Clinical trial results:
Prospective, multicenter, randomized, double-blind, parallel-group, dose-response study of three doses Xeomin® (incobotulinumtoxinA, NT 201) for the treatment of upper limb spasticity alone or combined upper and lower limb spasticity in children and adolescents (age 2 - 17 years) with cerebral palsy.

Summary

EudraCT number	2012-005496-14
Trial protocol	PL Outside EU/EEA
Global end of trial date	28 August 2018
Results information	
Result version number	v2 (current)
This version publication date	18 August 2019
First version publication date	10 March 2019
Version creation reason	• Correction of full data set Zero AEs observed replaced with zero participants analyzed for various data points in several AE-related endpoints

Trial information

Trial identification	
Sponsor protocol code	MRZ60201_3072_1
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02002884
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Merz Pharmaceuticals GmbH
Sponsor organisation address	Eckenheimer Landstrasse 100, Frankfurt/M, Germany, 60318
Public contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 6915031, clinicaltrials@merz.de
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 6915031, clinicaltrials@merz.de

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether injections of Botulinum toxin type A into muscles of one or both upper limbs (UL) alone or in combination with injections into one or both lower limbs (LL) are effective and safe in treating children/adolescents (age 2-17 years) with spasticity due to cerebral palsy.

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 patient safety while the study was ongoing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Mexico: 62
Country: Number of subjects enrolled	Argentina: 21
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Ukraine: 122
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Poland: 83
Worldwide total number of subjects	351
EEA total number of subjects	83

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)	271
Adolescents (12-17 years)	80
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 investigative sites in Mexico, Argentina, Russian federation, Ukraine, United States and Poland.

Pre-assignment

Screening details:

A total of 372 subjects were screened, 351 subjects were randomized and 350 subjects were randomized and treated in the study. 331 subjects completed the main period (MP) and moved to the open-label-extension period (OLEX) out of which 281 subjects completed the OLEX period.

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, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	MP Low Dose Group

Arm description:

In MP, subjects randomized to low dose group were injected with doses of NT 201 ranging from 2 to 5 Units per kilogram (U/kg) body weight (BW) up to a total body dose of 125 Units (U).

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Botulinum toxin type A (150 kiloDalton), free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

On Day 1 of MP, subjects randomized to low dose group received intramuscular injections of 2 U/kg NT 201 (maximum of 50 U in subjects with more than [>] 25 kilogram [kg] BW) into spastic muscles of one of the UL. Treatment with fixed doses of either flexed elbow or flexed wrist or both was mandatory. If the contralateral UL or one or both LL were also treated, subjects received additional doses of NT 201. The total body dose ranged from 2 U/kg (50 U for subjects with >25kg BW) to 5 U/kg (125 U for subjects with >25kg BW) depending on the combination of treated limbs and the subject's Gross Motor Function Classification System (GMFCS) level.

Arm title	MP Mid Dose Group

Arm description:

In MP, subjects randomized to mid dose group were injected with doses of NT 201 ranging from 6 to 15 U/kg BW up to a total body dose of 375 U.

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Botulinum toxin type A (150 kiloDalton), free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

On Day 1 of MP, subjects randomized to mid dose group received intramuscular injections of 6 U/kg NT 201 (maximum of 150 U in subjects with >25kg BW) into spastic muscles of one of the UL. Treatment with fixed doses of either flexed elbow or flexed wrist or both was mandatory. If the contralateral UL or

one or both LL were also treated, subjects received additional doses of NT 201. The total body dose ranged from 6 U/kg (150 U for subjects with >25kg BW) to 15 U/kg (375 U for subjects with >25kg BW) depending on the combination of treated limbs and the subject's GMFCS level.

Arm title	MP High Dose Group

Arm description:

In MP, subjects randomized to high dose group were injected with doses of NT 201 ranging from 8 to 20 U/kg BW up to a total body dose of 500 U.

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Botulinum toxin type A (150 kiloDalton), free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

On Day 1 of MP, subjects randomized to high dose group received intramuscular injections of 8 U/kg NT 201 (maximum of 200 U in subjects with >25kg BW) into spastic muscles of one of the UL. Treatment with fixed doses of either flexed elbow or flexed wrist or both was mandatory. If the contralateral UL or one or both LL were also treated, subjects received additional doses of NT 201. The total body dose ranged from 8 U/kg (200 U for subjects with >25kg BW) to 20 U/kg (500 U for subjects with >25kg BW) depending on the combination of treated limbs and the subject's GMFCS level.

Number of subjects in period 1	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group
Started	87	88	176
Treated	87	87	176
Completed	81	82	168
Not completed	6	6	8
Consent withdrawn by subject	6	2	2
Adverse event, non-fatal	-	1	1
Other	-	3	3
Lost to follow-up	-	-	2

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

Arm title	OLEX (3 Injections)

Arm description:

Subjects who completed MP and qualified for further participation in the study were treated with doses of NT 201 between 8 and 20 U/kg (maximum body dose of 500 U in subjects with >25kg BW) in each of the three injection cycles in OLEX.

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA
Investigational medicinal product code	NT 201
Other name	Xeomin; Botulinum toxin type A (150 kiloDalton), free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

On Day 1 of each of the three injection cycles of OLEX, subjects who qualified for further participation in the study received intramuscular injections of 8 U/kg NT 201 (maximum of 200 U in subjects with >25kg BW) into spastic muscles of the UL selected for treatment in MP. Treatment with fixed doses of either flexed elbow or flexed wrist or both was mandatory. If the contralateral UL or one or both LL were also treated, subjects received additional doses of NT 201. The total body dose ranged from 8 U/kg (200 U for subjects with >25kg BW) to 20 U/kg (500 U for subjects with >25kg BW) depending on the combination of treated limbs and the subject's GMFCS level.

Number of subjects in period 2	OLEX (3 Injections)
Started	331
Completed	281
Not completed	50
Consent withdrawn by subject	10
Physician decision	1
Adverse event, non-fatal	5
Other	24
Lost to follow-up	10

Baseline characteristics

Reporting groups	
Reporting group title	MP Low Dose Group
Reporting group description:	
In MP, subjects randomized to low dose group were injected with doses of NT 201 ranging from 2 to 5 Units per kilogram (U/kg) body weight (BW) up to a total body dose of 125 Units (U).	
Reporting group title	MP Mid Dose Group
Reporting group description:	
In MP, subjects randomized to mid dose group were injected with doses of NT 201 ranging from 6 to 15 U/kg BW up to a total body dose of 375 U.	
Reporting group title	MP High Dose Group
Reporting group description:	
In MP, subjects randomized to high dose group were injected with doses of NT 201 ranging from 8 to 20 U/kg BW up to a total body dose of 500 U.	

Reporting group values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group
Number of subjects	87	88	176
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)	64	71	136
Adolescents (12-17 years)	23	17	40
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.2	7.4	7.3
standard deviation	± 4.70	± 4.13	± 4.40
Gender categorical Units: Subjects			
Female	38	31	62
Male	49	57	114
Ethnicity characteristic Units: Subjects			
Hispanic or Latino	16	26	45
Not Hispanic or Latino	71	62	131
Race characteristic Units: Subjects			
White	81	75	160
Black or African American	3	2	2
Other	3	11	14

Reporting group values	Total		

Number of subjects	351		
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)	271		
Adolescents (12-17 years)	80		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	131		
Male	220		
Ethnicity characteristic Units: Subjects			
Hispanic or Latino	87		
Not Hispanic or Latino	264		
Race characteristic Units: Subjects			
White	316		
Black or African American	7		
Other	28		

End points

End points reporting groups

Reporting group title	MP Low Dose Group

Reporting group description:

In MP, subjects randomized to low dose group were injected with doses of NT 201 ranging from 2 to 5 Units per kilogram (U/kg) body weight (BW) up to a total body dose of 125 Units (U).

Reporting group title	MP Mid Dose Group

Reporting group description:

In MP, subjects randomized to mid dose group were injected with doses of NT 201 ranging from 6 to 15 U/kg BW up to a total body dose of 375 U.

Reporting group title	MP High Dose Group

Reporting group description:

In MP, subjects randomized to high dose group were injected with doses of NT 201 ranging from 8 to 20 U/kg BW up to a total body dose of 500 U.

Reporting group title	OLEX (3 Injections)

Reporting group description:

Subjects who completed MP and qualified for further participation in the study were treated with doses of NT 201 between 8 and 20 U/kg (maximum body dose of 500 U in subjects with >25kg BW) in each of the three injection cycles in OLEX.

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

Subject analysis set description:

The FAS was the subset in the safety analysis set (SES) of the MP for whom the primary efficacy variable or co-primary efficacy variable were available (that is, all subjects who had at least an AS score in the clinical pattern flexed elbow or flexed wrist at baseline [Day 1] or the Investigator’s global impression of change scales [GICS] at Day 29 [Week 4]).

Subject analysis set title	Safety Evaluation Set (SES)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once.

Subject analysis set title	MP Low Dose Group
Subject analysis set type	Safety analysis

Subject analysis set description:

In MP, subjects randomized to low dose group were injected with doses of NT 201 ranging from 2 to 5 U/kg BW up to a total body dose of 125 U.

Subject analysis set title	MP Mid Dose Group
Subject analysis set type	Safety analysis

Subject analysis set description:

In MP, subjects randomized to mid dose group were injected with doses of NT 201 ranging from 6 to 15 U/kg BW up to a total body dose of 375 U.

Subject analysis set title	MP High Dose Group
Subject analysis set type	Safety analysis

Subject analysis set description:

In MP, subjects randomized to high dose group were injected with doses of NT 201 ranging from 8 to 20 U/kg BW up to a total body dose of 500 U.

Subject analysis set title	OLEX (3 Injections)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who completed MP and qualified for further participation in the study were treated with doses of NT 201 between 8 and 20 U/kg (maximum body dose of 500 U in subjects with >25kg BW) in each of the three injection cycles in OLEX.

Primary: MP: Change From Baseline in Ashworth Scale (AS) in UL Primary Clinical Target Pattern at Week 4

End point title	MP: Change From Baseline in Ashworth Scale (AS) in UL Primary Clinical Target Pattern at Week 4

End point description:

The AS categorizes severity of spasticity by judging resistance to passive movement. Spasticity was assessed by using the 5-point AS with:0 (no increase in tone); 1 (slight increase in tone giving a "catch" when the limb was moved in flexion or extension); 2 (more marked increase in tone, but limb easily flexed); 3 (considerable increase in tone -passive movements difficult); 4 (limb rigid in flexion or extension). Values represent least square (LS) mean differences between baseline and Week 4 resulting from Mixed Model Repeated Measurement (MMRM) models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here "n" was the number of subjects who were evaluable for this measure at a given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model.

End point type	Primary

End point timeframe:

Baseline and Week 4

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[1]	87[2]	176[3]	
Units: unit on a scale				
least squares mean (standard error)				
High (n=172) versus Low (n=85)	-0.93 (± 0.078)	999 (± 999)	-1.15 (± 0.056)	
Mid (n=86) versus Low (n=85)	-0.96 (± 0.082)	-1.02 (± 0.082)	999 (± 999)	

Notes:

[1] - MP-FAS

[2] - MP-FAS

[3] - MP-FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline, Gross Motor Function Classification System–Extended and Revised (GMFCS-E&R) level at screening included as covariates. For MMRM visit*treatment is interaction term repeated factor.

Comparison groups	MP Low Dose Group v MP High Dose Group
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.04

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline, GMFCS-E&R level at screening included as covariates. For MMRM visit*treatment is interaction term repeated factor.

Comparison groups	MP Low Dose Group v MP Mid Dose Group
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	MMRM
Parameter estimate	LS-Mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.15

Primary: Co-primary Variable MP: Investigator's Global Impression of Change Scale (GICS) at Week 4

End point title	Co-primary Variable MP: Investigator's Global Impression of Change Scale (GICS) at Week 4

End point description:

The GICS was used to measure independently the investigator’s impression of change due to treatment. The response option was a common 7-point Likert scale, that ranges from +3 (very much improved); +2 (much improved); +1 (minimally improved); 0 (no change); -1 (minimally worse); -2 (much worse); -3 (very much worse). Values represent LS mean differences between baseline and Week 4 resulting from ANCOVA models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here “n” was the number of subjects who were evaluable for this measure at given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model.

End point type	Primary

End point timeframe:

Week 4

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[4]	87[5]	176[6]	
Units: unit on a scale				
least squares mean (standard error)				
High (n=176) versus Low (n=87)	1.55 (± 0.083)	999 (± 999)	1.64 (± 0.062)	
Mid (n=87) versus Low (n=87)	1.57 (± 0.089)	1.44 (± 0.092)	999 (± 999)	

Notes:

[4] - MP-FAS

[5] - MP-FAS

[6] - MP-FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS-Means are from analysis of covariance (ANCOVA) with treatment group, pooled site and pretreatment status included as fixed factors and maximum AS score of the two possible primary target patterns flexed elbow or flexed wrist baseline, GMFCS-E&R level at screening included as covariates.

Comparison groups	MP Low Dose Group v MP High Dose Group
Number of subjects included in analysis	263
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.34
Method	ANCOVA
Parameter estimate	LS-Mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.28

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS-Means are from ANCOVA with treatment group, pooled site and pre-treatment status included as fixed factors and maximum AS score of the two possible primary target patterns flexed elbow or flexed wrist baseline, GMFCS-E&R level at screening included as covariates.

Comparison groups	MP Low Dose Group v MP Mid Dose Group
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297
Method	ANCOVA
Parameter estimate	LS-Mean difference
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.11

Secondary: MP: Change From Baseline in AS score of the Other Treated UL Main Clinical Target Pattern at Week 4

End point title	MP: Change From Baseline in AS score of the Other Treated UL Main Clinical Target Pattern at Week 4

End point description:

The AS categorizes the severity of spasticity by judging resistance to passive movement. Spasticity was assessed by 5-point scale at visits, where: 0 (no increase in tone); 1(slight increase in tone giving a "catch" when the limb was moved in flexion or extension); 2(more marked increase in tone, but limb easily flexed); 3(considerable increase in tone - passive movements difficult); 4(limb rigid in flexion or extension). Values represent LS mean differences between baseline and Week 4 resulting from MMRM models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here "n" was the number of subjects who were evaluable for this measure at given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[7]	88[8]	176[9]	
Units: unit on a scale				
least squares mean (standard error)				
High (n=143) versus Low (n=67)	-1.03 (± 0.083)	999 (± 999)	-1.13 (± 0.061)	
Mid (n=69) versus Low (n=67)	-1.08 (± 0.087)	-1.22 (± 0.090)	999 (± 999)	

Notes:

[7] - MP-FAS

[8] - MP-FAS

[9] - MP-FAS

Statistical analyses

No statistical analyses for this end point

Secondary: MP: Change From Baseline in AS score in UL Treated Clenched Fist With Flexed Wrist at Week 4

End point title	MP: Change From Baseline in AS score in UL Treated Clenched Fist With Flexed Wrist at Week 4

End point description:

The AS categorizes the severity of spasticity by judging resistance to passive movement. Spasticity was assessed by 5-point scale at visits, where: 0 (no increase in tone); 1(slight increase in tone giving a

"catch" when the limb was moved in flexion or extension); 2(more marked increase in tone, but limb easily flexed); 3(considerable increase in tone - passive movements difficult); 4(limb rigid in flexion or extension). Values represent LS mean differences between baseline and Week 4 resulting from MMRM models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here "n" was the number of subjects who were evaluable for this measure at given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[10]	88[11]	176[12]	
Units: unit on a scale				
least squares mean (standard error)				
High (n=45) versus Low (n=18)	-0.53 (± 0.212)	999 (± 999)	-1.00 (± 0.133)	
Mid (n=20) versus Low (n=18)	-0.070 (± 0.202)	-1.04 (± 0.176)	999 (± 999)	

Notes:

[10] - MP-FAS

[11] - MP-FAS

[12] - MP-FAS

Statistical analyses

No statistical analyses for this end point

Secondary: MP: Change From Baseline in AS score for Each Treated Clinical Pattern of the UL at Week 4

End point title	MP: Change From Baseline in AS score for Each Treated Clinical Pattern of the UL at Week 4

End point description:

The AS categorizes the severity of spasticity by judging resistance to passive movement. Spasticity was assessed by 5-point scale at visits, where: 0 (no increase in tone); 1(slight increase in tone giving a "catch" when the limb was moved in flexion or extension); 2(more marked increase in tone, but limb easily flexed); 3(considerable increase in tone - passive movements difficult); 4(limb rigid in flexion or extension). Values represent LS mean differences between baseline and Week 4 resulting from MMRM models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here "n" was the number of subjects who were evaluable for this measure at given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[13]	88[14]	176[15]	
Units: unit on a scale				
least squares mean (standard error)				
Flexed elbow: High (n=166) versus Low (n=83)	-0.99 (± 0.076)	999 (± 999)	-1.18 (± 0.056)	
Flexed elbow: Mid (n=82) versus Low (n=83)	-1.01 (± 0.081)	-1.17 (± 0.082)	999 (± 999)	
Flexed wrist: High (n=149) versus Low (n=69)	-0.96 (± 0.085)	999 (± 999)	-1.08 (± 0.061)	
Flexed wrist: Mid (n=73) versus Low (n=69)	-1.01 (± 0.087)	-1.05 (± 0.087)	999 (± 999)	
Clenched fist: High (n=64) versus Low (n=34)	-0.64 (± 0.136)	999 (± 999)	-1.09 (± 0.096)	
Clenched fist: Mid (n=30) versus Low (n=34)	-0.58 (± 0.145)	-0.87 (± 0.141)	999 (± 999)	
Thumb in palm: High (n=98) versus Low (n=49)	-0.88 (± 0.116)	999 (± 999)	-1.11 (± 0.083)	
Thumb in palm: Mid (n=44) versus Low (n=49)	-0.93 (± 0.131)	-1.14 (± 0.123)	999 (± 999)	
Pronated forearm: High (n=150) versus Low (n=72)	-0.88 (± 0.080)	999 (± 999)	-1.02 (± 0.058)	
Pronated forearm: Mid (n=73) versus Low (n=72)	-0.87 (± 0.086)	-0.94 (± 0.088)	999 (± 999)	

Notes:

[13] - MP-FAS

[14] - MP-FAS

[15] - MP-FAS

Statistical analyses

No statistical analyses for this end point

Secondary: MP: Change From Baseline in Scores of Pain Intensity (From Subjects) and Pain Frequency (From Parent/Caregiver) Assessed With 'Questionnaire on Pain caused by Spasticity (QPS)'

End point title	MP: Change From Baseline in Scores of Pain Intensity (From Subjects) and Pain Frequency (From Parent/Caregiver) Assessed With 'Questionnaire on Pain caused by Spasticity (QPS)'

End point description:

Pain intensity (from subjects) and pain frequency (from parent/caregiver) to be assessed with QPS. The QPS Total Score for pain intensity ranges from 0 ('No Hurt') to 10 ('Hurt Worst'). The QPS Total Score for the observed pain frequency ranges from 0 (Never) to 4 (Always). Values represent LS mean differences between baseline and Week 4 resulting from MMRM models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here "n" was the number of subjects who were evaluable for this measure at given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model. P/C = Parent/Caregiver.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, and 14

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[16]	88[17]	176[18]	
Units: unit on a scale				
least squares mean (standard error)				
UL, Subject, Week 4 High (n=52) versus low (n=30)	-0.42 (± 0.217)	999 (± 999)	-0.75 (± 0.199)	
UL, Subject, Week 4 Mid (n=34) versus low (n=30)	-0.39 (± 0.256)	-0.67 (± 0.289)	999 (± 999)	
UL, Subject, Week 8 High (n=52) versus low (n=29)	-0.52 (± 0.206)	999 (± 999)	-0.64 (± 0.188)	
UL, Subject, Week 8 Mid (n=34) versus low (n=29)	-0.63 (± 0.259)	-0.55 (± 0.290)	999 (± 999)	
UL, Subject, Week 14 High (n=52) versus low (n=27)	-0.56 (± 0.217)	999 (± 999)	-0.59 (± 0.202)	
UL, Subject, Week 14 Mid (n=32) versus low (n=27)	-0.66 (± 0.327)	-0.59 (± 0.361)	999 (± 999)	
UL, P/C, Week 4 High (n=133) versus low (n=64)	-0.46 (± 0.102)	999 (± 999)	-0.44 (± 0.076)	
UL, P/C, Week 4 Mid (n=65) versus low (n=64)	-0.43 (± 0.106)	-0.28 (± 0.115)	999 (± 999)	
UL, P/C, Week 8 High (n=138) versus low (n=67)	-0.40 (± 0.095)	999 (± 999)	-0.44 (± 0.070)	
UL, P/C, Week 8 Mid (n=66) versus low (n=67)	-0.43 (± 0.100)	-0.34 (± 0.109)	999 (± 999)	
UL, P/C, Week 14 High (n=137) versus low (n=58)	-0.23 (± 0.105)	999 (± 999)	-0.24 (± 0.071)	
UL, P/C, Week 14 Mid (n=61) versus low (n=58)	-0.31 (± 0.100)	-0.25 (± 0.107)	999 (± 999)	
LL, Subject, Week 4 High (n=43) versus low (n=24)	-0.74 (± 0.282)	999 (± 999)	-0.62 (± 0.250)	
LL, Subject, Week 4 Mid (n=29) versus low (n=24)	-0.46 (± 0.305)	-0.55 (± 0.321)	999 (± 999)	
LL, Subject, Week 8 High (n=44) versus low (n=25)	-1.04 (± 0.241)	999 (± 999)	-0.69 (± 0.218)	
LL, Subject, Week 8 Mid (n=28) versus low (n=25)	-0.90 (± 0.261)	-0.81 (± 0.284)	999 (± 999)	
LL, Subject, Week 14 High (n=43) versus low (n=23)	-0.71 (± 0.275)	999 (± 999)	-0.57 (± 0.245)	
LL, Subject, Week 14 Mid (n=28) versus low (n=23)	-0.67 (± 0.315)	-0.63 (± 0.335)	999 (± 999)	
LL, P/C, Week 4 High (n=110) versus low (n=56)	-0.50 (± 0.105)	999 (± 999)	-0.52 (± 0.077)	
LL, P/C, Week 4 Mid (n=54) versus low (n=56)	-0.46 (± 0.103)	-0.42 (± 0.111)	999 (± 999)	
LL, P/C, Week 8 High (n=113) versus low (n=59)	-0.56 (± 0.098)	999 (± 999)	-0.51 (± 0.074)	
LL, P/C, Week 8 Mid (n=54) versus low (n=59)	-0.52 (± 0.102)	-0.36 (± 0.111)	999 (± 999)	
LL, P/C, Week 14 High (n=110) versus low (n=53)	-0.33 (± 0.108)	999 (± 999)	-0.32 (± 0.078)	
LL, P/C, Week 14 Mid (n=53) versus low (n=53)	-0.37 (± 0.086)	-0.31 (± 0.090)	999 (± 999)	

Notes:

[16] - MP-FAS

[17] - MP-FAS

[18] - MP-FAS

Statistical analyses

No statistical analyses for this end point

Secondary: MP: Child's/Adolescent's, and Parent's/Caregiver's GICS in UL at Week 4

End point title	MP: Child's/Adolescent's, and Parent's/Caregiver's GICS in UL at Week 4

End point description:

The GICS was used to measure independently the child's/adolescent's, and parent's or caregiver's impression of change due to treatment. The response option was a common 7-point Likert scale, that ranges from: +3(very much improved); +2(much improved); +1(minimally improved); 0(no change); -1(minimally worse); -2(much worse); -3(very much worse). Values represent LS mean differences between baseline and Week 4 resulting from ANCOVA models comparing high versus low and in a second step mid versus low dose groups, respectively. Values for the low group may differ slightly depending on the comparison and are therefore provided separately for each comparison. Here "n" was the number of subjects who were evaluable for this measure at a given time period and were included in the assessment. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Week 4

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[19]	88[20]	176[21]	
Units: unit on a scale				
least squares mean (standard error)				
Subject: High (n=55) versus Low (n=31)	1.51 (± 0.153)	999 (± 999)	1.63 (± 0.139)	
Subject: Mid (n=38) versus Low (n=31)	1.53 (± 0.180)	1.48 (± 0.190)	999 (± 999)	
Parent/Caregiver: High (n=176) versus Low (n=87)	1.41 (± 0.087)	999 (± 999)	1.60 (± 0.065)	
Parent/Caregiver: Mid (n=87) versus Low (n=87)	1.36 (± 0.094)	1.29 (± 0.097)	999 (± 999)	

Notes:

[19] - MP-FAS

[20] - MP-FAS

[21] - MP-FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of Treatment Emergent Adverse Events (TEAEs) Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of Treatment Emergent Adverse Events (TEAEs) Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once. Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[22]	87[23]	176[24]	331[25]
Units: Subjects				
Overall	21	13	42	114
First injection cycle (MP) (n=87,87,176,0)	21	13	42	0
Second injection cycle (OLEX) (n=0,0,0,331)	0	0	0	64
Third injection cycle (OLEX) (n=0,0,0,331)	0	0	0	43
Fourth injection cycle (OLEX) (n=0,0,0,331)	0	0	0	48

Notes:

[22] - SES

[23] - SES

[24] - SES

[25] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of TEAEs of Special Interest (TEAESIs) Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of TEAEs of Special Interest (TEAESIs) Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once. Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[26]	87[27]	176[28]	331[29]
Units: subjects				
Overall	1	1	1	5
First injection cycle (MP) (n=87,87,176,0)	1	1	1	0
Second injection cycle (OLEX) (n=0,0,0,331)	0	0	0	2
Third injection cycle (OLEX) (n=0,0,0,331)	0	0	0	3
Fourth injection cycle (OLEX) (n=0,0,0,331)	0	0	0	1

Notes:

[26] - SES

[27] - SES

[28] - SES

[29] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of Serious TEAEs (TESAEs) Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of Serious TEAEs (TESAEs) Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once. Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[30]	87[31]	176[32]	331[33]
Units: subjects				
Overall	2	1	2	16
First injection cycle (MP) (n=87,87,176,0)	2	1	2	0
Second injection cycle (OLEX) (n=0,0,0,331)	0	0	0	7
Third injection cycle (OLEX) (n=0,0,0,331)	0	0	0	9
Fourth injection cycle (OLEX) (n=0,0,0,331)	0	0	0	3

Notes:

[30] - SES

[31] - SES

[32] - SES

[33] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of TEAEs Related to Treatment Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of TEAEs Related to Treatment Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in MP and OLEX with study medication at least once. Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[34]	87[35]	176[36]	331[37]
Units: subjects				
Overall	0	0	3	5
First injection cycle (MP) (n=87,87,176,0)	0	0	3	0
Second injection cycle (OLEX) (n=0,0,0,331)	0	0	0	2
Third injection cycle (OLEX) (n=0,0,0,331)	0	0	0	2
Fourth injection cycle (OLEX) (n=0,0,0,331)	0	0	0	1

Notes:

[34] - SES

[35] - SES

[36] - SES

[37] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of TEAEs by Worst Intensity Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of TEAEs by Worst Intensity Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once.

Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[38]	87[39]	176[40]	331[41]
Units: subjects				
Overall: Mild	15	10	33	62
Overall: Moderate	6	2	7	44
Overall: Severe	0	1	2	8
First injection cycle (MP): Mild (n=87,87,176,0)	15	10	33	0
First injection cycle (MP):Moderate(n=87,87,176,0)	6	2	7	0
First injection cycle (MP): Severe (n=87,87,176,0)	0	1	2	0
Second injection cycle (OLEX): Mild (n=0,0,0,331)	0	0	0	43
Second injection cycle(OLEX):Moderate(n=0,0,0,331)	0	0	0	18
Second injection cycle (OLEX): Severe(n=0,0,0,331)	0	0	0	3
Third injection cycle (OLEX): Mild (n=0,0,0,331)	0	0	0	23
Third injection cycle (OLEX):Moderate(n=0,0,0,331)	0	0	0	15
Third injection cycle (OLEX): Severe (n=0,0,0,331)	0	0	0	4
Fourth injection cycle (OLEX): Mild (n=0,0,0,331)	0	0	0	28
Fourth injection cycle(OLEX):Moderate(n=0,0,0,331)	0	0	0	19
Fourth injection cycle (OLEX): Severe(n=0,0,0,331)	0	0	0	1

Notes:

[38] - SES

[39] - SES

[40] - SES

[41] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of TEAEs by Worst Causal Relationship Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of TEAEs by Worst Causal Relationship Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once.

Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[42]	87[43]	176[44]	331[45]
Units: subjects				
Overall: Related	0	0	3	5
Overall: Not related	21	13	39	109
First cycle (MP): Related (n=87,87,176,0)	0	0	3	0
First cycle (MP): Not related (n=87,87,176,0)	21	13	39	0
Second cycle (OLEX): Related (n=0,0,0,331)	0	0	0	2
Second cycle (OLEX): Not related (n=0,0,0,331)	0	0	0	62
Third cycle (OLEX): Related (n=0,0,0,331)	0	0	0	2
Third cycle (OLEX): Not related (n=0,0,0,331)	0	0	0	40
Fourth cycle (OLEX): Related (n=0,0,0,331)	0	0	0	1
Fourth cycle (OLEX): Not related (n=0,0,0,331)	0	0	0	47

Notes:

[42] - SES

[43] - SES

[44] - SES

[45] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of TEAEs by Final Outcome Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of TEAEs by Final Outcome Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once. Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[46]	87[47]	176[48]	331[49]
Units: subjects				
Overall: Resolved	18	10	39	96
Overall: Resolved with sequelae	1	0	0	1
Overall: Resolving	0	2	1	7
Overall: Not resolved	2	1	1	8
Overall: Unknown	0	0	1	2
Overall: Fatal	0	0	0	0
First cycle (MP): Resolved (n=87,87,176,0)	18	10	39	0
Firstcycle(MP):Resolvedwithsequelae(n=87,87,176,0)	1	0	0	0
First cycle (MP): Resolving(n=87,87,176,0)	0	2	1	0
First cycle (MP): Not resolved(n=87,87,176,0)	2	1	1	0
First cycle (MP): Unknown(n=87,87,176,0)	0	0	1	0
First cycle (MP): Fatal(n=87,87,176,0)	0	0	0	0
Second cycle (OLEX): Resolved(n=0,0,0,331)	0	0	0	57
Secondcycle(OLEX):Resolvedwithsequelae(n=0,0,0,331	0	0	0	0
Second cycle (OLEX): Resolving(n=0,0,0,331)	0	0	0	3
Second cycle (OLEX): Not resolved(n=0,0,0,331)	0	0	0	4
Second cycle (OLEX): Unknown(n=0,0,0,331)	0	0	0	0
Second cycle (OLEX): Fatal(n=0,0,0,331)	0	0	0	0
Third cycle (OLEX): Resolved(n=0,0,0,331)	0	0	0	37
Thirdcycle(OLEX):Resolvedwithsequelae(n=0,0,0,331)	0	0	0	0
Third cycle (OLEX): Resolving(n=0,0,0,331)	0	0	0	0
Third cycle (OLEX): Not resolved(n=0,0,0,331)	0	0	0	4
Third cycle (OLEX): Unknown(n=0,0,0,331)	0	0	0	1
Third cycle (OLEX): Fatal(n=0,0,0,331)	0	0	0	0
Fourth cycle (OLEX): Resolved(n=0,0,0,331)	0	0	0	39
Fourthcycle(OLEX):Resolvedwithsequelae(n=0,0,0,331	0	0	0	1
Fourth cycle (OLEX): Resolving(n=0,0,0,331)	0	0	0	4
Fourth cycle (OLEX): Not resolved(n=0,0,0,331)	0	0	0	2
Fourth cycle (OLEX): Unknown(n=0,0,0,331)	0	0	0	2
Fourth cycle (OLEX): Fatal(n=0,0,0,331)	0	0	0	0

Notes:

[46] - SES

[47] - SES

[48] - SES

[49] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of TEAEs Leading to Discontinuation Overall and per Treatment Cycle

End point title	Number of Subjects With Occurrence of TEAEs Leading to Discontinuation Overall and per Treatment Cycle

End point description:

The SES was the subset of all subjects treated in the MP and OLEX with study medication at least once. Number of subjects who were evaluable for this measure at a given time period and were included in the assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

End point values	MP Low Dose Group	MP Mid Dose Group	MP High Dose Group	OLEX (3 Injections)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87[50]	87[51]	176[52]	331[53]
Units: subjects				
Overall	0	1	1	5
First injection cycle (MP) (n=87,87,176,0)	0	1	1	0
Second injection cycle (OLEX) (n=0,0,0,331)	0	0	0	3
Third injection cycle (OLEX) (n=0,0,0,331)	0	0	0	2
Fourth injection cycle (OLEX) (n=0,0,0,331)	0	0	0	0

Notes:

[50] - SES

[51] - SES

[52] - SES

[53] - SES

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 66	
Adverse event reporting additional description:	
The investigator asked the participant for adverse events (AEs) systematically at each visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	MP: Low Dose Group
Reporting group description:	
In MP, subjects randomized to low dose group were injected with doses of NT 201 ranging from 2 to 5 U/kg BW up to a total body dose of 125 U.	
Reporting group title	MP: Mid Dose Group
Reporting group description:	
In MP, subjects randomized to mid dose group were injected with doses of NT 201 ranging from 6 to 15 U/kg BW up to a total body dose of 375 U.	
Reporting group title	MP: High Dose Group
Reporting group description:	
In MP, subjects randomized to high dose group were injected with doses of NT 201 ranging from 8 to 20 U/kg BW up to a total body dose of 500 U.	
Reporting group title	OLEX (3 Injections)
Reporting group description:	
Subjects who completed MP and qualified for further participation in the study were treated with doses of NT 201 between 8 and 20 U/kg (maximum body dose of 500 U in subjects with >25kg BW) in each of the three injection cycles in OLEX.	

Serious adverse events	MP: Low Dose Group	MP: Mid Dose Group	MP: High Dose Group
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 87 (2.30%)	1 / 87 (1.15%)	2 / 176 (1.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Electroencephalogram			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Spinal cord neoplasm			

subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Injury, poisoning and procedural complications			
Shunt malfunction			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Thermal burn			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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			
CSF shunt operation			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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			
Brain oedema			
subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 87 (1.15%)	0 / 87 (0.00%)	0 / 176 (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
Seizure			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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

Status epilepticus			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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			
Hiatus hernia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Cyclic vomiting syndrome			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Vomiting			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			

subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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			
Bronchitis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 87 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	2 / 176 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Bronchitis bacterial			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Peritonitis			

subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertussis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Pharyngitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 87 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 87 (0.00%)	0 / 176 (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
Urinary tract infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (0.00%)	0 / 176 (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 (3 Injections)		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 331 (4.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Electroencephalogram			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps)			
Spinal cord neoplasm			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Shunt malfunction			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
CSF shunt operation			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 331 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	0 / 331 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	0 / 331 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	0 / 331 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 331 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis bacterial				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pertussis			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MP: Low Dose Group	MP: Mid Dose Group	MP: High Dose Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)	3 / 87 (3.45%)	6 / 176 (3.41%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 87 (5.75%)	3 / 87 (3.45%)	6 / 176 (3.41%)
occurrences (all)	5	5	6

Non-serious adverse events	OLEX (3 Injections)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 331 (5.44%)		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 331 (5.44%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2015	Incorporated FDA recommendations based on the draft FDA Guidance for Industry, 'Suicidal ideation and behavior: prospective assessment of occurrence in clinical trials'.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported