Clinical trial results:
Open-label, non-controlled, multicenter long-term study to investigate the safety and efficacy of Xeomin® (incobotulinumtoxinA, NT 201) for the treatment of spasticity of the lower limb(s) or of combined spasticity of upper and lower limb in children and adolescents (age 2 - 17 years) with cerebral palsy

Summary

EudraCT number	2012-005055-17
Trial protocol	AT EE SK CZ Outside EU/EEA FR
Global end of trial date	16 January 2017
Results information	
Result version number	v2 (current)
This version publication date	26 November 2017
First version publication date	15 July 2017
Version creation reason	• Correction of full data set Adding number of participants not assessed data to 1st secondary endpoint to make it match with CTgov

Trial information

Trial identification	
Sponsor protocol code	MRZ60201_3071_1
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01905683
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 January 2017
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 the leg(s) or of leg(s) and one arm are safe in treating children/adolescents (age 2-17 years) long-term with increased muscle tension/uncontrollable muscle stiffness (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	27 November 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: 67
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Ukraine: 170
Country: Number of subjects enrolled	Romania: 22
Worldwide total number of subjects	370
EEA total number of subjects	102

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)	317
Adolescents (12-17 years)	53
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 391 subjects were screened, of which 370 subjects were enrolled and treated in this study. Of these, 124 subjects were recruited from the lead-in study (62, 29 and 33 subjects from the IncobotulinumtoxinA high, mid and low dose group respectively of the study MRZ60201_3070_1 [2012-005054-30]) and 246 subjects were newly recruited.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)

Arm description:

Subjects received total doses of 16 to 20 unit per kilogram (U/kg) body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 400 to 500 units per injection treatment via intramuscular injection into spastic muscles on Day 1 of 4 treatment cycles (12 to 16 weeks treatment per each cycle). The higher dose could only be administered to subjects with GMFCS-E&R levels I to III.

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:

All subjects received 8U/kg per pes equinus into at least one pes equinus and 12 to 16U/kg total into their lower limb(s). Newly recruited subjects were eligible to receive additional 4U into their UL. Subjects who were enrolled after completion of the lead-in study MRZ60201_3070_1 (2012-005054-30) all received 16 U/kg (max. 400 U) per injection treatment into the same LL only treatment patterns chosen in the previous study.

Number of subjects in period 1	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Started	370
Completed	319
Not completed	51
Consent withdrawn by subject	20
Physician decision	1
Other	13
Adverse Events	4
Lost to follow-up	4

Lack of efficacy	8
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received total doses of 16 to 20 unit per kilogram (U/kg) body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 400 to 500 units per injection treatment via intramuscular injection into spastic muscles on Day 1 of 4 treatment cycles (12 to 16 weeks treatment per each cycle). The higher dose could only be administered to subjects with GMFCS-E&R levels I to III.	

Reporting group values	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)	Total	
Number of subjects	370	370	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	317	317	
Adolescents (12-17 years)	53	53	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	6.2		
standard deviation	± 4.1	-	
Gender categorical Units: Subjects			
Female	150	150	
Male	220	220	

End points

End points reporting groups

Reporting group title	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)

Reporting group description:

Subjects received total doses of 16 to 20 unit per kilogram (U/kg) body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 400 to 500 units per injection treatment via intramuscular injection into spastic muscles on Day 1 of 4 treatment cycles (12 to 16 weeks treatment per each cycle). The higher dose could only be administered to subjects with GMFCS-E&R levels I to III.

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

Subject analysis set description:

The SES included all subjects treated with investigational product (IP) at least once.

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

Subject analysis set description:

The FAS included all subjects in the SES for whom at least a baseline value (Day 1 of the first cycle, Visit 2) of ashworth scale (AS) score of plantar flexors was available. For subjects from lead-in study at least one post-baseline value was available.

Primary: 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[1]

End point description:

TEAEs are events observed from the time point of first injection until end of study visit (Week 50-66). Values reported here refer to the number of subjects affected. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Primary

End point timeframe:

From the timepoint of first injection up to end of study visit (Week 50-66)

Notes:

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

End point values	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[2]			
Units: subjects				
1st Injection Cycle (n=370)	53			
2nd Injection Cycle (n=350)	44			
3rd Injection Cycle (n=340)	26			
4th Injection Cycle (n=323)	31			
Overall Period (n=370)	109			

Notes:

[2] - SES

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of TEAEs of Special Interest (TEAESIs) Overall and Per Injection Cycle

End point title	Occurrence of TEAEs of Special Interest (TEAESIs) Overall and Per Injection Cycle[3]

End point description:

TEAE occurring after treatment that were thought to possibly indicate toxin spread throughout the trial conduct are defined as TEAE of Special Interests. Values reported here refer to the number of subjects affected. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Primary

End point timeframe:

From the timepoint of first injection until end of study visit (Week 50-66)

Notes:

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

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[4]			
Units: subjects				
1st Injection Cycle (n=370)	1			
2nd Injection Cycle (n=350)	2			
3rd Injection Cycle (n=340)	1			
4th Injection Cycle (n=323)	0			
Overall Period (n=370)	3			

Notes:

[4] - SES

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of Treatment-emergent Serious Adverse Events (TESAEs) Overall and Per Injection Cycle

End point title	Occurrence of Treatment-emergent Serious Adverse Events (TESAEs) Overall and Per Injection Cycle[5]

End point description:

TESAEs are events observed from the time point of first injection until end of study visit (Week 50-66). Values reported here refer to the number of subjects affected. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Primary

End point timeframe:

From the timepoint of first injection until end of study visit (Week 50-66)

Notes:

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

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[6]			
Units: subjects				
1st Injection Cycle (n=370)	6			
2nd Injection Cycle (n=350)	5			
3rd Injection Cycle (n=340)	5			
4th Injection Cycle (n=323)	1			
Overall Period (n=370)	16			

Notes:

[6] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator’s Global Assessment of Tolerability at Day 99 (Week 14) Of Each Injection Cycle

End point title	Investigator’s Global Assessment of Tolerability at Day 99 (Week 14) Of Each Injection Cycle

End point description:

The investigator’s global assessment of tolerability was assessed on a 4-point ordinal scale where 1 = very good, 2 = good, 3 = moderate, and 4 = poor. Results for Day 99 (Week 14) of 4th injection cycles were collected at the end of study visit. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Secondary

End point timeframe:

Day 99 (Week 14) of 1st, 2nd, 3rd and 4th injection cycle (IC)

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[7]			
Units: subjects				
1st IC: Very Good (n=350)	203			
1st IC: Good (n=350)	119			
1st IC: Moderate (n=350)	23			
1st IC: Poor (n=350)	5			
2nd IC: Very Good (n=340)	225			
2nd IC: Good (n=340)	87			
2nd IC: Moderate (n=340)	24			
2nd IC: Poor (n=340)	4			
3rd IC: Very Good (n=323)	223			
3rd IC: Good (n=323)	74			
3rd IC: Moderate (n=323)	17			
3rd IC: Poor (n=323)	9			

4th IC: Very Good (n=370)	241			
4th IC: Good (n=370)	76			
4th IC: Moderate (n=370)	16			
4th IC: Poor (n=370)	8			
4th IC: Not assessed (n=370)	29			

Notes:

[7] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Ashworth Scale (AS) Score of Left and Right Plantar Flexors (PF) From Baseline to all Other Visits, From Day 1 of Each Injection Cycle to Day 29 (Week 4), Day 57 (Week 8, 1st IC Cycle Only) and Day 99 (Week 14) of the Respective Injection Cycle

End point title	Changes in Ashworth Scale (AS) Score of Left and Right Plantar Flexors (PF) From Baseline to all Other Visits, From Day 1 of Each Injection Cycle to Day 29 (Week 4), Day 57 (Week 8, 1st IC Cycle Only) and Day 99 (Week 14) of the Respective 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 efficacy analysis i.e. “primary body side” was decided by investigator at screening and was kept throughout the entire study. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles. V3 = Week 4 of 1st IC; V4 = Week 8 of 1st IC; V5 = Day 1 of 2nd IC; V6 = Week 4 of 2nd IC; V7 = Day 1 of 3rd IC; V8 = Week 4 of 3rd IC; V9 = Day 1 of 4th IC; V10 = Week 4 of 4th IC; V11 = Week 14 of 4th IC = end of study visit.

End point type	Secondary

End point timeframe:

Baseline (Day 1, Visit[V] 2) to all other visits (V3, V4, V5, V6, V7, V8, V9, V10, and V11); From Day 1 of Each IC to Day 29 (Week 4), Day 57 (Week 8, 1st IC cycle only) and Day 99 (Week 14) of the respective IC

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[8]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Left PF Baseline (V2) to V3 (n=302)	-0.8 (± 0.7)			
Left PF Baseline (V2) to V4 (n=304)	-0.7 (± 0.7)			
Left PF Baseline (V2) to V5 (n=288)	-0.2 (± 0.5)			
Left PF Baseline (V2) to V6 (n=288)	-1.1 (± 0.8)			
Left PF Baseline (V2) to V7 (n=282)	-0.3 (± 0.6)			
Left PF Baseline (V2) to V8 (n=281)	-1.2 (± 0.8)			
Left PF Baseline (V2) to V9 (n=268)	-0.3 (± 0.6)			
Left PF Baseline (V2) to V10 (n=268)	-1.3 (± 0.8)			
Left PF Baseline (V2) to V11 (n=282)	-0.9 (± 0.8)			

Left PF 2nd IC: Day 1 to Day 29 (n=288)	-0.9 (± 0.8)			
Left PF 2nd IC: Day 1 to Day 99 (n=282)	-0.1 (± 0.4)			
Left PF 3rd IC: Day 1 to Day 29 (n=281)	-0.9 (± 0.7)			
Left PF 3rd IC: Day 1 to Day 99 (n=268)	-0.1 (± 0.4)			
Left PF 4th IC: Day 1 to Day 29 (n=268)	-1 (± 0.7)			
Left PF 4th IC: Day 1 to Day 99 (n=264)	-0.6 (± 0.7)			
Right PF Baseline (V2) to V3 (n=306)	-0.8 (± 0.7)			
Right PF Baseline (V2) to V4 (n=308)	-0.7 (± 0.7)			
Right PF Baseline (V2) to V5 (n=293)	-0.2 (± 0.5)			
Right PF Baseline (V2) to V6 (n=291)	-1 (± 0.8)			
Right PF Baseline (V2) to V7 (n=285)	-0.2 (± 0.5)			
Right PF Baseline (V2) to V8 (n=284)	-1.2 (± 0.8)			
Right PF Baseline (V2) to V9 (n=273)	-0.3 (± 0.5)			
Right PF Baseline (V2) to V10 (n=273)	-1.2 (± 0.8)			
Right PF Baseline (V2) to V11 (n=287)	-0.9 (± 0.8)			
Right PF 2nd IC: Day 1 to Day 29 (n=291)	-0.8 (± 0.7)			
Right PF 2nd IC: Day 1 to Day 99 (n=285)	-0.1 (± 0.4)			
Right PF 3rd IC: Day 1 to Day 29 (n=284)	-1 (± 0.7)			
Right PF 3rd IC: Day 1 to Day 99 (n=273)	0 (± 0.4)			
Right PF 4th IC: Day 1 to Day 29 (n=273)	-1 (± 0.7)			
Right PF 4th IC: Day 1 to Day 99 (n=270)	-0.6 (± 0.7)			

Notes:

[8] - 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 Each 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 Each 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). Here, 'n' indicates number of subjects exposed to each dose group for each injection cycle. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Secondary

End point timeframe:

Day 29 (Week 4) of 1st, 2nd, 3rd and 4th IC

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[9]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Investigator, Day 29 of 1st IC (n=366)	1.7 (± 0.7)			
Investigator, Day 29 of 2nd IC (n=348)	1.8 (± 0.8)			
Investigator, Day 29 of 3rd IC (n=339)	1.9 (± 0.8)			
Investigator, Day 29 of 4th IC (n=323)	2 (± 0.9)			
Subject, Day 29 of 1st IC (n=124)	1.6 (± 0.8)			
Subject, Day 29 of 2nd IC (n=117)	1.7 (± 1)			
Subject, Day 29 of 3rd IC (n=109)	1.7 (± 0.9)			
Subject, Day 29 of 4th IC (n=98)	1.8 (± 0.9)			
Parent/Caregiver, Day 29 of 1st IC (n=366)	1.6 (± 0.8)			
Parent/Caregiver, Day 29 of 2nd IC (n=348)	1.8 (± 0.8)			
Parent/Caregiver, Day 29 of 3rd IC (n=339)	1.8 (± 0.8)			
Parent/Caregiver, Day 29 of 4th IC (n=323)	1.9 (± 0.9)			

Notes:

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Global Impression of Change of Plantar Flexor Spasticity Scale (GICS-PF) of Left and Right Plantar Flexors at Day 29 (Week 4) of Each Injection Cycle

End point title	Investigator's Global Impression of Change of Plantar Flexor Spasticity Scale (GICS-PF) of Left and Right Plantar Flexors at Day 29 (Week 4) of Each 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). For subjects with bilateral pes equinus, the body side for efficacy analysis i.e. "primary body side" was decided by investigator at screening and was kept throughout the entire study. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Secondary

End point timeframe:

Day 29 (Week 4) of 1st, 2nd, 3rd and 4th IC

End point values	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[10]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Left PF Day 29 of 1st IC (n=302)	1.7 (± 0.7)			
Left PF Day 29 of 2nd IC (n=288)	1.8 (± 0.8)			
Left PF Day 29 of 3rd IC (n=281)	1.9 (± 0.8)			
Left PF Day 29 of 4th IC (n=268)	2 (± 0.9)			
Right PF Day 29 of 1st IC (n=306)	1.7 (± 0.7)			
Right PF Day 29 of 2nd IC (n=291)	1.8 (± 0.8)			
Right PF Day 29 of 3rd IC (n=284)	1.9 (± 0.8)			
Right PF Day 29 of 4th IC (n=273)	2 (± 0.9)			

Notes:

[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Modified Tardieu Scale (MTS) of Left and Right Plantar Flexors From Baseline to all Other Visits, From Day 1 of Each Injection Cycle to Day 29 (Week 4), Day 57 (Week 8, 1st IC Cycle Only) and Day 99 (Week 14) of the Respective Injection Cycle

End point title	Changes in Modified Tardieu Scale (MTS) of Left and Right Plantar Flexors From Baseline to all Other Visits, From Day 1 of Each Injection Cycle to Day 29 (Week 4), Day 57 (Week 8, 1st IC Cycle Only) and Day 99 (Week 14) of the Respective Injection Cycle

End point description:

The Modified Tardieu Scale (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. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles. V3 = Week 4 of 1st IC; V4 = Week 8 of 1st IC; V5 = Day 1 of 2nd IC; V6 = Week 4 of 2nd IC; V7 = Day 1 of 3rd IC; V8 = Week 4 of 3rd IC; V9 = Day 1 of 4th IC; V10 = Week 4 of 4th IC; V11 = Week 14 of 4th IC = end of study visit.

End point type	Secondary

End point timeframe:

Baseline (Day 1, Visit[V] 2) to all other visits (V3, V4, V5, V6, V7, V8, V9, V10, and V11); From Day 1 of Each IC to Day 29 (Week 4), Day 57 (Week 8, 1st IC cycle only) and Day 99 (Week 14) of the respective IC

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[11]			
Units: degrees				
arithmetic mean (standard deviation)				
Left PF Baseline(V2) to V3 (n=302)	-1.4 (± 10.6)			
Left PF Baseline (V2) to V4(n=304)	-1.8 (± 9.8)			
Left PF Baseline (V2) to V5(n=288)	-1 (± 7.1)			
Left PF Baseline (V2) to V6(n=288)	-1 (± 12.3)			
Left PF Baseline (V2) to V7(n=282)	-1.7 (± 8.1)			
Left PF Baseline (V2) to V8(n=281)	-0.5 (± 13.8)			
Left PF Baseline (V2) to V9(n=268)	-2.5 (± 8.1)			
Left PF Baseline (V2) to V10(n=268)	-1.1 (± 14.6)			
Left PF Baseline (V2) to V11(n=283)	-2.8 (± 10.9)			
Left PF 2nd IC: Day 1 to Day 29(n=288)	0 (± 11.1)			
Left PF 2nd IC: Day 1 to Day 99(n=282)	-0.7 (± 5.8)			
Left PF 3rd IC: Day 1 to Day 29(n=281)	1.2 (± 10.9)			
Left PF 3rd IC: Day 1 to Day 99(n=268)	-1 (± 5.8)			
Left PF 4th IC: Day 1 to Day 29(n=268)	1.5 (± 11.7)			
Left PF 4th IC: Day 1 to Day 99(n=264)	0 (± 7.9)			
Right PF Baseline (V2) to V3(n=306)	-1.3 (± 10.6)			
Right PF Baseline(V2)to V4(n=308)	-2.1 (± 9.3)			
Right PF Baseline(V2)to V5(n=293)	-1.3 (± 7)			
Right PF Baseline(V2)to V6(n=291)	-0.7 (± 12.4)			
Right PF Baseline(V2)to V7(n=285)	-2.2 (± 8.3)			
Right PF Baseline(V2)to V8(n=284)	-0.1 (± 13.9)			
Right PF Baseline(V2)to V9(n=273)	-2.6 (± 8.5)			
Right PF Baseline(V2)to V10(n=273)	-0.7 (± 14.4)			
Right PF Baseline (V2) to V11 (n=287)	-2.6 (± 11.7)			
Right PF 2nd IC: Day 1 to Day 29(n=291)	0.6 (± 11.1)			
Right PF 2nd IC: Day 1 to Day 99(n=285)	-1 (± 7.2)			
Right PF 3rd IC: Day 1 to Day 29(n=284)	2.1 (± 11.5)			
Right PF 3rd IC: Day 1 to Day 99(n=273)	-0.5 (± 6.2)			
Right PF 4th IC: Day 1 to Day 29(n=273)	1.9 (± 11.7)			
Right PF 4th IC: Day 1 to Day 99(n=270)	0.4 (± 9.3)			

Notes:

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Scores of Pain Intensity (From Subjects) and Frequency (From Parent/Caregiver) From Baseline to all Visits, From Day 1 of Each Injection Cycle to Day 29 (Week 4), Day 57 (Week 8, 1st IC Cycle Only) and Day 99 (Week 14) of Respective Injection

End point title	Change in Scores of Pain Intensity (From Subjects) and Frequency (From Parent/Caregiver) From Baseline to all Visits, From Day 1 of Each Injection Cycle to Day 29 (Week 4), Day 57 (Week 8, 1st IC Cycle Only) and Day 99 (Week 14) of Respective Injection

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 participants) 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). Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles. V3 = Week 4 of 1st IC; V4 = Week 8 of 1st IC; V5 = Day 1 of 2nd IC; V6 = Week 4 of 2nd IC; V7 = Day 1 of 3rd IC; V8 = Week 4 of 3rd IC; V9 = Day 1 of 4th IC; V10 = Week 4 of 4th IC; V11 = Week 14 of 4th IC = end of study visit.

End point type	Secondary

End point timeframe:

Baseline (Day 1, Visit[V] 2) to all other visits (V3, V4, V5, V6, V7, V8, V9, V10, and V11); From Day 1 of Each IC to Day 29 (Week 4), Day 57 (Week 8, 1st IC cycle only) and Day 99 (Week 14) of the respective IC

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[12]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Subjects Baseline(V2) to V3 (n=124)	-0.6 (± 1.7)			
Subjects Baseline (V2) to V4(n=126)	-0.5 (± 2)			
Subjects Baseline (V2) to V5(n=117)	-0.5 (± 1.7)			
Subjects Baseline (V2) to V6(n=115)	-0.9 (± 1.9)			
Subjects Baseline (V2) to V7(n=109)	-0.7 (± 1.7)			
Subjects Baseline (V2) to V8(n=106)	-1.1 (± 1.9)			
Subjects Baseline (V2) to V9(n=100)	-0.8 (± 1.7)			
Subjects Baseline (V2) to V10(n=98)	-1.2 (± 2)			
Subjects Baseline (V2) to V11(n=112)	-1 (± 1.8)			
Subjects 2nd IC: Day 1 to Day 29(n=119)	-0.4 (± 1.4)			
Subjects 2nd IC: Day 1 to Day 99(n=113)	-0.2 (± 1.2)			
Subjects 3rd IC: Day 1 to Day 29(n=109)	-0.4 (± 1.2)			
Subjects 3rd IC: Day 1 to Day 99(n=103)	-0.1 (± 0.9)			
Subjects 4th IC: Day 1 to Day 29(n=101)	-0.4 (± 1.3)			
Subjects 4th IC: Day 1 to Day 99(n=101)	-0.3 (± 1)			
Parent/Caregiver Baseline (V2) to V3(n=329)	-0.5 (± 0.8)			
Parent/Caregiver Baseline (V2) to V4(n=337)	-0.4 (± 0.8)			
Parent/Caregiver Baseline (V2) to V5(n=325)	-0.3 (± 0.8)			
Parent/Caregiver Baseline (V2) to V6(n=320)	-0.7 (± 0.9)			

Parent/Caregiver Baseline (V2) to V7(n=309)	-0.4 (± 0.9)			
Parent/Caregiver Baseline (V2) to V8(n=310)	-0.7 (± 1)			
Parent/Caregiver Baseline (V2) to V9(n=290)	-0.5 (± 0.9)			
Parent/Caregiver Baseline (V2) to V10(n=294)	-0.8 (± 1)			
Parent/Caregiver Baseline (V2) to V11(n=315)	-0.6 (± 0.9)			
Parent/Caregiver 2nd IC:Day 1 to Day 29(n=325)	-0.4 (± 0.7)			
Parent/Caregiver 2nd IC:Day 1 to Day 99(n=313)	-0.1 (± 0.6)			
Parent/Caregiver 3rd IC: Day 1 to Day 29(n=307)	-0.3 (± 0.7)			
Parent/Caregiver 3rd IC: Day 1 to Day 99(n=290)	-0.1 (± 0.5)			
Parent/Caregiver 4th IC: Day 1 to Day 29(n=288)	-0.3 (± 0.7)			
Parent/Caregiver 4th IC: Day 1 to Day 99(n=286)	-0.1 (± 0.6)			

Notes:

[12] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Gross Motor Function Measure (GMFM)-66 Score From Baseline to All Injection Visits and End of Study

End point title	Changes in Gross Motor Function Measure (GMFM)-66 Score From Baseline to All Injection Visits and End of Study

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 participants with cerebral palsy. Score values represent the total GMFM-66 score. Total GMFM scores range from 0 (worst) to 100 (best). Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Secondary

End point timeframe:

Baseline to Day 1 of 2nd (V5), 3rd (V7), 4th (V9) IC and End of study (Week 44-68) (V11)

End point values	16 - 20 U/kg Body Weight Incobotulinumtoxin A (Xeomin)			
Subject group type	Reporting group			
Number of subjects analysed	370[13]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (V2) to V5 (n=349)	1.5 (± 3.2)			
Baseline (V2) to V7 (n=340)	2.6 (± 4)			
Baseline (V2) to V9 (n=322)	3.8 (± 5.1)			
Baseline (V2) to V11 (n=339)	4.8 (± 5.9)			

Notes:
[13] - 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 up to end of study visit (Week 50-66)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)

Reporting group description:

Newly enrolled subjects received 16 to 20 U/kg body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 400 to 500 units per injection treatment and subjects who were enrolled after completion of the lead-in study MRZ60201_3070_1 (2012-005054-30) received 16 U/kg body weight of IncobotulinumtoxinA (Xeomin) with a maximum of 400 units per injection treatment via intramuscular injection into spastic muscles on Day 1 of the 4 treatment cycles (12 to 16 weeks treatment cycle each).

Serious adverse events	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 370 (4.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Tenotomy			
subjects affected / exposed	2 / 370 (0.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cast application			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Epilepsy				
subjects affected / exposed	2 / 370 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Clonic convulsion				
subjects affected / exposed	1 / 370 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile convulsion				
subjects affected / exposed	1 / 370 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 370 (0.27%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastritis				
subjects affected / exposed	1 / 370 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Gastroenteritis				
subjects affected / exposed	3 / 370 (0.81%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 370 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Adenoiditis				
subjects affected / exposed	1 / 370 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Adenovirus infection			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Croup infectious			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza			
subjects affected / exposed	1 / 370 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 370 (0.27%)		
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	16 - 20 U/kg Body Weight IncobotulinumtoxinA (Xeomin)		
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 370 (5.41%)		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 370 (5.41%) 34		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2013	The following changes were made with relevance to safety: 1) Clarification that occurrence of severe AESI of respiratory function or severe swallowing disorders were criteria for premature study discontinuation of subjects without any further re-exposure to investigational product. 2) Addition of swallowing disorders to respiratory disorders as AESI category that could lead to premature termination of the study. 3) Clarification that hospitalization for analgosedation starting one day before or on the day of injection treatments was not regarded as a serious adverse event (SAE), if performed for organizational reasons only. The following changes were made with relevance to assessment: 1) Addition of the estimated glomerular filtration rate (eGFR) to assess subjects' renal function based on the height and creatinine levels. 2) Clarification that in case of casting of the target limb(s), casts were to be removable to allow for scheduled study assessments on visit days. 3) Clarification of regulation to keep clinical patterns of spasticity treatment throughout participation in MRZ60201_3071_1 and to keep the patterns also in subjects rolling-over from MRZ60201_3070_1. 4) Clarification of the calculation of the visit window in case of visits where the GMFM could be performed one day prior to all other assessments. 5) Correction of ranges for injection sites for the gastrocnemius muscle and for all other muscles in Appendix 16.5 of the CSP to be in line with the regulation of maximum of 25 units per injection site in subjects <25 kg BW and maximum of 50 units in subjects with BW >=25 kg. 6) Description how confidential data were handled on the GMFM-66 source form.
24 April 2015	The following changes were made: 1)Addition of a new safety assessment to prospectively monitor suicidality: the columbia suicide severity rating scale C-SSRS was to be considered as the most important source of information considering suicidality. 2) Addition of a new safety variable (classified as other safety variable) based on the results of the C-SSRS. 3) Addition of an exclusion criterion specifying that subjects with significant risk of suicidality at the baseline assessment were to be excluded. 4) Addition of a new discontinuation criterion: subjects were to be discontinued if there was a positive report on suicidality based on the C-SSRS. 5) Modification of data management procedures clarifying documentation of the C-SSRS results. 6) Modification of the definition of SAEs further specifying suicidal ideation (a response of "yes" to questions 4 or 5) or any suicidal behavior as "medically important condition". 7) Description of the analysis of C-SSRS data. 8) Changes to the risk-benefit assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported