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

Summary

EudraCT number	2012-005054-30
Trial protocol	EE AT DE SK CZ ES Outside EU/EEA FR
Global end of trial date	11 May 2016

Results information

Result version number	v2 (current)
This version publication date	18 August 2017
First version publication date	24 November 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MRZ60201_3070_1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01893411
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 69 1503 1, clinicaltrials@merz.de
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001039-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to investigate the dose-response of Botulinum neurotoxin type A free from complexing proteins (NT 201) in subjects with Lower limb (LL) spasticity due toCerebral palsy (CP) after injection treatment in three parallel dose groups: 16 Units [U]/kg body weight [BW] NT 201 with a maximum total dose of 400 U in the high dose group, 12 U/kg BW NT 201 with a maximum total dose of 300 U in the mid dose group, and 4 U/kg BW NT 201 with a maximum total dose of 100 U in the low dose group. Two injection treatments were followed by 12 to 36 weeks observation each (overall duration: 24-72 weeks).

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	23 July 2013
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: 61
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Ukraine: 107
Country: Number of subjects enrolled	Korea, Republic of: 54
Country: Number of subjects enrolled	Romania: 9
Worldwide total number of subjects	311
EEA total number of subjects	113

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)	261
Adolescents (12-17 years)	50
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 338 subjects were screened and 311 subjects were randomised and treated with high dose (156 subjects), mid dose (77 subjects) and low dose (78 subjects). The safety evaluation set (SES) is the subset of all subjects treated with study medication at least once.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)

Arm description:

Subjects received 16 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 400 U per injection treatment via intramuscular injection into spastic muscles.

Arm type	Experimental
Investigational medicinal product name	Incobotulinumtoxin A
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:

Subjects received 16 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 400 U per injection treatment via intramuscular injection into spastic muscles.

Arm title	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)

Arm description:

Subjects received 12 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 300 U per injection treatment via intramuscular injection into spastic muscles.

Arm type	Experimental
Investigational medicinal product name	Incobotulinumtoxin A
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:

Subjects received 12 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 300 U per injection treatment via intramuscular injection into spastic muscles.

Arm title	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)

Arm description:

Subjects received 4 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 100 U per injection treatment via intramuscular injection into spastic muscles.

Arm type	Experimental

Investigational medicinal product name	Incobotulinumtoxin A
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:

Subjects received 4 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 100 U per injection treatment via intramuscular injection into spastic muscles.

Number of subjects in period 1	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Started	156	77	78
Completed	139	70	69
Not completed	17	7	9
Physician decision	1	1	2
Consent withdrawn by subject	7	4	3
Adverse event, non-fatal	1	-	-
Not specified	3	1	3
Lost to follow-up	2	-	1
Lack of efficacy	2	1	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 16 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 400 U per injection treatment via intramuscular injection into spastic muscles.	
Reporting group title	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 12 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 300 U per injection treatment via intramuscular injection into spastic muscles.	
Reporting group title	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 4 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 100 U per injection treatment via intramuscular injection into spastic muscles.	

Reporting group values	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Number of subjects	156	77	78
Age categorical Units: Subjects			
Children (2-11 years)	131	67	63
Adolescents (12-17 years)	25	10	15
Age continuous Units: years			
arithmetic mean	6.4	6.6	7.1
standard deviation	± 3.9	± 3.8	± 4.6
Gender categorical Units: Subjects			
Female	83	44	42
Male	73	33	36

Reporting group values	Total		
Number of subjects	311		
Age categorical Units: Subjects			
Children (2-11 years)	261		
Adolescents (12-17 years)	50		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	169		
Male	142		

End points

End points reporting groups

Reporting group title	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 16 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 400 U per injection treatment via intramuscular injection into spastic muscles.	
Reporting group title	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 12 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 300 U per injection treatment via intramuscular injection into spastic muscles.	
Reporting group title	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 4 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 100 U per injection treatment via intramuscular injection into spastic muscles.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS population is subset in the Safety evaluation set (SES) for whom the primary efficacy variable (for all subjects who had at least an Ashworth Scale [AS] score of plantar flexor at baseline [Day 1 of the first injection cycle] or the investigator's Global Impression of Change of Plantar Flexor Spasticity Scale (GICS-PF) [for subjects with bilateral treatment on same body side as chosen for the primary efficacy variable] at Day 29 [Week 4] of the first injection cycle) were available as part of end points reporting groups	

Primary: Change From Baseline in the Ashworth Scale (AS) Score of Plantar Flexors of the Primary Body Side at Day 29 (Week 4) of the First Injection Cycle (1st IC)

End point title	Change From Baseline in the Ashworth Scale (AS) Score of Plantar Flexors of the Primary Body Side at Day 29 (Week 4) of the First Injection Cycle (1st IC)
End point description:	
The Ashworth Scale(AS) is a well known and commonly used scale in clinical trials with spasticity. In spastic muscles, resistance to passive movement is assessed. It is a 5-point scale that ranges from 0 (= no increase in tone) to 4 (=limb rigid in flexion or extension). Subjects with bilateral pes equinus, body side for primary efficacy analysis i.e. "primary body side" was decided by investigator at screening and was kept throughout the entire study. Subjects with unilateral treatment, treated body side was kept throughout the entire study. Values represent least square (LS) mean differences between baseline and Week 4 resulting from MMRM (Mixed Model Repeated Measurement) 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. The value 999 indicates that no data is available from the respective specific model.	
End point type	Primary
End point timeframe:	
Baseline, Week 4	

End point values	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[1]	77[2]	78[3]	
Units: Units on a scale				

least squares mean (standard error)				
Week 4 of 1st IC (high versus low; n=156, 78)	-0.7 (± 0.061)	999 (± 999)	-0.66 (± 0.084)	
Week 4 of 1st IC (mid versus low; n=77, n=78)	999 (± 999)	-0.7 (± 0.089)	-0.66 (± 0.088)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin) v High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Mixed Model Repeated Measure
Parameter estimate	LS-Mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.14

Statistical analysis title	Statistical analysis 2
Comparison groups	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin) v Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741
Method	Mixed Model Repeated Measure
Parameter estimate	LS-Mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.18

Primary: Co-primary Variable: Investigator's Global Impression of Change of Plantar Flexor Spasticity Scale (GICS-PF) of the Primary Body Side at Day 29 (Week 4) of the First Injection Cycle (1st IC)

End point title	Co-primary Variable: Investigator's Global Impression of Change of Plantar Flexor Spasticity Scale (GICS-PF) of the Primary Body Side at Day 29 (Week 4) of the First Injection Cycle (1st IC)

End point description:

This variable is classified as co-primary to satisfy Food and Drug Administration(FDA) request. The GICS-PF scale is a 7-Point Likert Scale for the assessment of the functional change due to treatment of plantar flexor spasticity only. Ranges from +3 (very much improved function) to -3 (very much worse function). For subjects with bilateral pes equinus, body side for primary efficacy analysis i.e. "primary body side" was decided by investigator at screening and was kept throughout the entire study. For subjects with unilateral treatment, treated body side was kept throughout the entire study. 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. The value 999 indicates that no data is available from the respective specific model

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[4]	77[5]	78[6]	
Units: Units on a scale				
least squares mean (standard error)				
Week 4 of 1st IC (high versus low; n=156, 78)	1.53 (± 0.059)	999 (± 999)	1.37 (± 0.081)	
Week 4 of 1st IC (mid versus low; n=77, n=78)	999 (± 999)	1.38 (± 0.092)	1.32 (± 0.09)	

Notes:

[4] - FAS

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin) v Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	Mixed Model Repeated Measure
Parameter estimate	LS-Mean difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.34

Statistical analysis title	Statistical analysis 2
Comparison groups	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin) v Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603
Method	Mixed Model Repeated Measure
Parameter estimate	LS-Mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.27

Secondary: Change From Baseline in the AS Score of Plantar Flexors of the Nonprimary Body Side in Subjects With Bilateral Treatment at Day 29 (Week 4) of the First (1st) and Second Injection Cycle (2nd IC)

End point title	Change From Baseline in the AS Score of Plantar Flexors of the Nonprimary Body Side in Subjects With Bilateral Treatment at Day 29 (Week 4) of the First (1st) and Second Injection Cycle (2nd IC)

End point description:

The AS is a well known and commonly used scale in clinical trials with spasticity. In spastic muscles the resistance to passive movement is assessed. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension).
Values represent least square (LS) mean differences between baseline and the respective week (w) resulting from MMRM (Mixed Model Repeated Measurement) 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 and are therefore provided separately for each comparison. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline, Week 4 of 1st IC and Week 16-40 of 2nd IC

End point values	High Dose: 16 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[7]	77[8]	78[9]	
Units: Units on a scale				
least squares mean (standard error)				

Week 4 of 1st IC (high versus low; n=114, 54)	-0.76 (± 0.073)	999 (± 999)	-0.61 (± 0.104)	
Week 4 of 1st IC (mid versus low; n=58, 54)	999 (± 999)	-0.6 (± 0.105)	-0.58 (± 0.108)	
Week 4 of 2nd IC (high versus low; n=104, 53)	-0.95 (± 0.077)	999 (± 999)	-0.74 (± 0.106)	
Week 4 of 2nd IC (mid versus low; n=53, 53)	999 (± 999)	-0.85 (± 0.124)	-0.76 (± 0.123)	

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the AS Score of Plantar Flexors of the Primary Body Side at Day 29 (week 4) of the Second Injection Cycle

End point title	Change From Baseline in the AS Score of Plantar Flexors of the Primary Body Side at Day 29 (week 4) of the Second Injection Cycle

End point description:

The AS is a well known and commonly used scale in clinical trials with spasticity. In spastic muscles the resistance to passive movement is assessed. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension). For subjects with bilateral pes equinus, the body side for primary efficacy analysis i.e. "primary body side" was decided by investigator at screening and was kept throughout the entire study. For subjects with unilateral treatment, the treated body side was kept throughout the entire study. Values represent LS mean differences between baseline and the respective week (w) 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. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 4 of 2nd IC (Week 16-40)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[10]	77[11]	78[12]	
Units: Units on a scale				
least squares mean (standard error)				
Week 4 of 2nd IC (high versus low; n=143, 73)	-0.89 (± 0.061)	999 (± 999)	-0.82 (± 0.082)	
Week 4 of 2nd IC (mid versus low; n=71, n=73)	999 (± 999)	-1.03 (± 0.094)	-0.85 (± 0.091)	

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in AS Score of Plantar Flexors of the Primary Body Side at Day 57 (Week 8) and Day 85 (Week 12) of the 1st and of the 2nd Injection Cycle (IC)

End point title	Changes From Baseline in AS Score of Plantar Flexors of the Primary Body Side at Day 57 (Week 8) and Day 85 (Week 12) of the 1st and of the 2nd Injection Cycle (IC)

End point description:

The Ashworth Scale (AS) is a well known and commonly used scale in clinical trials with spasticity. In spastic muscles the resistance to passive movement is assessed. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension). Subjects with bilateral pes equinus, the body side for primary efficacy analysis i.e. "primary body side" was decided by investigator at screening and was kept throughout the entire study. Subjects with unilateral treatment, the treated body side was kept throughout the entire study. Values represent LS mean differences between baseline and the respective week (w) 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. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to week 8 and 12 of 1st IC and 2nd IC (week 20-44 and 24-48)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	77	78	
Units: Units on a scale				
least squares mean (standard error)				
Week 8 of 1st IC (high versus low; n=156, 78)	-0.62 (± 0.059)	999 (± 999)	-0.69 (± 0.08)	
Week 8 of 1st IC (mid versus low; n=77, n=78)	999 (± 999)	-0.74 (± 0.088)	-0.69 (± 0.086)	
Week 12 of 1st IC (high versus low; n=156, 78)	-0.43 (± 0.056)	999 (± 999)	-0.58 (± 0.077)	
Week 12 of 1st IC (mid versus low; n=77, n=78)	999 (± 999)	-0.45 (± 0.086)	-0.59 (± 0.085)	
Week 8 of 2nd IC (high versus low; n=143, 73)	-0.76 (± 0.058)	999 (± 999)	-0.76 (± 0.079)	
Week 8 of 2nd IC (mid versus low; n=71, 73)	999 (± 999)	-0.92 (± 0.092)	-0.79 (± 0.09)	
Week 12 of 2nd IC (high versus low; n=143, 73)	-0.57 (± 0.058)	999 (± 999)	-0.65 (± 0.079)	
Week 12 of 2nd IC (mid versus low; n=71, 73)	999 (± 999)	-0.64 (± 0.088)	-0.68 (± 0.085)	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in AS Score of Knee Flexors or Thigh Adductors in Subjects With Unilateral Treatment at Day 29 (Week 4) of the First and Second Injection Cycle (IC)

End point title	Changes From Baseline in AS Score of Knee Flexors or Thigh Adductors in Subjects With Unilateral Treatment at Day 29 (Week 4) of the First and Second Injection Cycle (IC)

End point description:

The AS is a well known and commonly used scale in clinical trials with spasticity. In spastic muscles the resistance to passive movement is assessed. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension).
Values represent least square (LS) mean differences between baseline and the respective week (w) 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.
KF = Knee Flexors; TA = Thigh Adductors; w = week. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 4 of 1st IC and 2nd IC (Week 16-40)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[13]	77[14]	78[15]	
Units: Units on a scale				
least squares mean (standard error)				
KF, w 4 of 1st IC (high versus low; n=30, 19)	-0.6 (± 0.18)	999 (± 999)	-0.39 (± 0.214)	
KF, w 4 of 1st IC (mid versus low; n=11, 19)	999 (± 999)	-0.07 (± 0.285)	-0.32 (± 0.204)	
KF, w 4 of 2nd IC (high versus low; n=27, 16)	-0.64 (± 0.173)	999 (± 999)	-0.79 (± 0.2)	
KF, w 4 of 2nd IC (mid versus low; n=10, 16)	999 (± 999)	-0.31 (± 0.269)	-0.67 (± 0.19)	
TA, w 4 of 1st IC (high versus low; n=12, 5)	-0.61 (± 0.287)	999 (± 999)	-0.76 (± 0.506)	
TA, w 4 of 1st IC (mid versus low; n=8, 5)	999 (± 999)	999 (± 999)	999 (± 999)	
TA, w 4 of 2nd IC (high versus low; n=11, 4)	999 (± 999)	999 (± 999)	999 (± 999)	
TA, w 4 of 2nd IC (mid versus low; n=8, 4)	999 (± 999)	999 (± 999)	999 (± 999)	

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Modified Tardieu Scale (MTS) of Plantar Flexors of Primary Body Side at Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12) of the First and of the Second Injection Cycle (IC)

End point title	Changes From Baseline in Modified Tardieu Scale (MTS) of Plantar Flexors of Primary Body Side at Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12) of the First and of the Second Injection Cycle (IC)

End point description:

The MTS assesses spastic muscle tone by subtraction of two angles measured at different conditions of passive muscle stretch. R2 is the angle of passive range of motion with a passive movement at slow speed. R1 is the angle where a "catch-and-release" or clonus can be triggered at the fastest possible speed. Score values represent the measured (R2-R1) difference, i.e. the dynamic tone component of the examined muscle(s). Decreases of (R2-R1) represent reductions in the dynamic component of spasticity, i.e. improvement of dynamic muscle spasticity.
Values represent LS mean differences between baseline and the respective week (w) 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 model used for comparison and are therefore provided separately for each comparison. The value 999 indicates that no data is available respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 8, and 12 of 1st IC and 2nd IC (Week 16-40, 20-44 and 24-48)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[16]	77[17]	78[18]	
Units: Units on a scale				
least squares mean (standard error)				
Week 4 of 1st IC (high versus low; n=156, 78)	-2.38 (± 0.897)	999 (± 999)	-2.56 (± 1.231)	
Week 4 of 1st IC (mid versus low; n=77, 78)	999 (± 999)	-0.88 (± 1.389)	-2.47 (± 1.367)	
Week 8 of 1st IC (high versus low; n=156, 78)	-3.15 (± 0.921)	999 (± 999)	-2.63 (± 1.267)	
Week 8 of 1st IC (mid versus low; n=77, 78)	999 (± 999)	-1.74 (± 1.393)	-2.56 (± 1.372)	
Week 12 of 1st IC (high versus low; n=156, 78)	-3.1 (± 0.848)	999 (± 999)	-2.67 (± 1.157)	
Week 12 of 1st IC (mid versus low; n=77, 78)	999 (± 999)	-0.07 (± 1.231)	-2.59 (± 1.213)	
Week 4 of 2nd IC (high versus low; n=143, 73)	-4.72 (± 1.173)	999 (± 999)	-3.83 (± 1.594)	
Week 4 of 2nd IC (mid versus low; n=71, 73)	999 (± 999)	-3.24 (± 1.773)	-3.6 (± 1.713)	
Week 8 of 2nd IC (high versus low; n=143, 73)	-4.72 (± 1.065)	999 (± 999)	-4.25 (± 1.44)	
Week 8 of 2nd IC (mid versus low; n=71, 73)	999 (± 999)	-2.97 (± 1.634)	-4.04 (± 1.575)	
Week 12 of 2nd IC (high versus low; n=143, 73)	-4.27 (± 0.968)	999 (± 999)	-5.68 (± 1.298)	
Week 12 of 2nd IC (mid versus low; n=71, 73)	999 (± 999)	-2.12 (± 1.519)	-5.45 (± 1.455)	

Notes:

[16] - FAS

[17] - FAS

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's, Child's/Adolescent's, and Parent's/Caregiver's Global Impression of Change Scale [GICS] at Day 29 (week 4) of the 1st and 2nd Injection Cycle

End point title	Investigator's, Child's/Adolescent's, and Parent's/Caregiver's Global Impression of Change Scale [GICS] at Day 29 (week 4) of the 1st and 2nd Injection Cycle

End point description:

The Global Impression of Change Scales (GICS) are global outcomes to assess the impression of change due to treatment. GICS were assessed by the investigator, by the participant (if feasible) and by parents'/caregiver (if applicable). GICS are 7-Point Likert Scales ranging from +3 (very much improved function) to -3 (very much worse function).
Values represent LS mean differences between baseline and the respective week (w) 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. Inv = Investigator; S = Subject; P/C = Parent/Caregiver. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 4 of 1st IC and 2nd IC (Week 16-40)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[19]	77[20]	78[21]	
Units: Units on a scale				
least squares mean (standard error)				
Inv, 1st IC (high versus low; n=156, 78)	1.5 (± 0.056)	999 (± 999)	1.35 (± 0.076)	
Inv, 1st IC (mid versus low; n=77, 78)	999 (± 999)	1.36 (± 0.087)	1.33 (± 0.086)	
S, 1st IC (high versus low; n=67, 41)	1.72 (± 0.205)	999 (± 999)	1.64 (± 0.223)	
S, 1st IC (mid versus low; n=42, 41)	999 (± 999)	1.17 (± 0.203)	1.3 (± 0.216)	
P/C, 1st IC (high versus low; n=156, 78)	1.53 (± 0.068)	999 (± 999)	1.43 (± 0.092)	
P/C, 1st IC (mid versus low; n=77, 78)	999 (± 999)	1.26 (± 0.107)	1.39 (± 0.105)	
Inv, 2nd IC (high versus low; n=143, 73)	1.46 (± 0.071)	999 (± 999)	1.38 (± 0.096)	
Inv, 2nd IC (mid versus low; n=77, 73)	999 (± 999)	1.56 (± 0.11)	1.46 (± 0.104)	
S, 2nd IC (high versus low; n=60, 36)	1.53 (± 0.21)	999 (± 999)	1.66 (± 0.224)	
S, 2nd IC (mid versus low; n=39, 36)	999 (± 999)	1.44 (± 0.276)	1.53 (± 0.283)	
P/C, 2nd IC (high versus low; n=143, 73)	1.45 (± 0.076)	999 (± 999)	1.34 (± 0.101)	

P/C, 2nd IC (mid versus low; n=71, 73)	999 (± 999)	1.67 (± 0.115)	1.4 (± 0.109)	

Notes:

[19] - FAS

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Global Impression of Change of GICS-Plantar-Flexor of Primary Body Side at Day 29 (Week 4) of the First and Second Injection Cycle

End point title	Investigator's Global Impression of Change of GICS-Plantar-Flexor of Primary Body Side at Day 29 (Week 4) of the First and Second Injection Cycle

End point description:

The GICS are global outcomes to assess the impression of change due to treatment. GICS were assessed by the investigator, by the subject(if feasible) and by parents'/caregiver (if applicable). GICS are 7-Point Likert Scales ranging from +3 (very much improved function) to -3 (very much worse function). Subjects with bilateral pes equinus, body side for primary efficacy analysis i.e. "primary body side" was decided by investigator at screening and was kept throughout the entire study. Subjects with unilateral treatment, treated body side was kept throughout the entire study.
Values represent LS mean differences between baseline and the respective week (w) 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.The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 4 of 1st IC and 2nd IC (Week 16-40)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[22]	77[23]	78[24]	
Units: Units on a scale				
least squares mean (standard error)				
Week 4 of 1st IC (high versus low; n=156, 78)	1.53 (± 0.059)	999 (± 999)	1.37 (± 0.081)	
Week 4 of 1st IC (mid versus low; n=77, 78)	999 (± 999)	1.38 (± 0.092)	1.32 (± 0.09)	
Week 4 of 2nd IC (high versus low; n=143, 73)	1.43 (± 0.073)	999 (± 999)	1.38 (± 0.098)	
Week 4 of 2nd IC (mid versus low; n=71, 73)	999 (± 999)	1.54 (± 0.11)	1.48 (± 0.103)	

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Gross Motor Function Measure [GMFM]-66 Score at the End of First Injection Cycle and at the End of Study Visit

End point title	Changes From Baseline in Gross Motor Function Measure [GMFM]-66 Score at the End of First Injection Cycle and at the End of Study Visit

End point description:

The GMFM-66 is a standardized observational 66-item instrument designed and validated to measure change in gross motor function over time in subjects with cerebral palsy. Score values represent the total GMFM-66 score. Total GMFM scores range from 0 (worst) to 100 (best).
Values represent LS mean differences between baseline and the respective week (w) 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. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 12-36 of 1st IC and 2nd IC (End of study = Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[25]	77[26]	78[27]	
Units: Units on a scale				
least squares mean (standard error)				
W 12-36 of 1st IC (high versus low; n=155, 77)	1.23 (± 0.288)	999 (± 999)	1.64 (± 0.392)	
W 12-36 of 1st IC (mid versus low; n=77, 77)	999 (± 999)	1.14 (± 0.448)	1.49 (± 0.445)	
W 12-36 of 2nd IC (high versus low; n=155, 77)	2.31 (± 0.359)	999 (± 999)	2.46 (± 0.488)	
W 12-36 of 2nd IC (mid versus low; n=77, 77)	999 (± 999)	3.1 (± 0.542)	2.59 (± 0.539)	

Notes:

[25] - FAS

[26] - FAS

[27] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Scores of Pain Intensity (From Subjects) and Pain Frequency (From Parent/Caregiver) to all Post Baseline Visits of the 1st and of the 2nd Injection Cycle

End point title	Change in Scores of Pain Intensity (From Subjects) and Pain Frequency (From Parent/Caregiver) to all Post Baseline Visits of the 1st and of the 2nd Injection Cycle

End point description:

The QPS is a patient-reported outcome for children and adolescents (2-17 years) with cerebral palsy on spasticity-related pain. Pain intensity (from subjects) and pain frequency (from parent/caregiver) to be

assessed with 'Questionnaire on Pain caused by Spasticity [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 the respective week (w) 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. S = Subject; P/C = Parent/Caregiver; w = week. The value 999 indicates that no data is available from the respective specific model.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 8, and 12 of 1st IC and 2nd IC (Week 16-40, 20-44 and 24-48)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[28]	77[29]	78[30]	
Units: Units on a scale				
least squares mean (standard error)				
S, w 4 of 1st IC (high versus low; n=72, 42)	-0.66 (± 0.198)	999 (± 999)	-1.32 (± 0.23)	
S, w 4 of 1st IC (mid versus low; n=42, 42)	999 (± 999)	-1.02 (± 0.301)	-1.61 (± 0.31)	
S, w 8 of 1st IC (high versus low; n=72, 42)	-0.6 (± 0.228)	999 (± 999)	-0.93 (± 0.265)	
S, w 8 of 1st IC (mid versus low; n=42, 42)	999 (± 999)	-0.94 (± 0.299)	-1.06 (± 0.308)	
S, w 12 of 1st IC (high versus low; n=72, 42)	-0.42 (± 0.207)	999 (± 999)	-1.13 (± 0.241)	
S, w 12 of 1st IC (mid versus low; n=42, 42)	999 (± 999)	-1.14 (± 0.253)	-1.47 (± 0.261)	
P/C, w 4 of 1st IC (high versus low; n=64, 39)	-0.44 (± 0.067)	999 (± 999)	-0.49 (± 0.089)	
P/C, w 4 of 1st IC (mid versus low; n=39, 39)	999 (± 999)	-0.31 (± 0.094)	-0.34 (± 0.093)	
P/C, w 8 of 1st IC (high versus low; n=64, 39)	-0.48 (± 0.069)	999 (± 999)	-0.47 (± 0.092)	
P/C, w 8 of 1st IC (mid versus low; n=39, 39)	999 (± 999)	-0.29 (± 0.092)	-0.33 (± 0.091)	
P/C, w 12, 1st IC (high versus low; n=64, 39)	-0.44 (± 0.071)	999 (± 999)	-0.37 (± 0.095)	
P/C, w 12, 1st IC (mid versus low; n=39, 39)	999 (± 999)	-0.21 (± 0.095)	-0.3 (± 0.095)	
S, w 4 of 2nd IC (high versus low; n=72, 42)	-0.53 (± 0.26)	999 (± 999)	-1.03 (± 0.289)	
S, w 4 of 2nd IC (mid versus low; n=42, 42)	999 (± 999)	-1.36 (± 0.347)	-1.53 (± 0.351)	
S, w 8 of 2nd IC (high versus low; n=72, 42)	-0.78 (± 0.272)	999 (± 999)	-1.16 (± 0.302)	
S, w 8 of 2nd IC (mid versus low; n=42, 42)	999 (± 999)	-1.56 (± 0.312)	-1.61 (± 0.315)	
S, w 12 of 2nd IC (high versus low; n=72, 42)	-0.34 (± 0.299)	999 (± 999)	-0.97 (± 0.333)	
S, w 12 of 2nd IC (mid versus low; n=72, 42)	999 (± 999)	-1.37 (± 0.333)	-1.4 (± 0.336)	

P/C, w 4 of 2nd IC (high versus low; n=64, 39)	-0.54 (± 0.078)	999 (± 999)	-0.47 (± 0.102)	
P/C, w 4 of 2nd IC (mid versus low; n=39, 39)	999 (± 999)	-0.59 (± 0.111)	-0.46 (± 0.105)	
P/C, w 8 of 2nd IC (high versus low; n=64, 39)	-0.55 (± 0.08)	999 (± 999)	-0.47 (± 0.104)	
P/C, w 8 of 2nd IC (mid versus low; n=39, 39)	999 (± 999)	-0.54 (± 0.119)	-0.44 (± 0.113)	
P/C, w 12, 2nd IC (high versus low; n=64, 39)	-0.49 (± 0.085)	999 (± 999)	-0.4 (± 0.112)	
P/C, w 12, 2nd IC (mid versus low; n=39, 39)	999 (± 999)	-0.52 (± 0.128)	-0.33 (± 0.121)	

Notes:

[28] - FAS

[29] - FAS

[30] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reinjection for Each of the Three Dose Groups for the 1st and 2nd Injection Cycle

End point title	Time to Reinjection for Each of the Three Dose Groups for the 1st and 2nd Injection Cycle

End point description:

End point type	Secondary

End point timeframe:

Baseline up to Week 24-72

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[31]	77[32]	78[33]	
Units: Weeks				
arithmetic mean (standard deviation)				
1st Injection cycle (n=143, 77, 73)	15.3 (± 4.6)	15.9 (± 5.7)	15.7 (± 5.9)	
2nd Injection Cycle (n= 110, 51, 57)	17 (± 6.5)	17.9 (± 7.8)	15.5 (± 4.9)	

Notes:

[31] - FAS

[32] - FAS

[33] - FAS

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Treatment-emergent Adverse Events (TEAEs) are events observed from the time point of first injection until end of study visit (week 24-72). Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to End of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[34]	77[35]	78[36]	
Units: Subjects				
1st Injection Cycle	53	15	18	
2nd Injection Cycle	44	15	21	
Overall Period	77	26	30	

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Subjects with TEAEs of Special Interest (TEAESIs) Overall and per Injection Cycle

End point title	Occurrence of Subjects with TEAEs of Special Interest (TEAESIs) Overall and per Injection Cycle

End point description:

Adverse Events (AE's) occurring after treatment that were thought to possibly indicate toxin spread throughout the trial conduct are defined as AE's of Special Interests. Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to end of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[37]	77[38]	78[39]	
Units: Subjects				
1st Injection Cycle	4	1	0	

2nd Injection Cycle	2	0	1	
Overall Period	5	1	1	

Notes:

[37] - FAS

[38] - FAS

[39] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Serious TEAEs (TESAEs) Overall and per Injection Cycle

End point title	Occurrence of Serious TEAEs (TESAEs) Overall and per Injection Cycle

End point description:

Treatment-emergent Serious Adverse Events (TESAEs) are events observed from the time point of first injection until end of study visit (week 24-72). Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to end of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[40]	77[41]	78[42]	
Units: Subjects				
1st Injection Cycle	4	0	3	
2nd Injection Cycle	3	1	3	
Overall Period	7	1	6	

Notes:

[40] - FAS

[41] - FAS

[42] - FAS

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Treatment-emergent Adverse Events (TEAEs) are events observed from the time point of first injection until end of study visit (week 24-72). Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to end of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[43]	77[44]	78[45]	
Units: Subjects				
1st Injection Cycle	7	1	2	
2 nd Injection Cycle	4	1	1	
Overall Period	11	2	2	

Notes:

[43] - FAS

[44] - FAS

[45] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of TEAEs by Worst Intensity Overall and per Injection Cycle

End point title	Occurrence of TEAEs by Worst Intensity Overall and per Injection Cycle

End point description:

Treatment-emergent Adverse Events (TEAEs) are events observed from the time point of first injection until end of study visit (week 24-72). Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to end of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[46]	77[47]	78[48]	
Units: Subjects				
1st Injection Cycle: Mild AE’s	35	6	14	
1st Injection Cycle: Moderate AE’s	17	9	4	
1st Injection Cycle: Severe AE’s	1	0	0	
2nd Injection Cycle: Mild AE’s	24	9	11	
2nd Injection Cycle: Moderate AE’s	18	5	9	
2nd Injection Cycle: Severe AE’s	2	1	1	
Overall: Mild AE’s	41	14	19	
Overall: Moderate AE’s	33	11	10	
Overall: Severe AE’s	3	1	1	

Notes:
[46] - FAS
[47] - FAS
[48] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of TEAEs by Final Outcome Overall and per Injection Cycle

End point title	Occurrence of TEAEs by Final Outcome Overall and per Injection Cycle

End point description:

Treatment-emergent Adverse Events (TEAEs) are events observed from the time point of first injection until end of study visit (week 24-72). Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to end of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[49]	77[50]	78[51]	
Units: Subjects				
1st Injection Cycle: recovered/resolved	52	15	17	
1st Injection Cycle: recovering/resolving	0	0	0	
1st Injection Cycle: not recovered/ not resolved	3	0	1	
1st Injection Cycle: recovered/resolved w/ sequela	1	0	0	
1st Injection Cycle: fatal	0	0	0	
1st Injection Cycle: unknown	1	0	0	
2nd Injection Cycle: recovered/resolved	42	14	20	
2nd Injection Cycle: recovering/resolving	2	1	0	
2nd Injection Cycle: not recovered/ not resolved	3	2	2	
2nd Injection Cycle: recovered/resolved w/ sequela	0	0	0	
2nd Injection Cycle: fatal	0	0	0	
2nd Injection Cycle: unknown	0	0	0	
Overall: recovered/resolved	74	25	28	
Overall: recovering/resolving	2	1	0	
Overall: not recovered/ not resolved	6	2	3	
Overall: recovered/resolved w/ sequelae	1	0	0	
Overall: fatal	0	0	0	
Overall: unknown	1	0	0	

Notes:

[49] - FAS

[50] - FAS

[51] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of TEAEs leading to Discontinuation Overall and per Injection Cycle

End point title	Occurrence of TEAEs leading to Discontinuation Overall and per Injection Cycle

End point description:

Treatment-emergent Adverse Events (TEASs) are events observed from the time point of first injection until end of study visit (week 24-72). Values reported here refer to the number of subjects affected.

End point type	Secondary

End point timeframe:

Up to end of study visit (Week 24-72)

End point values	High Dose: 16 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Mid Dose: 12 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	Low Dose: 4 U/kg Body Weight Incobotulinumtoxin A (Xeomin)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156[52]	77[53]	78[54]	
Units: Subjects				
1st Injection Cycle	1	0	0	
2nd Injection Cycle	0	0	0	
Overall Period	1	0	0	

Notes:

[52] - FAS

[53] - FAS

[54] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the timepoint of first injection until end of study visit (week 24-72)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	High Dose: 16 U/kg body weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 16 U/kg BW of IncobotulinumtoxinA (Xeomin) with a maximum of 400 U per injection treatment via intramuscular injection into spastic muscles.	
Reporting group title	Low Dose: 4 U/kg body weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 4 U/kg body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 100 U per injection treatment via intramuscular injection into spastic muscles.	
Reporting group title	Mid Dose: 12 U/kg body weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 12 U/kg body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 300 U per injection treatment via intramuscular injection into spastic muscles.	

Serious adverse events	High Dose: 16 U/kg body weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg body weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg body weight IncobotulinumtoxinA (Xeomin)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 156 (4.49%)	6 / 78 (7.69%)	1 / 77 (1.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Brain contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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
Concussion			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Craniocerebral injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Humerus fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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
Laceration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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			
Strabismus correction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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			
Epilepsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Febrile convulsion			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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
Partial seizures			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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			
Bronchial obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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			
Arthritis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Arthritis reactive			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Bursitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Synovitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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			
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	1 / 78 (1.28%)	0 / 77 (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
Borrelia infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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 infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 77 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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
Tonsillitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 77 (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 viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	High Dose: 16 U/kg body weight IncobotulinumtoxinA (Xeomin)	Low Dose: 4 U/kg body weight IncobotulinumtoxinA (Xeomin)	Mid Dose: 12 U/kg body weight IncobotulinumtoxinA (Xeomin)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 156 (14.74%)	15 / 78 (19.23%)	10 / 77 (12.99%)
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 156 (1.92%)	4 / 78 (5.13%)	1 / 77 (1.30%)
occurrences (all)	5	5	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 156 (10.90%)	9 / 78 (11.54%)	8 / 77 (10.39%)
occurrences (all)	32	11	15
Bronchitis			
subjects affected / exposed	3 / 156 (1.92%)	7 / 78 (8.97%)	1 / 77 (1.30%)
occurrences (all)	6	7	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2013	This amendment includes clarification that occurrence of severe Adverse event of special interest (AESI) of respiratory function or severe swallowing disorders were criteria for premature study discontinuation of subjects without any further re-exposure to Investigational product (IP). Addition of swallowing disorders to respiratory disorders as AESI category that could lead to premature discontinuation of the study. Clarification that an End of Study Visit was to be conducted whenever possible at any time point, if a subject discontinued study participation, not only after the first injection cycle. Clarification that hospitalization for analgosedation starting one day before or on the day of injection treatments was not regarded as an Serious adverse event (SAE), if performed for organizational reasons only. Addition of estimated Glomerular filtration rate (GFR) to assess subject's renal function based on the height and creatinine levels. Clarification of regulation to keep clinical patterns of spasticity treatment throughout participation in this trial and to keep these patterns also in subjects rolling over to the open-label study. Clarification of the calculation of the visit window in case of visits where the Gross Motor Function Measure (GMFM) was performed one day prior to all other assessments. Correction of ranges for injection sites for the gastrocnemius muscle and for all other muscles in the Gross Motor Function Measure (CSP) to be in line with the regulation of maximum of 25 units (U) per injection site in subjects less than (<) 25 kilogram (kg) body weight (BW) and maximum of 50 U in subjects with BW greater than or equal to (≥) 25 kg. Description how confidential data were handled on the GMFM-66 source form. Change in order of appearance of assessments in overview of study activities were aligned with descriptions in separate outcome manual for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported