Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

Summary

EudraCT number	2018-003742-17
Trial protocol	GB DK PL ES IT
Global end of trial date	21 July 2022

Results information

Result version number	v2 (current)
This version publication date	27 October 2023
First version publication date	07 February 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	TV50717-CNS-30080

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, USMedInfo@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, USMedInfo@tevapharm.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2022
Global end of trial reached?	Yes
Global end of trial date	21 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of TEV-50717 to reduce the severity of dyskinetic involuntary movements associated with CP.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2019
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	United States: 8
Country: Number of subjects enrolled	Ukraine: 14
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Denmark: 2
Worldwide total number of subjects	63
EEA total number of subjects	22

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)	37
Adolescents (12-17 years)	23
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants received oral tablets once daily for up to 15 weeks (7 weeks dose titration and 8 weeks maintenance). From Week 1 through Week 7, the dose of TEV-50717 was adjusted as determined by the investigator. After titration, participants continued to receive their maintenance dose over the next 8 weeks.

Pre-assignment

Screening details:

63 participants with Dyskinesia in Cerebral Palsy (DCP) were randomized (41 participants in the TEV-50717 group and 22 participants in the placebo group).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo administered as oral tablets once daily for up to 15 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

Arm title	TEV-50717

Arm description:

TEV-50717 administered as oral tablets once daily for up to 15 weeks (7 weeks dose titration and 8 weeks maintenance). From Week 1 through Week 7, the dose of TEV-50717 was adjusted according to the titrations scheme (based on body weight and CYP2D6 impairment status at baseline) to identify a dose level that optimally reduced dyskinesia (as determined by the investigator, as indicated by a reduction in the ClinRO of the assessment of the CGI-I) and was well tolerated. After titration, participants continued to receive their maintenance dose over the next 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Deutetrabenazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage ranging from 6 mg to 48 mg

Number of subjects in period 1	Placebo	TEV-50717
Started	22	41
Received at least 1 dose of study drug	22	40
Modified intent-to-treat analysis set	21	40
Completed	21	30
Not completed	1	11
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	6
Other than specified	1	2
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo administered as oral tablets once daily for up to 15 weeks.	
Reporting group title	TEV-50717
Reporting group description:	
TEV-50717 administered as oral tablets once daily for up to 15 weeks (7 weeks dose titration and 8 weeks maintenance). From Week 1 through Week 7, the dose of TEV-50717 was adjusted according to the titrations scheme (based on body weight and CYP2D6 impairment status at baseline) to identify a dose level that optimally reduced dyskinesia (as determined by the investigator, as indicated by a reduction in the ClinRO of the assessment of the CGI-I) and was well tolerated. After titration, participants continued to receive their maintenance dose over the next 8 weeks.	

Reporting group values	Placebo	TEV-50717	Total
Number of subjects	22	41	63
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	13	24	37
Adolescents (12-17 years)	8	15	23
Adults (18-64 years)	1	2	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	11.5	11.3	
standard deviation	± 3.98	± 3.14	-
Sex: Female, Male Units: participants			
Female	10	12	22
Male	12	29	41
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	20	36	56
Unknown or Not Reported	1	2	3
Race/Ethnicity, Customized Units: Subjects			
White	21	40	61
Other	1	1	2
MD-CRS Part II Total Score (Movement Disorder Severity, Centrally Read)			
MD-CRS part II evaluates the severity of movement disorder in a scale of 0 to 4 in 7 body regions, where 0 = absence of a movement disorder and 4 = movement disorder is present during all tasks for the region examined and/or involves 3 or more of other regions. The 7 body regions are eye and			

periorbital region, face, tongue and perioral region, neck, trunk, upper limb, and lower limb. Total score was obtained by summing the individual items scores and ranges from 0 (absent of a movement disorder) to 28 (marked/prolonged movement disorder), with higher scores indicating more movement disorder.			
Units: units on a scale			
arithmetic mean	10.4	11.7	
standard deviation	± 6.09	± 6.85	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo administered as oral tablets once daily for up to 15 weeks.	
Reporting group title	TEV-50717
Reporting group description:	
TEV-50717 administered as oral tablets once daily for up to 15 weeks (7 weeks dose titration and 8 weeks maintenance). From Week 1 through Week 7, the dose of TEV-50717 was adjusted according to the titrations scheme (based on body weight and CYP2D6 impairment status at baseline) to identify a dose level that optimally reduced dyskinesia (as determined by the investigator, as indicated by a reduction in the ClinRO of the assessment of the CGI-I) and was well tolerated. After titration, participants continued to receive their maintenance dose over the next 8 weeks.	

Primary: Change From Baseline in the Movement Disorder-Childhood Rating Scale (MD-CRS) Part II Total Score (Movement Disorder Severity, Centrally Read) at Week 15

End point title	Change From Baseline in the Movement Disorder-Childhood Rating Scale (MD-CRS) Part II Total Score (Movement Disorder Severity, Centrally Read) at Week 15
End point description:	
MD-CRS part II evaluates the severity of movement disorder in a scale of 0 to 4 in 7 body regions, all areas in which dyskinesia can be seen. In rating the movement disorder, 0 refers to absence of a movement disorder and 4 refers to a situation where movement disorder is present during all the tasks for the region examined and/or involves 3 or more of other regions, making completion impossible. The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and perioral region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb. Total score was obtained by summing the individual items scores and ranges from 0 (absent of a movement disorder) to 28 (marked/prolonged movement disorder), with higher scores indicating more movement disorder. Least square (LS) mean and standard error (SE) was calculated using a mixed-model repeated-measure (MMRM). mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment.	
End point type	Primary
End point timeframe:	
Baseline, Week 15	

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 1.09)	-1.5 (± 0.88)		

Statistical analyses

Statistical analysis title	LS mean of the change in MDCRS part II total score
Statistical analysis description:	
The LS mean of the change in MDCRS part II total score from baseline to Week 15 was compared (TEV-50717 arm versus placebo) using a 1-sided test for superiority at a nominal significance level of α=0.	

025.

Comparison groups	Placebo v TEV-50717
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.335
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	1.19

Secondary: Change From Baseline in the MD-CRS Part I Total Score (General Assessment, Centrally Read) at Week 15

End point title	Change From Baseline in the MD-CRS Part I Total Score (General Assessment, Centrally Read) at Week 15

End point description:

The MD-CRS part I evaluates the impact of dyskinesia in cerebral palsy (DCP) on the activities of the participant and provides a general assessment of the movement disorder of motor function (7 items), oral/verbal function (3 items), self-care (3 items), and attention/alertness (2 items) on a scale of 0 (present) to 4 (absent). All items were scored by the rater in the clinic and were centrally read based on video recording. The total score was obtained by summing the individual items scores and ranges from 0 (marked/prolonged disorder) to 60 (absent of a disorder), with higher scores indicating lesser disorder. he mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.8 (± 2.51)	-0.7 (± 2.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Caregiver Global Impression of Improvement (CaGI-I) Scale Score (Global, Caregiver Rated) at Week 15

End point title	Caregiver Global Impression of Improvement (CaGI-I) Scale Score (Global, Caregiver Rated) at Week 15

End point description:

The CaGI-I is single item questionnaire to assess the caregiver's impression of improvement in dyskinesia symptoms after initiating therapy. The scale is a caregiver-reported outcome that aims to evaluate all aspects of participants' health and determine if there has been an overall improvement or not in dyskinesia symptoms. The caregiver selected the 1 response from the response options that gave the most accurate description of change in dyskinesia symptoms of the participant they cared for from the beginning of the study: 1=very much improved (since the initiation of treatment); 2=much improved; 3=minimally improved; 4=no change from baseline (symptoms remain essentially unchanged); 5=minimally worse; 6=much worse; 7=very much worse (since the initiation of treatment). The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: units on a scale				
arithmetic mean (standard deviation)	3.3 (± 0.83)	3.3 (± 0.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD) Score (Centrally Read) at Week 15

End point title	Change From Baseline in Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD) Score (Centrally Read) at Week 15

End point description:

The UHDRS-TMD is part of the UHDRS-TMS assessment and assesses the severity of dystonia in the 5 body parts: trunk and the 4 extremities (right and left upper extremities, right and left lower extremities). Each part was rated from 0 (absent) to 4 (prolonged). The central rating was done for all participants, based on the videos collected for the central rating of MD-CRS. The TMD score was obtained by adding up each of the separate scores and ranged from 0 (absent) to 20 (marked/prolonged), with higher scores indicating the worse symptoms. The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.6 (± 1.46)	-0.2 (± 1.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC) Score (Centrally Read) at Week 15

End point title	Change From Baseline in Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC) Score (Centrally Read) at Week 15

End point description:

The UHDRS-TMC is part of the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) assessment and assesses the severity of chorea in the 7 body parts: face, mouth, trunk, and the 4 extremities (right and left upper extremities, right and left lower extremities). Each part was rated from 0 (absent) to 4 (prolonged). The central rating was done for all participants, based on the videos collected for the central rating of MD-CRS. The TMC score was obtained by adding up each of the separate scores and ranged from 0 (absent) to 28 (marked/prolonged), with higher scores indicating the worse symptoms. The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: units on a scale				
arithmetic mean (standard deviation)	0.3 (± 2.87)	-1.2 (± 2.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Improvement (CGI-I) Scale Score (Global, Physician Rated) at Week 15

End point title	Clinical Global Impression of Improvement (CGI-I) Scale Score (Global, Physician Rated) at Week 15

End point description:

CGI-I is a clinician-reported outcome that uses a 7-point Likert scale to compare participant's condition at the visit to the baseline condition: 1=very much improved (nearly all better; good level of functioning; minimal symptoms); 2=much improved (notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain); 3=minimally improved

(slightly better with little or no clinically meaningful reduction of symptoms; represents very little change in basic clinical status, level of care, or functional capacity); 4=no change from baseline (symptoms remain unchanged); 5=minimally worse (slightly worse but may not be clinically meaningful); 6=much worse (clinically significant increase in symptoms and diminished functioning); 7=very much worse (severe exacerbation of symptoms and loss of functioning). The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: units on a scale				
arithmetic mean (standard deviation)	3.5 (± 0.87)	3.4 (± 0.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in MD-CRS Global Index Score (Calculated From MD-CRS Parts I and II Total Scores, Centrally Read) at Week 15

End point title	Change From Baseline in MD-CRS Global Index Score (Calculated From MD-CRS Parts I and II Total Scores, Centrally Read) at Week 15

End point description:

MD-CRS Global Index consolidates the information from MD-CRS parts I and II using the method of weighted means of the 2 normalized indexes obtained from each part. Standardized/normalized score for each item of MD-CRS parts I and II with value X calculated using formula: Xst = X – Xmin divided by Xmax – Xmin, where Xmax is the maximum value, and Xmin is the minimum value for the score, or 4 and 0 respectively. Normalized index, MD-CRS parts I or II, Index I or II, calculated as the mean value of Xst. MD-CRS Global index = n1 * index 1 + n2 * index 2 divided by n1 + n2, where n1 and n2 are the numbers of items in MD-CRS parts I and II respectively. The minimum score is 0 (better) and the maximum score is 1 (worse). A higher score indicates more severe movement disorder. mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.0 (± 0.08)	-0.0 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the MD-CRS Part I Total Score (General Assessment, Physician Rated) at Week 15

End point title	Change From Baseline in the MD-CRS Part I Total Score (General Assessment, Physician Rated) at Week 15

End point description:

The MD-CRS part I evaluates the impact of DCP on the activities of the participant and provides a general assessment of the movement disorder of motor function (7 items), oral/verbal function (3 items), self-care (3 items), and attention/alertness (2 items) on a scale of 0 (present) to 4 (absent). All items were scored by the investigational center physician. The total score was obtained by summing the individual items scores and ranges from 0 (marked/prolonged movement disorder) to 60 (absent of a movement disorder), with higher scores indicating lesser movement disorder. The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.7 (± 3.21)	-1.0 (± 3.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the MD-CRS Part II Total Score (General Assessment, Physician Rated) at Week 15

End point title	Change From Baseline in the MD-CRS Part II Total Score (General Assessment, Physician Rated) at Week 15

End point description:

MD-CRS part II evaluates the severity of movement disorder in a scale of 0 to 4 in 7 body regions, all areas in which dyskinesia can be seen. In rating the movement disorder, 0 refers to absence of a movement disorder and 4 refers to a situation where movement disorder is present during all of the tasks for the region examined and/or involves 3 or more of the other regions, making completion impossible. The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and perioral region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb. Total score was obtained by summing the individual items scores and ranges from 0 (absent of a movement disorder) to 28 (marked/prolonged movement disorder), with higher scores indicating more movement disorder. mITT

analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.5 (± 3.20)	-2.4 (± 3.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in MD-CRS Global Index Score (Calculated From MD-CRS Parts I and II Total Scores, Physician Rated) at Week 15

End point title	Change From Baseline in MD-CRS Global Index Score (Calculated From MD-CRS Parts I and II Total Scores, Physician Rated) at Week 15

End point description:

MD-CRS Global Index consolidates the information from MD-CRS parts I and II using the method of weighted means of 2 normalized indexes obtained from each part. Standardized/normalized score for each item of MD-CRS parts I and II with value X calculated using formula: Xst = X – Xmin divided by Xmax – Xmin, where Xmax is the maximum value, and Xmin is the minimum value for the score, or 4 and 0 respectively. Normalized index, MD-CRS parts I or II, Index I or II, calculated as the mean value of Xst. MD-CRS Global index = n1 * index 1 + n2 * index 2 divided by n1 + n2, where n1 and n2 are the numbers of items in MD-CRS parts I and II respectively. Minimum score is 0 (better) and the maximum score is 1 (worse). A higher score indicates more severe movement disorder. mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.0 (± 0.06)	-0.0 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT) Score (Activities of Daily Living [ADL], Caregiver Completed, Content-Balanced Version) at Week 15

End point title	Change From Baseline in Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT) Score (Activities of Daily Living [ADL], Caregiver Completed, Content-Balanced Version) at Week 15

End point description:

PEDI-CAT measures function in 4 domains: Daily Activities; Mobility; Social/Cognitive, and Responsibility. A total of approximately 30 items were administered. PEDI-CAT software utilizes Item Response Theory statistical models to estimate a child's abilities from a minimal number of the most relevant items or from a set number of items within each domain. The CAT program then displays the results: normative standard scores, scaled scores and SE. Scaled score is reported in this endpoint. Scaled scores are based on an estimate of the placement of an individual child along the hierarchical scale within each domain. PEDI-CAT scaled scores are currently on a 20 (lesser improvement) to 80 (more improvement) scale metric. Higher scores indicate greater improvement in functional skills. mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	29		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.4 (± 1.78)	-0.6 (± 3.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UHDRS-TMD Score (Physician Rated) at Week 15

End point title	Change From Baseline in UHDRS-TMD Score (Physician Rated) at Week 15

End point description:

The UHDRS-TMD is part of the UHDRS-TMS assessment and assesses the severity of dystonia in the 5 body parts: trunk and the 4 extremities (right and left upper extremities, right and left lower extremities). Each part was rated from 0 (absent) to 4 (prolonged). All items were scored by the investigational center physician. The TMD score was obtained by adding up each of the separate scores and ranged from 0 (absent) to 20 (marked/prolonged), with higher scores indicating the worse symptoms. The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	0.6 (± 1.86)	-1.3 (± 1.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UHDRS-TMS Score (Physician Rated) at Week 15

End point title	Change From Baseline in UHDRS-TMS Score (Physician Rated) at Week 15

End point description:

The UHDRS comprises a broad assessment of features associated with Huntington's disease (HD). It is a research tool that has been developed to provide a uniform assessment of the clinical features and course of HD. The Total Motor Score assessment of the UHDRS (UHDRS-TMS) comprises 15 items and assesses eye movements, speech, alternating hand movements, dystonia, chorea, and gait. The UHDRS-TMS was calculated as the sum of the 31 motor assessments; each of which ranged between 0 (absent) to 4 (worst). All items were scored by the investigational center physician. TMS score is a sum of individual scores ranging from 0 (normal motor function) to 124 (severely impaired motor function), with lower scores indicating better motor function. The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-4.1 (± 8.35)	-7.6 (± 10.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UHDRS-TMC Score (Physician Rated) at Week 15

End point title	Change From Baseline in UHDRS-TMC Score (Physician Rated) at Week 15

End point description:

The UHDRS-TMC is part of the UHDRS-TMS assessment and assesses the severity of chorea in the 7 body parts: face, mouth, trunk, and the 4 extremities (right and left upper extremities, right and left lower extremities). Each part was rated from 0 (absent) to 4 (prolonged). All items were scored by the investigational center physician. The TMC score was obtained by adding up each of the separate scores and ranged from 0 (absent) to 28 (marked/prolonged), with higher scores indicating the worse symptoms. The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.2 (± 4.05)	-2.9 (± 3.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Improvement (PGI-I) Scale Score (Global, Participant/Caregiver) at Week 15

End point title	Patient Global Impression of Improvement (PGI-I) Scale Score (Global, Participant/Caregiver) at Week 15

End point description:

The PGI-I is single item questionnaire to assess the participant's impression of improvement in dyskinesia symptoms after initiating therapy. The scale is a participant-reported outcome that aims to evaluate all aspects of participants' health and determine if there has been an overall improvement or not in dyskinesia symptoms. The participant selected the 1 response from the visual response options ("emojis") that gave the most accurate description of his/her state of health and overall status: 1=much improved (since the initiation of treatment); 2=somewhat improved; 3=no change; 4=somewhat worse; 5=much worse (since the initiation of treatment). The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	31		
Units: units on a scale				
arithmetic mean (standard deviation)	2.4 (± 0.81)	2.4 (± 0.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the CP Module of the Pediatric Quality of Life Inventory (PedsQL) Total Score (Quality of Life [QoL], Participant/Caregiver) at Week 15

End point title	Change From Baseline in the CP Module of the Pediatric Quality of Life Inventory (PedsQL) Total Score (Quality of Life [QoL], Participant/Caregiver) at Week 15

End point description:

The 35-item PedsQL 3.0 CP module encompasses 7 scales: Daily Activities (9 items); School Activities (4 items); Movement and Balance (5 items); Pain and Hurt (4 items); Fatigue (4 items); Eating Activities (5 items); and Speech and Communication (4 items). A 5-point response scale is utilized across child self-report and parent proxy report: 0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem. Items are reverse scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better quality of life. Total score = sum of 35 items divided by the number of items answered. Change from baseline scores can range from -100 to 100. mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Overall number of participants analyzed = participants evaluable for this endpoint. 'n' = participants evaluable for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	33		
Units: units on a scale				
arithmetic mean (standard deviation)				
Self-report (n = 18, 33)	1.9 (± 11.17)	3.2 (± 14.96)		
Proxy-report (n = 11, 23)	4.1 (± 8.80)	-0.7 (± 16.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression of Severity (CGI-S) Scale Score (Global, Physician Rated) at Week 15

End point title	Change From Baseline in Clinical Global Impression of Severity (CGI-S) Scale Score (Global, Physician Rated) at Week 15

End point description:

CGI-S uses a 7-point Likert scale to assess dyskinesia severity as follows: 1=normal (not at all ill, symptoms of disorder not present past 7 days); 2=borderline (subtle or suspected pathology); 3=mild

(clearly established symptoms with minimal, if any, distress or difficulty in social and/or occupational function); 4=moderate (overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication); 5=marked (intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress); 6=severe (disruptive symptoms, behavior and function are frequently influenced by symptoms, may require assistance from others); 7=extreme (symptoms drastically interferes in many life functions; may be hospitalized). mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.6 (± 0.75)	-0.7 (± 0.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

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

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. SAEs included death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A summary of serious and non-serious AEs regardless of causality is located in 'Reported Adverse Events module'. Safety analysis set included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 17

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	40		
Units: participants	15	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with PGI-I Response

End point title	Number of Participants with PGI-I Response

End point description:

PGI-I response was defined as participants who were described as "Much Improved" or "Somewhat Improved" in the PGI-I score. PGI-I is single item questionnaire to assess the participant's impression of improvement in dyskinesia symptoms after initiating therapy. The scale is a participant-reported outcome that aims to evaluate all aspects of participants' health and determine if there has been an overall improvement or not in dyskinesia symptoms. The participant selected the 1 response from the visual response options ("emojis") that gave the most accurate description of his/her state of health and overall status: 1=much improved (since the initiation of treatment); 2=somewhat improved; 3=no change; 4=somewhat worse; 5=much worse (since the initiation of treatment). The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	31		
Units: participants	9	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with CGI-S Response

End point title	Number of Participants with CGI-S Response

End point description:

CGI-S response was defined as participants who had a reduction of ≥1 point in the CGI-S score. CGI-S uses a 7-point Likert scale to assess dyskinesia severity as follows: 1=normal (not at all ill, symptoms of disorder not present past 7 days); 2=borderline (subtle or suspected pathology); 3=mild (clearly established symptoms with minimal, if any, distress or difficulty in social and/or occupational function); 4=moderate (overt symptoms causing noticeable, but modest, functional impairment or distress); 5=marked (intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress); 6=severe (disruptive symptoms, behavior and function are frequently influenced by symptoms); 7=extreme (symptoms drastically interferes in many life functions). mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: participants	9	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with CaGI-I Response

End point title	Number of Participants with CaGI-I Response

End point description:

CaGI-I response was defined as participants who were described by the caregiver as "Much Improved" or "Very Much Improved" in the CaGI-I score. The scale is a caregiver-reported outcome that aims to evaluate all aspects of participants' health and determine if there has been an overall improvement or not in dyskinesia symptoms. The caregiver selected 1 response from the response options that gave the most accurate description of change in dyskinesia symptoms of the participant they cared for from the beginning of study: 1=very much improved (since the initiation of treatment); 2=much improved; 3=minimally improved; 4=no change from baseline (symptoms remain essentially unchanged); 5=minimally worse; 6=much worse; 7=very much worse (since the initiation of treatment). The mITT analysis set included all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	31		
Units: participants	4	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with CGI-I Response

End point title	Number of Participants with CGI-I Response

End point description:

CGI-I response was defined as participants who were described as "Much Improved" or "Very Much Improved" in the CGI-I score. CGI-I uses a 7-point Likert scale to compare participant's condition at the visit to the baseline condition as follows: 1=very much improved (nearly all better; good level of functioning); 2=much improved (notably better with significant reduction of symptoms; increase in the level of functioning); 3=minimally improved (slightly better with little or no clinically meaningful reduction of symptoms); 4=no change from baseline (symptoms remain unchanged); 5=minimally worse (slightly worse but may not be clinically meaningful); 6=much worse (clinically significant increase in symptoms and diminished functioning); 7=very much worse (severe exacerbation of symptoms). mITT analysis set: all randomized participants with at least 1 postbaseline centrally read MD-CRS part II assessment. Overall number of participants analyzed = participants evaluable for this

endpoint.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: participants	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shift From Baseline to Week 15 in Electrocardiogram (ECG) Findings

End point title	Number of Participants With Shift From Baseline to Week 15 in Electrocardiogram (ECG) Findings

End point description:

ECG parameters included: Heart rate, PR interval, QRS interval, RR interval, QT interval, and QT interval corrected using the Fridericia formula (QTcF). Shifts represented as Baseline - Week 15 value (last observed postbaseline value). Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	32		
Units: participants				
Normal - Normal	14	20		
Normal - Abnormal	1	5		
Abnormal - Normal	1	3		
Abnormal - Abnormal	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Extrapyramidal Symptom Rating Scale (ESRS)

Subscale I Total Score at Week 15

End point title	Change From Baseline in Extrapyramidal Symptom Rating Scale (ESRS) Subscale I Total Score at Week 15

End point description:

The ESRS subscale I is a 7-item subjective questionnaire to evaluate parkinsonism, akathisia, dystonia and dyskinesia. The ESRS I is scored on 4-point scale (0=absent, 1=Mild, 2=Moderate, 3=Severe) for each item. The evaluation takes into account the verbal report of the participant on 1) the frequency and duration of the symptom during the day, 2) the number of days the symptom was present during the last week, and 3) the subjective evaluation of the intensity of the symptom by the participant. Total score was the sum of the 7 items which ranges from 0 (absent) to 28 (severe). Higher scores indicate greater severity of disorder. Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.4 (± 1.40)	-1.5 (± 2.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Behavior Checklist (CBCL) Syndrome Total Score at Week 15

End point title	Change From Baseline in Child Behavior Checklist (CBCL) Syndrome Total Score at Week 15

End point description:

The full CBCL has two parts, a Competence Scale (Parts I to VII) and a Syndrome Scale (behavioral items). The Syndrome Scale comprises 113 questions related to problem behaviors. For each item, the responses are recorded on a scale: 0 = Not True; 1 = Somewhat or Sometimes True; 2 = Very True or Often True. The problem behaviors are scored on the following 8 empirically based syndromes: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. CBCL syndrome total score ranged from 0 (no problem) to 226 (lesser problem), was calculated by adding individual score of each domain. Higher scores indicate greater problems in child behavior. Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-7.1 (± 11.34)	-11.6 (± 15.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Behavior Checklist (CBCL) Competence Total Score at Week 15

End point title	Change From Baseline in Child Behavior Checklist (CBCL) Competence Total Score at Week 15

End point description:

The full CBCL has two parts, a Competence Scale (Parts I to VII) and a Syndrome Scale (behavioral items). The Competence Scale (Parts I to VII) assesses various activities (for example, sports, hobbies, games, organizations, clubs, teams, groups, jobs, and chores), interpersonal relationships, and academic performance. The checklists having 120 questions consist of a number of statements about the child's behavior and responses which are recorded on a scale: 0 = Not True; 1 = Somewhat or Sometimes True; 2 = Very True or Often True. CBCL competence total score ranged from 0 (no problem) to 240 (lesser problem), was calculated by adding individual score of each domain. Higher scores indicate greater problems in child behavior. Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	28		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.12 (± 4.279)	-0.08 (± 2.716)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Epworth Sleepiness Scale (ESS) Total Score at Week 15

End point title	Change From Baseline in Epworth Sleepiness Scale (ESS) Total Score at Week 15

End point description:

The ESS is a self-administered questionnaire composed of 8 questions that provide a measure of a participant’s general level of daytime sleepiness. The ESS is composed of 8 items. The responders were

asked to rate their chances of falling asleep while engaged at 8 different activities, on a 4-point scale: 0 = would never fall asleep; 1=slight chance of falling asleep; 2=moderate chance of falling asleep; 3=high chance of falling asleep. Total score was calculated as the sum of 8 item scores which ranges from 0 (never) to 24 (high chance of falling asleep). Higher scores indicate high chances of falling asleep. Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	29		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.9 (± 1.74)	1.6 (± 5.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Extrapyramidal Symptom Rating Scale (ESRS) Subscale II Total Score at Week 15

End point title	Change From Baseline in Extrapyramidal Symptom Rating Scale (ESRS) Subscale II Total Score at Week 15

End point description:

The ESRS subscale II is a 17-item questionnaire to evaluate parkinsonism and akathisia. The ESRS II consists of the following parts: tremor (0 [none]–48 [severe]), gait and posture (0 [none]–6 [severe]), postural stability (0 [none]-6 [severe]), rigidity (0 [none]–24 [severe]), expressive automatic movements (0 [none]–6 [severe]), bradykinesia (0 [none]-6 [severe]), and akathisia (0 [none]–6 [severe]). Total score was the sum of the 17 items which from ranges from 0 (absent) to 102 (severe). Higher scores indicate greater severity of disorder. Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.6 (± 5.64)	-1.8 (± 6.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Columbia-Suicide Severity Rating Scale (C-SSRS) Outcomes (Suicidal Ideation and Suicidal Behavior) at Week 15

End point title	Number of Participants With Columbia-Suicide Severity Rating Scale (C-SSRS) Outcomes (Suicidal Ideation and Suicidal Behavior) at Week 15

End point description:

Participants were placed into categories for suicidal ideation and suicidal behavior based on their responses to various questions. For suicidal ideation, following categories were used: None; Wish to be dead; Non-specific active suicidal thoughts; Any methods (not plan) without intent to act; Some intent to act, without specific plan; and Specific plan and intent. For suicidal behavior, following categories were used: None; Preparatory acts or behavior; Aborted attempt; Interrupted attempt; Actual attempt; and Suicide. Safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 15

End point values	Placebo	TEV-50717		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: participants				
Suicidal ideation - None	8	9		
Suicidal behavior - None	8	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 17	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	TEV-50717
Reporting group description: TEV-50717	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	TEV-50717	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	TEV-50717	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 40 (85.00%)	10 / 22 (45.45%)	
Investigations			
Weight increased			
subjects affected / exposed	3 / 40 (7.50%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Drooling			
subjects affected / exposed	4 / 40 (10.00%)	1 / 22 (4.55%)	
occurrences (all)	4	1	
Dysarthria			

subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Dyskinesia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Somnolence			
subjects affected / exposed	17 / 40 (42.50%)	0 / 22 (0.00%)	
occurrences (all)	23	0	
Lethargy			
subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Dystonia			
subjects affected / exposed	4 / 40 (10.00%)	1 / 22 (4.55%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 40 (10.00%)	0 / 22 (0.00%)	
occurrences (all)	5	0	
Pyrexia			
subjects affected / exposed	2 / 40 (5.00%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	1 / 40 (2.50%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	5 / 40 (12.50%)	0 / 22 (0.00%)	
occurrences (all)	6	0	
Salivary hypersecretion			
subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Nausea			

subjects affected / exposed	3 / 40 (7.50%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 40 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	2 / 40 (5.00%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	0 / 40 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	3	
Respiratory tract infection			
subjects affected / exposed	2 / 40 (5.00%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	2 / 40 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	3 / 40 (7.50%)	0 / 22 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2018	Updates to scales
17 October 2019	Clarify inclusion/exclusion criteria
08 June 2020	COVID-19 updates
09 March 2021	Clarify inclusion/exclusion criteria
24 March 2022	Adjust sample size

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported