 3.18	± 3.50
Modified Craniocervical Dystonia Questionnaire (mCDQ-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.			
Units: units on a scale			
arithmetic mean	40.9	36.8	34.4
standard deviation	± 19.90	± 20.36	± 19.45

Reporting group values	SD-809 36 mg/day	Total	
Number of subjects	75	298	
Age categorical			
Units: Subjects			
< 21 years	0	0	
21 - 81 years	75	298	
Age Continuous			
Units: years			
arithmetic mean	58.2		
standard deviation	± 11.48	-	

Sex: Female, Male Units: Subjects			
Female	42	163	
Male	33	135	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	2	4	
Asian	0	0	
Black or African American	10	60	
Native Hawaiian or Pacific Islander	0	0	
White	61	232	
Other	2	2	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or latino	8	24	
Not hispanic or latino	65	266	
Not reported	1	5	
Unknown	1	3	
Education Level Units: Subjects			
<= 12 years	40	170	
> 12 years	35	128	
Use of a Dopamine Receptor Antagonist			
The randomization was stratified by baseline use of DRA (currently taking versus not currently taking a DRA).			
Units: Subjects			
Yes - Use of DRA	54	227	
No Use of DRA	21	71	
Weight Units: kg			
arithmetic mean	78.5		
standard deviation	± 17.45	-	
Height Units: cm			
arithmetic mean	167.7		
standard deviation	± 10.52	-	
Body Mass Index Units: kg/m^2			
arithmetic mean	27.97		
standard deviation	± 6.138	-	
Time Since Tardive Dyskinesia (TD) Diagnosis Units: years			
arithmetic mean	6.23		
standard deviation	± 6.059	-	
Total Motor 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. Total Motor assessment 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.			
Units: units on a scale			

arithmetic mean	8.6		
standard deviation	± 3.82	-	
Modified Craniocervical Dystonia Questionnaire (mCDQ-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.			
Units: units on a scale			
arithmetic mean	34.8		
standard deviation	± 18.23	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo tablets taken twice daily for 12 weeks.	
Reporting group title	SD-809 12 mg/day
Reporting group description:	
SD-809 tablets 6 mg taken twice a day (BID) for 12 weeks.	
Reporting group title	SD-809 24 mg/day
Reporting group description:	
SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 12 mg BID. The total daily dose of 24 mg was maintained for an additional 8 weeks.	
Reporting group title	SD-809 36 mg/day
Reporting group description:	
SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 18 mg BID. The total daily dose of 36 mg was maintained for an additional 8 weeks.	

Primary: Change in Total Motor Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Using a Mixed Model For Repeated Measures (MMRM)

End point title	Change in Total Motor Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Using a Mixed Model For Repeated Measures (MMRM)
End point description:	
AIMS is an assessment tool used to detect and follow the severity of tardive dyskinesia (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 (the total motor AIMS score). 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. MMRM with treatment group, visit, treatment group-by-visit interaction, and baseline use of dopamine receptor antagonist (DRAs) as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.	
End point type	Primary
End point timeframe:	
Day 0 (Baseline), Weeks 2, 4, 8 and 12	

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56[1]	53[2]	45[3]	52[4]
Units: units on a scale				
least squares mean (standard error)	-1.4 (± 0.41)	-2.1 (± 0.42)	-3.2 (± 0.45)	-3.3 (± 0.42)

Notes:

[1] - mITT Population
Participants with baseline and during-study readings through Week 12
[2] - mITT Population
Participants with baseline and during-study readings through Week 12

[3] - mITT Population
Participants with baseline and during-study readings through Week 12
[4] - mITT Population
Participants with baseline and during-study readings through Week 12

Statistical analyses

Statistical analysis title	Placebo, SD-809 36 mg/Day

Statistical analysis description:

A hierarchical (fixed-sequence) testing approach was used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. The primary endpoint compared the change in total motor AIMS score from baseline to week 12 between the SD-809 36 mg/day group and the placebo group.

Comparison groups	Placebo v SD-809 36 mg/day
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [5]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	-0.79

Notes:

[5] - Treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Statistical analysis title	Placebo, SD-809 24 mg/Day

Statistical analysis description:

A hierarchical (fixed-sequence) testing approach was used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. This key secondary endpoint compared the change in total motor AIMS score from baseline to week 12 between the SD-809 24 mg/day group and the placebo group, and is the third analysis in the fixed-sequence.

Comparison groups	Placebo v SD-809 24 mg/day
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [6]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-0.63

Notes:

[6] - Treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Statistical analysis title	Placebo, SD-809 12 mg/Day

Statistical analysis description:

A hierarchical (fixed-sequence) testing approach was used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. This key secondary endpoint compared the change in total motor AIMS score from baseline to week 12 between the SD-809 12 mg/day group and the placebo group, and is the fifth analysis in the fixed-sequence.

Comparison groups	Placebo v SD-809 12 mg/day
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.217 [7]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.84
upper limit	0.42

Notes:

[7] - Treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

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

End point title	Percentage of Patients Considered 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. The success 95% confidence interval (CI) was calculated with the Wilson (score) confidence limits.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[8]	60[9]	49[10]	55[11]
Units: percentage of participants				
number (confidence interval 95%)	26 (16.3 to 38.4)	28 (18.5 to 40.8)	49 (35.6 to 62.5)	44 (31.4 to 56.7)

Notes:

[8] - mITT population

[9] - mITT population

[10] - mITT population

[11] - mITT population

Statistical analyses

Statistical analysis title	Placebo, SD-809 36 mg/Day

Statistical analysis description:

A hierarchical (fixed-sequence) testing approach was used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. This key secondary endpoint compared the percentage of patients considered a treatment success at week 12 between the SD-809 36 mg/day group and the placebo group, and is the second analysis in the fixed-sequence.

Comparison groups	Placebo v SD-809 36 mg/day
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	4.645

Notes:

[12] - The statistical test was a Cochran-Mantel-Haenszel (CMH) test stratified by baseline use of dopamine receptor antagonist (DRAs).

Statistical analysis title	Placebo, SD-809 24 mg/Day

Statistical analysis description:

A hierarchical (fixed-sequence) testing approach was used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. This key secondary endpoint compared the percentage of patients considered a treatment success at week 12 between the SD-809 24 mg/day group and the placebo group, and is the fourth analysis in the fixed-sequence.

Comparison groups	Placebo v SD-809 24 mg/day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.211
upper limit	6.052

Notes:

[13] - The statistical test was a CMH test stratified by baseline use of DRAs.

Statistical analysis title	Placebo, SD-809 12 mg/Day

Statistical analysis description:

A hierarchical (fixed-sequence) testing approach was used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. This key secondary endpoint compared the percentage of patients considered a treatment success at week 12 between the SD-809 12 mg/day group and the placebo group, and is the sixth (last) analysis in the fixed-sequence.

Comparison groups	Placebo v SD-809 12 mg/day
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.734 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.509
upper limit	2.61

Notes:

[14] - The statistical test was a CMH test stratified by baseline use of DRAs.

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

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

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 mCDQ-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. For patients with missing data at week 12, the baseline or last available value was used as the week 12 value.

End point type	Secondary

End point timeframe:

Day 0 (Baseline), Week 12

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[15]	59[16]	49[17]	55[18]
Units: units on a scale				
least squares mean (standard error)	-7.1 (± 2.06)	-5.8 (± 2.03)	-10.2 (± 2.21)	-10.7 (± 2.04)

Notes:

[15] - mITT Population

[16] - mITT Population
One participant was missing a baseline mCDQ-24.

[17] - mITT Population

[18] - mITT Population

Statistical analyses

Statistical analysis title	Placebo, SD-809 36 mg/Day
Comparison groups	Placebo v SD-809 36 mg/day
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.207 [19]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.18
upper limit	2

Notes:

[19] - 5% level of significance (2-sided)
ANCOVA with treatment group and baseline use of DRAs as fixed effects and the baseline value as a covariate.

Statistical analysis title	Placebo, SD-809 24 mg/Day
Comparison groups	Placebo v SD-809 24 mg/day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281 [20]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.86
upper limit	2.59

Notes:

[20] - 5% level of significance (2-sided)
ANCOVA with treatment group and baseline use of DRAs as fixed effects and the baseline value as a covariate.

Statistical analysis title	Placebo, SD-809 12 mg/Day
Comparison groups	Placebo v SD-809 12 mg/day
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627 [21]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	6.79

Notes:

[21] - 5% level of significance (2-sided)
ANCOVA with treatment group and baseline use of DRAs as fixed effects and the baseline value as a covariate.

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

End point title	Percentage of Patients Considered 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. The success 95% CI was calculated with the Wilson (score) confidence limits.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[22]	60[23]	49[24]	55[25]
Units: percentage of participants				
number (confidence interval 95%)	31 (20.6 to 43.8)	23 (14.4 to 35.4)	45 (31.9 to 58.7)	40 (28.1 to 53.2)

Notes:

[22] - mITT population

[23] - mITT population

[24] - mITT population

[25] - mITT population

Statistical analyses

Statistical analysis title	Placebo, SD-809 36 mg/Day
Comparison groups	Placebo v SD-809 36 mg/day
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.296 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.694
upper limit	3.285

Notes:

[26] - 5% level of significance (2-sided)
CMH test stratified by baseline use of DRAs.

Statistical analysis title	Placebo, SD-809 24 mg/Day
Comparison groups	Placebo v SD-809 24 mg/day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 [27]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.826
upper limit	3.994

Notes:

[27] - 5% level of significance (2-sided)
CMH test stratified by baseline use of DRAs.

Statistical analysis title	Placebo, SD-809 12 mg/Day
Comparison groups	Placebo v SD-809 12 mg/day
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.302
upper limit	1.563

Notes:

[28] - 5% level of significance (2-sided)
CMH test stratified by baseline use of DRAs.

Secondary: Percentage of Participants Who Had a 50% or Greater Reduction in Total Motor Abnormal Involuntary Movement Scale (AIMS) From Baseline to Week 12

End point title	Percentage of Participants Who Had a 50% or Greater Reduction in Total Motor Abnormal Involuntary Movement Scale (AIMS) From Baseline to Week 12

End point description:

Responders who had a 50% or greater improvement in total motor modified AIMS at Week 12 as compared to baseline were reported as a percentage of participants with an outcome at Week 12. The responder 95% CI is calculated with the Wilson (score) confidence limits. 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 (the total motor AIMS score). 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.

End point type	Secondary
End point timeframe:	
Day 0 (Baseline), Week 12	

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[29]	60[30]	49[31]	55[32]
Units: percentage of participants				
number (confidence interval 95%)	12 (6.0 to 22.9)	13 (6.9 to 24.2)	35 (22.9 to 48.7)	33 (21.8 to 45.9)

Notes:

[29] - mITT population.
Participants with missing Week 12 data were considered non-responders.
[30] - mITT population.
Participants with missing Week 12 data were considered non-responders.
[31] - mITT population.
Participants with missing Week 12 data were considered non-responders.
[32] - mITT population.
Participants with missing Week 12 data were considered non-responders.

Statistical analyses

Statistical analysis title	Placebo, SD-809 36 mg/Day
Comparison groups	Placebo v SD-809 36 mg/day
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [33]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.395
upper limit	10.359

Notes:

[33] - 5% level of significance (2-sided)
CMH test stratified by baseline use of DRAs.

Statistical analysis title	Placebo, SD-809 24 mg/Day
Comparison groups	Placebo v SD-809 24 mg/day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [34]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	10.716

Notes:

[34] - 5% level of significance (2-sided)
CMH test stratified by baseline use of DRAs.

Statistical analysis title	Placebo, SD-809 12 mg/Day
Comparison groups	Placebo v SD-809 12 mg/day
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.829 [35]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.383
upper limit	3.316

Notes:

[35] - 5% level of significance (2-sided)
CMH test stratified by baseline use of DRAs.

Secondary: Percent Change in Total Motor Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Using a Mixed Model for Repeated Measures (MMRM)

End point title	Percent Change in Total Motor Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Using a Mixed Model for Repeated Measures (MMRM)

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 (the total motor AIMS score). 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. MMRM with treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

End point type	Secondary

End point timeframe:

Day 0 (Baseline), Weeks 2, 4, 8 and 12

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56[36]	53[37]	45[38]	52[39]
Units: percentage of baseline				
least squares mean (standard error)	-11.6 (± 4.32)	-20.0 (± 4.34)	-31.9 (± 4.73)	-33.1 (± 4.38)

Notes:

[36] - mITT population; participants with baseline and data through Week 12 are included.

[37] - mITT population; participants with baseline and data through Week 12 are included.

[38] - mITT population; participants with baseline and data through Week 12 are included.

[39] - mITT population; participants with baseline and data through Week 12 are included.

Statistical analyses

Statistical analysis title	Placebo, SD-809 36 mg/Day
Comparison groups	Placebo v SD-809 36 mg/day
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [40]
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-21.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.44
upper limit	-9.52

Notes:

[40] - 5% level of significance (2-sided). Treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Statistical analysis title	Placebo, SD-809 24 mg/Day
Comparison groups	Placebo v SD-809 24 mg/day
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [41]
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-20.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.57
upper limit	-7.92

Notes:

[41] - 5% level of significance (2-sided). Treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Statistical analysis title	Placebo, SD-809 12 mg/Day
Comparison groups	Placebo v SD-809 12 mg/day

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16 [42]
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.15
upper limit	3.34

Notes:

[42] - 5% level of significance (2-sided). Treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Secondary: Cumulative Percentage of Responders Based on Change in in Total Motor Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Recorded in Incremental Steps of 10 Percentage Points

End point title	Cumulative Percentage of Responders Based on Change in in Total Motor Abnormal Involuntary Movement Scale (AIMS) Score from Baseline to Week 12 Recorded in Incremental Steps of 10 Percentage Points

End point description:

AIMS is an assessment tool used to detect and follow the severity of TD over time, 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 (the total motor AIMS score). 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. Participants with missing data are classified as non-responders. The responder 95% CI is calculated with the Wilson (score) confidence limits. If any of the expected cell counts are < 5, exact Clopper Pearson limits are presented. Data report the percentage of participants who responded to the percentage improvement indicated in each row.

End point type	Secondary

End point timeframe:

Day 0 (Baseline), Week 12

End point values	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[43]	60[44]	49[45]	55[46]
Units: percentage of participants				
number (confidence interval 95%)				
10% Improvement|	50 (37.5 to 62.5)	62 (49.0 to 72.9)	67 (53.4 to 78.8)	71 (57.9 to 81.2)
20% Improvement|	40 (28.1 to 52.5)	47 (34.6 to 59.1)	59 (45.2 to 71.8)	60 (46.8 to 71.9)
30% Improvement|	31 (20.6 to 43.8)	32 (21.3 to 44.2)	49 (35.6 to 62.5)	49 (36.4 to 61.9)
40% Improvement|	16 (8.4 to 26.9)	23 (14.4 to 35.4)	45 (31.9 to 58.7)	40 (28.1 to 53.2)
50% Improvement|	12 (6.0 to 22.9)	13 (6.9 to 24.2)	35 (22.9 to 48.7)	33 (21.8 to 45.9)

60% Improvement|	5 (1.8 to 14.1)	7 (2.6 to 15.9)	20 (11.5 to 33.6)	18 (10.2 to 30.3)
70% Improvement|	2 (0.0 to 9.2)	3 (0.4 to 11.5)	12 (4.6 to 24.8)	16 (7.8 to 28.8)
80% Improvement|	2 (0.0 to 9.2)	2 (0.0 to 8.9)	2 (0.1 to 10.9)	13 (5.3 to 24.5)
90% Improvement|	2 (0.0 to 9.2)	0 (0.0 to 6.0)	0 (0.0 to 7.3)	5 (1.1 to 15.1)

Notes:

[43] - mITT population

[44] - mITT population

[45] - mITT population

[46] - mITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Adverse Events During the Overall Treatment Period

End point title	Participants with Adverse Events During 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	Placebo	SD-809 12 mg/day	SD-809 24 mg/day	SD-809 36 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[47]	74[48]	73[49]	74[50]
Units: participants				
Overall Treatment Period: any AE|	34	36	32	38
Overall Treatment Period: SAE|	4	2	6	4
Overall Treatment Period: Severe AE|	2	2	4	1
Overall Treatment Period: treatment-related AE|	19	13	11	18
Dose reduction because of AE|	0	0	1	3
Dose suspension because of AE|	2	3	1	1
Withdrawn from study because of AE|	2	4	2	3

Notes:

[47] - Safety population

[48] - Safety population

[49] - Safety population

[50] - 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 12 mg/day
Reporting group description:	
SD-809 tablets 6 mg taken twice a day (BID) for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets taken twice daily for 12 weeks.	
Reporting group title	SD-809 24 mg/day
Reporting group description:	
SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 12 mg BID. The total daily dose of 24 mg was maintained for an additional 8 weeks.	
Reporting group title	SD-809 36 mg/day
Reporting group description:	
SD-809 tablets dose starting at 6 mg twice a day (BID) and titrated over 4 weeks to 18 mg BID. The total daily dose of 36 mg was maintained for an additional 8 weeks.	

Serious adverse events	SD-809 12 mg/day	Placebo	SD-809 24 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 74 (2.70%)	4 / 72 (5.56%)	6 / 73 (8.22%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	1 / 74 (1.35%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Head injury			
subjects affected / exposed	0 / 74 (0.00%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skeletal injury			
subjects affected / exposed	1 / 74 (1.35%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Alcohol interaction			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic mass			

subjects affected / exposed	0 / 74 (0.00%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 74 (1.35%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SD-809 36 mg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 74 (5.41%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skeletal injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Alcohol interaction				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic mass				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Bipolar disorder				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 74 (1.35%)		
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	SD-809 12 mg/day	Placebo	SD-809 24 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 74 (12.16%)	14 / 72 (19.44%)	9 / 73 (12.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 74 (6.76%)	4 / 72 (5.56%)	2 / 73 (2.74%)
occurrences (all)	7	4	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 74 (1.35%)	2 / 72 (2.78%)	3 / 73 (4.11%)
occurrences (all)	1	2	4
Nausea			
subjects affected / exposed	1 / 74 (1.35%)	7 / 72 (9.72%)	1 / 73 (1.37%)
occurrences (all)	1	8	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 74 (5.41%)	1 / 72 (1.39%)	3 / 73 (4.11%)
occurrences (all)	4	1	3

Non-serious adverse events	SD-809 36 mg/day		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	10 / 74 (13.51%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 5 / 74 (6.76%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 5 / 74 (6.76%) 6 1 / 74 (1.35%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 74 (2.70%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2014	Amendment 1 (dated 28 August 2014) was issued before the enrollment period began; no patients were enrolled into the study while this amendment was in effect. - Removal of video recording of AIMS assessment at week 13 - Measurement of orthostatic BP and pulse to be performed after the patient was in the supine position for at least 5 minutes and the standing position for at least 3 minutes - Change of timing of blood sampling for pharmacokinetic assessments to include scheduled visits at weeks 8 and 12 only - Requirement of a 12-lead ECG for all patients, regardless of the use of drugs that prolong the QT interval, at weeks 2, 4, and 8 - Clarification that dose suspensions or decreases for patients who experienced an adverse event or clinically significant adverse event were to be made by the investigator - Removal of the interactive web response system as the mechanism for randomization, change of doses, and re-ordering of study drug - Addition of IRT for randomization and dose changes - Modified to allow study drug to only be dispensed at clinic visits (a 2-week supply at baseline and week 2, a 4-week supply at week 4 and week 8, and a new supply for dose reductions as needed at unscheduled visits) - Removal of a maximal dose of SD-809 of 36 mg/day (or matching placebo) for patients receiving strong CYP2D6 inhibitors
15 September 2014	Amendment 2 (dated 15 September 2014) also was issued before any patients were enrolled into the study; all patients enrolled while this amendment was in effect. - Removal of AIMS at week 13 - HADS and C-SSRS required at unscheduled visits - Addition of the following assessments at the investigator's discretion at unscheduled visits, if required: AIMS, video recording of AIMS, CGIC, PGIC, MoCA, mCDQ-24, assessment of study drug accountability and compliance and collection of all study drug if a dose reduction is required (maintenance period only), and provide diary card and remind patients to complete their diary card and bring to their next clinic visit (if unscheduled visit is replacing the week 4 or week 8 visits) - Addition of the following laboratory tests at the investigator's discretion at unscheduled visits, if required: UDS, pregnancy test (women of childbearing potential only), virology screen (HBsAg), and prothrombin time (with INR)
29 October 2015	Amendment 3 was approved on 29 October 2015; 102 patients enrolled into the study while this amendment was in effect. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study at that time. - Increase in the number of study sites from approximately 60 to approximately 75 and the number of patients from approximately 200 to approximately 288 - Increase in the upper limit of age for inclusion in the study to 80 years of age - Clarification that patients with a positive UDS were not excluded if they had a valid corresponding prescription for a medical condition - Removal of blinded interim analysis of variability - Change from co-primary analyses to a single primary analysis using a 2-sided test at the alpha=0.05 level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28668671