Clinical trial results:
Prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of children and adolescents (2–17 years) with chronic troublesome sialorrhea associated with neurological disorders, and/or intellectual disability

Summary

EudraCT number	2013-004532-30
Trial protocol	HU PL Outside EU/EEA
Global end of trial date	07 May 2019

Results information

Result version number	v1 (current)
This version publication date	20 November 2019
First version publication date	20 November 2019

Trial information

Trial identification

Sponsor protocol code	MRZ60201_3091_1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merz Pharmaceuticals GmbH
Sponsor organisation address	Eckenheimer Landstrasse 100, Frankfurt/Main, Germany, 60318
Public contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.com
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001039-PIP02-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to investigate the efficacy and safety of NT 201 compared with placebo for the treatment of chronic troublesome sialorrhea associated with neurological disorders (example cerebral palsy, traumatic brain injury) and/or intellectual disability in children and adolescents naive to Botulinum neurotoxin treatment and aged 2–17 years.

Protection of trial subjects:

High medical and ethical standards were followed in accordance with Good Clinical Practice and other applicable regulations. In addition, an independent data monitoring committee was in charge of monitoring subject safety while the study was ongoing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2015
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	Poland: 51
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Ukraine: 121
Country: Number of subjects enrolled	Georgia: 25
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Serbia: 1
Worldwide total number of subjects	255
EEA total number of subjects	64

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)	179
Adolescents (12-17 years)	76
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 28 investigational sites in Georgia, Hungary, Poland, Russia, Serbia, and Ukraine.

Pre-assignment

Screening details:

A total of 281 subjects were screened, out of which 256 subjects were randomized/assigned into the study. Of these 256 subjects, 255 subjects received the study treatment. A total of 247 subjects who completed the Main Period (MP) entered the Open-label Extension Period (OLEX) of the study.

Period 1

Period 1 title	Main Period (MP)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind MP: Placebo (age 6 to 17 years)

Arm description:

Subjects received placebo via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks. Volumes were matched to the volumes of NT 201 (incobotulinumtoxinA; Xeomin) injected in the experimental arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

Subjects received placebo via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks. Volumes were matched to the volumes of NT 201 (incobotulinumtoxinA; Xeomin) injected in the experimental arm.

Arm title	Double-blind, MP: NT 201 (age 6 to 17 years)

Arm description:

Subjects received NT 201 (up to 2.5 Units per kilogram [U/kg] body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Incobotulinumtoxin A; Botulinum neurotoxin type A free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

Subjects received NT 201 (up to 2.5 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Arm title	Open-label, MP: NT 201 (age 2 to 5 years)

Arm description:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Incobotulinumtoxin A; Botulinum neurotoxin type A free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Number of subjects in period 1	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)
Started	72	148	35
Completed	70	146	34
Not completed	2	2	1
Consent withdrawn by subject	2	-	1
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	1	-

Period 2

Period 2 title	Open-label Extension Period (OLEX)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	OLEX: NT 201 (age 6 to 17 years)

Arm description:

Subjects received NT 201 (up to 2.5 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total). This arm consisted of subjects who participated in MP arms “Double-blind, MP: placebo (age 6 to 17 years)” and “Double-blind, MP: NT 201 (age 6 to 17 years)”.

Arm type	Experimental

Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Incobotulinumtoxin A; Botulinum neurotoxin type A free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

Subjects received NT 201 (up to 2.5 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total). This arm consisted of subjects who participated in MP arms "Double-blind, MP: placebo (age 6 to 17 years)" and "Double-blind, MP: NT 201 (age 6 to 17 years)".

Arm title	OLEX: NT 201 (age 2 to 5 years)

Arm description:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total).

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Incobotulinumtoxin A; Botulinum neurotoxin type A free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total).

Number of subjects in period 2[1]	OLEX: NT 201 (age 6 to 17 years)	OLEX: NT 201 (age 2 to 5 years)
Started	214	33
Completed	189	33
Not completed	25	0
Consent withdrawn by subject	16	-
Physician decision	1	-
Adverse event, non-fatal	4	-
Lost to follow-up	2	-
Lack of efficacy	2	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 3 subjects, 1 in each MP treatment group, did not enter the OLEX due to AE(s) (1 subject) and withdrawal of consent (2 subjects).

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind MP: Placebo (age 6 to 17 years)
Reporting group description:	
Subjects received placebo via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks. Volumes were matched to the volumes of NT 201 (incobotulinumtoxinA; Xeomin) injected in the experimental arm.	
Reporting group title	Double-blind, MP: NT 201 (age 6 to 17 years)
Reporting group description:	
Subjects received NT 201 (up to 2.5 Units per kilogram [U/kg] body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.	
Reporting group title	Open-label, MP: NT 201 (age 2 to 5 years)
Reporting group description:	
Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.	

Reporting group values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)
Number of subjects	72	148	35
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)	48	96	35
Adolescents (12-17 years)	24	52	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	27	55	13
Male	45	93	22
Race characteristic Units: Subjects			
White	72	148	35
Height characteristic Units: centimeter (cm)			
arithmetic mean	135.3	132.8	101.1
standard deviation	± 16.92	± 17.15	± 8.09
Weight characteristic Units: kilogram (kg)			
arithmetic mean	30.8	28.8	15.7
standard deviation	± 11.67	± 11.48	± 3.00

Body Mass Index (BMI)			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	16.4	15.8	15.3
standard deviation	± 3.65	± 3.25	± 1.85

Reporting group values	Total		
Number of subjects	255		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	179		
Adolescents (12-17 years)	76		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	95		
Male	160		
Race characteristic			
Units: Subjects			
White	255		
Height characteristic			
Units: centimeter (cm)			
arithmetic mean			
standard deviation	-		
Weight characteristic			
Units: kilogram (kg)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Double-blind MP: Placebo (age 6 to 17 years)

Reporting group description:

Subjects received placebo via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks. Volumes were matched to the volumes of NT 201 (incobotulinumtoxinA; Xeomin) injected in the experimental arm.

Reporting group title	Double-blind, MP: NT 201 (age 6 to 17 years)

Reporting group description:

Subjects received NT 201 (up to 2.5 Units per kilogram [U/kg] body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Reporting group title	Open-label, MP: NT 201 (age 2 to 5 years)

Reporting group description:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Reporting group title	OLEX: NT 201 (age 6 to 17 years)

Reporting group description:

Subjects received NT 201 (up to 2.5 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total). This arm consisted of subjects who participated in MP arms "Double-blind, MP: placebo (age 6 to 17 years)" and "Double-blind, MP: NT 201 (age 6 to 17 years)".

Reporting group title	OLEX: NT 201 (age 2 to 5 years)

Reporting group description:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total).

Subject analysis set title	MP: Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS is identical to the subset of subjects in the safety evaluation set of the MP (SES [MP]). The SES (MP) is the subset of all subjects who received study medication (NT 201 or placebo) during the MP of the study.

Subject analysis set title	MP: SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The SES (MP) is the subset of all subjects who received study medication (NT 201 or placebo) during the MP of the study.

Subject analysis set title	OLEX: SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The SES of the OLEX is the subset of all subjects who received study medication (NT 201) at least once during the OLEX of the study.

Primary: Change From Baseline in Unstimulated Salivary Flow Rate (uSFR) at Week 4

End point title	Change From Baseline in Unstimulated Salivary Flow Rate (uSFR) at Week 4[1]

End point description:

This endpoint was analysed in double-blind, MP, 6 to 17 years subjects. uSFR was assessed by weighing of absorbent swabs with safety threads soaked with saliva over 5 minutes and the procedure was repeated after 30 minutes. Salivary flow rate was equal to weight increase of swabs/time of collection. The average of the 2 results for flow rate was calculated. The reduction of measured weight over the

study relates to improvement of sialorrhea.

End point type	Primary

End point timeframe:

Baseline and Week 4

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed only for two reporting groups: Double-blind MP: Placebo (age 6 to 17 years) and Double-blind, MP: NT 201 (age 6 to 17 years).

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[2]	148[3]		
Units: gram per minute (g/min)				
least squares mean (standard error)	-0.07 (± 0.015)	-0.14 (± 0.012)		

Notes:

[2] - MP-FAS

[3] - MP-FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Least square mean (LS-Mean) is from a mixed model repeated measurement (MMRM) analysis with treatment group, pooled investigation sites, and age groups as fixed factors, visit*treatment as interaction term, visit as repeated factor, and baseline uSFR score as covariate.

Comparison groups	Double-blind MP: Placebo (age 6 to 17 years) v Double-blind, MP: NT 201 (age 6 to 17 years)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.019

Primary: Global Impression of Change Scale (GICS) at Week 4 Assessed by the Carer/Parent(s)

End point title	Global Impression of Change Scale (GICS) at Week 4 Assessed by the Carer/Parent(s)[4]

End point description:

This endpoint was analysed in double-blind, MP, 6 to 17 years subjects. The GICS was used to measure

the carer's/parent's impression of change due to treatment. The response option was a common 7-point Likert scale, with the following values: +3 (very much improved); +2 (much improved); +1 (minimally improved); 0 (no change); -1 (minimally worse); -2 (much worse); -3 (very much worse).

End point type	Primary

End point timeframe:

Week 4

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed only for two reporting groups: Double-blind MP: Placebo (age 6 to 17 years) and Double-blind, MP: NT 201 (age 6 to 17 years).

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[5]	148[6]		
Units: units on a scale				
least squares mean (standard error)	0.63 (± 0.104)	0.91 (± 0.075)		

Notes:

[5] - MP-FAS

[6] - MP-FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS-Mean is from a MMRM analysis model with treatment group, pooled investigation sites, and age groups as fixed factors, visit*treatment as interaction term, visit as repeated factor, and baseline Modified Teacher Drooling Scale (mTDS) score as covariate.

Comparison groups	Double-blind MP: Placebo (age 6 to 17 years) v Double-blind, MP: NT 201 (age 6 to 17 years)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.127

Primary: Occurrence of Treatment Emergent Adverse Events (TEAEs) Overall and per Treatment Cycle

End point title	Occurrence of Treatment Emergent Adverse Events (TEAEs) Overall and per Treatment Cycle[7]

End point description:

"n" is the number of subjects evaluable for this measure at a given time period and who were included in the assessment.

End point type	Primary

End point timeframe:

Baseline up to Week 64

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)	OLEX: NT 201 (age 6 to 17 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[8]	148[9]	35[10]	214[11]
Units: subjects				
Overall (n=72,148,35,214,33)	11	27	5	92
First injection cycle (MP) (n=72,148,35,0,0)	11	27	5	0
Second injection cycle (OLEX) (n=0,0,0,214,33)	0	0	0	44
Third injection cycle (OLEX) (n=0,0,0,205,33)	0	0	0	35
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0	0	0	40

Notes:

[8] - MP-SES

[9] - MP-SES

[10] - MP-SES

[11] - OLEX-SES

End point values	OLEX: NT 201 (age 2 to 5 years)			
Subject group type	Reporting group			
Number of subjects analysed	33[12]			
Units: subjects				
Overall (n=72,148,35,214,33)	15			
First injection cycle (MP) (n=72,148,35,0,0)	0			
Second injection cycle (OLEX) (n=0,0,0,214,33)	7			
Third injection cycle (OLEX) (n=0,0,0,205,33)	5			
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	11			

Notes:

[12] - OLEX-SES

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in uSFR at Weeks 8 and 12

End point title	Change From Baseline in uSFR at Weeks 8 and 12[13]

End point description:

This endpoint was analysed in double-blind, MP, 6 to 17 years subjects. uSFR was assessed by weighing of absorbent swabs with safety threads soaked with saliva over 5 minutes and then procedure was repeated after 30 minutes. Salivary flow rate was equal to weight increase of swabs/time of collection. The average of the 2 results for flow rate was calculated. The reduction of measured weight over the study relates to improvement of sialorrhea.

End point type	Secondary

End point timeframe:

Baseline and Weeks 8 and 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed only for two reporting groups: Double-blind MP: Placebo (age 6 to 17 years) and Double-blind, MP: NT 201 (age 6 to 17 years).

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[14]	148[15]		
Units: g/min				
least squares mean (standard error)				
Change at Week 8	-0.07 (± 0.015)	-0.16 (± 0.012)		
Change at Week 12	-0.06 (± 0.016)	-0.16 (± 0.013)		

Notes:

[14] - MP-FAS

[15] - MP-FAS

Statistical analyses

Statistical analysis title	Statistical Analysis at Week 8

Statistical analysis description:

LS-Mean is from a MMRM analysis with treatment group, pooled investigation sites, and age groups as fixed factors, visit*treatment as interaction term, visit as repeated factor, and baseline uSFR score as covariate.

Comparison groups	Double-blind MP: Placebo (age 6 to 17 years) v Double-blind, MP: NT 201 (age 6 to 17 years)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	Statistical Analysis at Week 12

Statistical analysis description:

LS-Mean is from a MMRM analysis with treatment group, pooled investigation sites, and age groups as fixed factors, visit*treatment as interaction term, visit as repeated factor, and baseline uSFR score as covariate.

Comparison groups	Double-blind MP: Placebo (age 6 to 17 years) v Double-blind, MP: NT 201 (age 6 to 17 years)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.021

Secondary: GICS at Weeks 8 and 12

End point title	GICS at Weeks 8 and 12[16]

End point description:

This endpoint was analysed in double-blind, MP, 6 to 17 years subjects. The GICS was used to measure the carer's/parent's impression of change due to treatment. The response option was a common 7-point Likert scale with the following values: +3 (very much improved); +2 (much improved); +1 (minimally improved); 0 (no change); -1 (minimally worse); -2 (much worse); -3 (very much worse).

End point type	Secondary

End point timeframe:

Baseline and Weeks 8 and 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed only for two reporting groups: Double-blind MP: Placebo (age 6 to 17 years) and Double-blind, MP: NT 201 (age 6 to 17 years).

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[17]	148[18]		
Units: units on a scale				
least squares mean (standard error)				
Week 8	0.54 (± 0.096)	0.94 (± 0.068)		
Week 12	0.47 (± 0.111)	0.87 (± 0.073)		

Notes:
[17] - MP-FAS
[18] - MP-FAS

Statistical analyses

Statistical analysis title	Statistical Analysis at Week 8

Statistical analysis description:

LS-Mean is from a MMRM analysis model with treatment group, pooled investigation sites, and age groups as fixed factors, visit*treatment as interaction term, visit as repeated factor, and baseline mTDS score as covariate.

Comparison groups	Double-blind MP: Placebo (age 6 to 17 years) v Double-blind, MP: NT 201 (age 6 to 17 years)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.63
Variability estimate	Standard error of the mean
Dispersion value	0.116

Statistical analysis title	Statistical Analysis at Week 12

Statistical analysis description:

LS-Mean is from a MMRM analysis model with treatment group, pooled investigation sites, and age groups as fixed factors, visit*treatment as interaction term, visit as repeated factor, and baseline mTDS score as covariate.

Comparison groups	Double-blind MP: Placebo (age 6 to 17 years) v Double-blind, MP: NT 201 (age 6 to 17 years)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.66

Variability estimate	Standard error of the mean
Dispersion value	0.132

Secondary: Occurrence of Treatment Emergent Adverse Events of Special Interest (AESI) Overall and by Injection Cycle

End point title	Occurrence of Treatment Emergent Adverse Events of Special Interest (AESI) Overall and by Injection Cycle

End point description:

"n" is the number of subjects evaluable for this measure at a given time period and who were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 64

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)	OLEX: NT 201 (age 6 to 17 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[19]	148[20]	35[21]	214[22]
Units: subjects				
Overall (n=72,148,35,214,33)	0	1	0	4
First injection cycle (MP) (n=72,148,35,0,0)	0	1	0	0
Second injection cycle (OLEX) (n=0,0,0,214,33)	0	0	0	3
Third injection cycle (OLEX) (n=0,0,0,205,33)	0	0	0	1
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0	0	0	0

Notes:

[19] - MP-SES

[20] - MP-SES

[21] - MP-SES

[22] - OLEX-SES

End point values	OLEX: NT 201 (age 2 to 5 years)			
Subject group type	Reporting group			
Number of subjects analysed	33[23]			
Units: subjects				
Overall (n=72,148,35,214,33)	0			
First injection cycle (MP) (n=72,148,35,0,0)	0			
Second injection cycle (OLEX) (n=0,0,0,214,33)	0			
Third injection cycle (OLEX) (n=0,0,0,205,33)	0			
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0			

Notes:

[23] - OLEX-SES

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Treatment Emergent Serious Adverse Events (TESAEs) Overall and by Injection Cycle

End point title	Occurrence of Treatment Emergent Serious Adverse Events (TESAEs) Overall and by Injection Cycle

End point description:

"n" is the number of subjects evaluable for this measure at a given time period and who were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 64

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)	OLEX: NT 201 (age 6 to 17 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[24]	148[25]	35[26]	214[27]
Units: subjects				
Overall (n=72,148,35,214,33)	1	0	1	8
First injection cycle (MP) (n=72,148,35,0,0)	1	0	1	0
Second injection cycle (OLEX) (n=0,0,0,214,33)	0	0	0	3
Third injection cycle (OLEX) (n=0,0,0,205,33)	0	0	0	5
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0	0	0	0

Notes:

[24] - MP-SES

[25] - MP-SES

[26] - MP-SES

[27] - OLEX-SES

End point values	OLEX: NT 201 (age 2 to 5 years)			
Subject group type	Reporting group			
Number of subjects analysed	33[28]			
Units: subjects				
Overall (n=72,148,35,214,33)	0			
First injection cycle (MP) (n=72,148,35,0,0)	0			

Second injection cycle (OLEX) (n=0,0,0,214,33)	0			
Third injection cycle (OLEX) (n=0,0,0,205,33)	0			
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0			

Notes:

[28] - OLEX-SES

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of TEAEs Related to Treatment as Assessed by the Investigator Overall and by Injection Cycle

End point title	Occurrence of TEAEs Related to Treatment as Assessed by the Investigator Overall and by Injection Cycle

End point description:

"n" is the number of subjects evaluable for this measure at a given time period and who were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 64

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)	OLEX: NT 201 (age 6 to 17 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[29]	148[30]	35[31]	214[32]
Units: subjects				
Overall (n=72,148,35,214,33)	0	2	1	10
First injection cycle (MP) (n=72,148,35,0,0)	0	2	1	0
Second injection cycle (OLEX) (n=0,0,0,214,33)	0	0	0	5
Third injection cycle (OLEX) (n=0,0,0,205,33)	0	0	0	5
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0	0	0	1

Notes:

[29] - MP-SES

[30] - MP-SES

[31] - MP-SES

[32] - OLEX-SES

End point values	OLEX: NT 201 (age 2 to 5 years)			
Subject group type	Reporting group			
Number of subjects analysed	33[33]			
Units: subjects				
Overall (n=72,148,35,214,33)	0			

First injection cycle (MP) (n=72,148,35,0,0)	0			
Second injection cycle (OLEX) (n=0,0,0,214,33)	0			
Third injection cycle (OLEX) (n=0,0,0,205,33)	0			
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0			

Notes:

[33] - OLEX-SES

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of TEAEs Leading to Discontinuation Overall and by Injection Cycle

End point title	Occurrence of TEAEs Leading to Discontinuation Overall and by Injection Cycle

End point description:

"n" is the number of subjects evaluable for this measure at a given time period and who were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 64

End point values	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)	OLEX: NT 201 (age 6 to 17 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[34]	148[35]	35[36]	214[37]
Units: subjects				
Overall (n=72,148,35,214,33)	1	1	1	4
First injection cycle (MP) (n=72,148,35,0,0)	1	1	1	0
Second injection cycle (OLEX) (n=0,0,0,214,33)	0	0	0	2
Third injection cycle (OLEX) (n=0,0,0,205,33)	0	0	0	2
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0	0	0	0

Notes:

[34] - MP-SES

[35] - MP-SES

[36] - MP-SES

[37] - OLEX-SES

End point values	OLEX: NT 201 (age 2 to 5 years)			
Subject group type	Reporting group			
Number of subjects analysed	33[38]			

Units: subjects				
Overall (n=72,148,35,214,33)	0			
First injection cycle (MP) (n=72,148,35,0,0)	0			
Second injection cycle (OLEX) (n=0,0,0,214,33)	0			
Third injection cycle (OLEX) (n=0,0,0,205,33)	0			
Fourth injection cycle (OLEX) (n=0,0,0,193,33)	0			

Notes:

[38] - OLEX-SES

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 64

Adverse event reporting additional description:

The investigator asked the subject for adverse events (AEs) systematically at each visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Double-blind MP: Placebo (age 6 to 17 years)

Reporting group description:

Subjects received placebo via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks. Volumes were matched to the volumes of NT 201 (incobotulinumtoxinA; Xeomin) injected in the experimental arm.

Reporting group title	Double-blind, MP: NT 201 (age 6 to 17 years)

Reporting group description:

Subjects received NT 201 (up to 2.5 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Reporting group title	Open-label, MP: NT 201 (age 2 to 5 years)

Reporting group description:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands in one injection session on Day 1 (Visit 2) of the MP, followed by an observation period of 16 weeks.

Reporting group title	OLEX: NT 201 (age 6 to 17 years)

Reporting group description:

Subjects received NT 201 (up to 2.5 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total). This arm consisted of subjects who participated in MP arms "Double-blind, MP: placebo (age 6 to 17 years)" and "Double-blind, MP: NT 201 (age 6 to 17 years)".

Reporting group title	OLEX: NT 201 (age 2 to 5 years)

Reporting group description:

Subjects received NT 201 (about 1.5-2 U/kg body weight) via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 of second (Visit 6), third (Visit 10), and fourth (Visit 14) injection cycle of the OLEX, followed by an observation period of 16 weeks each (48 weeks in total).

Serious adverse events	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 72 (1.39%)	0 / 148 (0.00%)	1 / 35 (2.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			

Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Joint dislocation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Surgical and medical procedures			
Gastric operation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 72 (1.39%)	0 / 148 (0.00%)	0 / 35 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Gastrointestinal disorders			
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Haematemesis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Musculoskeletal and connective tissue disorders			
Limb deformity			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Infections and infestations			
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	1 / 35 (2.86%)
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	1 / 72 (1.39%)	0 / 148 (0.00%)	0 / 35 (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
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Influenza			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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

Respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (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

Serious adverse events	OLEX: NT 201 (age 6 to 17 years)	OLEX: NT 201 (age 2 to 5 years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 214 (3.74%)	0 / 33 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastric operation			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 214 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 214 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Functional gastrointestinal disorder			
subjects affected / exposed	2 / 214 (0.93%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Limb deformity			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 214 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 214 (0.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Double-blind MP: Placebo (age 6 to 17 years)	Double-blind, MP: NT 201 (age 6 to 17 years)	Open-label, MP: NT 201 (age 2 to 5 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 72 (4.17%)	3 / 148 (2.03%)	2 / 35 (5.71%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 72 (4.17%)	3 / 148 (2.03%)	2 / 35 (5.71%)
occurrences (all)	3	3	3
Pharyngitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Rhinitis			

subjects affected / exposed	0 / 72 (0.00%)	0 / 148 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	OLEX: NT 201 (age 6 to 17 years)	OLEX: NT 201 (age 2 to 5 years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 214 (15.89%)	12 / 33 (36.36%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 214 (6.07%)	1 / 33 (3.03%)	
occurrences (all)	16	1	
Pharyngitis			
subjects affected / exposed	12 / 214 (5.61%)	3 / 33 (9.09%)	
occurrences (all)	13	3	
Respiratory tract infection			
subjects affected / exposed	6 / 214 (2.80%)	3 / 33 (9.09%)	
occurrences (all)	6	4	
Viral infection			
subjects affected / exposed	4 / 214 (1.87%)	2 / 33 (6.06%)	
occurrences (all)	7	3	
Respiratory tract infection viral			
subjects affected / exposed	1 / 214 (0.47%)	4 / 33 (12.12%)	
occurrences (all)	2	5	
Rhinitis			
subjects affected / exposed	2 / 214 (0.93%)	3 / 33 (9.09%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2015	The draft FDA guidance for Industry, 'Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials' was incorporated.
16 June 2016	The confirmatory primary analysis was changed from an analysis of covariance (ANCOVA) with missing value replacement strategy (baseline observation carried forward [BOCF] approach) to an MMRM approach for primary and secondary efficacy variables analysis, and exclusion criteria were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported