Clinical trial results:
Multi-center Open Comparative Randomized Trial of Clinical and Neurophysiological Efficacy and Safety of Xeomin (Botulinum Toxin Type A) vs. Botox (Complex of Botulinum Toxin Type A and Hemagglutinin) in Children With Spastic Equine and Equinovarus Foot Deformation in Pediatric Cerebral Palsy

Summary

EudraCT number	2016-005049-21
Trial protocol	Outside EU/EEA
Global end of trial date	15 December 2016

Results information

Result version number	v1 (current)
This version publication date	29 June 2017
First version publication date	29 June 2017

Trial information

Trial identification

Sponsor protocol code	MRZ-R-201212_01001_N_2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02188277
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to assess the clinical and neurophysiological efficacy of Xeomin vs. Botox in children with spastic equine and equinovarus foot deformation in pediatric cerebral palsy.

Protection of trial subjects:

"High medical and ethical standards were followed in accordance with Good Clinical Practice and other applicable regulations."

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 64
Worldwide total number of subjects	64
EEA total number of subjects	0

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

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 3 sites located in Russia.

Pre-assignment

Screening details:

A total of 64 subjects who were suffering from spastic paraplegia or hemiparesis in pediatric cerebral palsy were enrolled and randomized into Xeomin or Botox groups in a 1:1 ratio (32 subjects in each group).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IncobotulinumtoxinA (Xeomin)

Arm description:

Subjects received 4 (8) units per kilogram (U/kg) body weight incobotulinumtoxinA (Xeomin)

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:

Subjects received 4 U/kg body weight incobotulinumtoxinA (Xeomin) treatment via intramuscular injection into gastrocnemius muscles for one leg and 8 U/kg body weight incobotulinumtoxinA (Xeomin) for both legs on Day 0.

Arm title	Onabotulinumtoxin A (Botox)

Arm description:

Subjects received 4 (6) units per kilogram (U/kg) body weight onabotulinumtoxin A (Botox)

Arm type	Active comparator
Investigational medicinal product name	Onabotulinumtoxin A
Investigational medicinal product code	
Other name	Botox; Complex of botulinum toxin type A and hemagglutinin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 4 U/kg body weight onabotulinumtoxin A (Botox) treatment via intramuscular injection into gastrocnemius muscles for one leg and 6 U/kg bodyweight Onabotulinumtoxin A (Botox) for both legs on Day 0.

Number of subjects in period 1	IncobotulinumtoxinA (Xeomin)	Onabotulinumtoxin A (Botox)
Started	32	32
Completed	31	27
Not completed	1	5
Refusal to participate	-	5
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 4 (8) units per kilogram (U/kg) body weight incobotulinumtoxinA (Xeomin)	
Reporting group title	Onabotulinumtoxin A (Botox)
Reporting group description:	
Subjects received 4 (6) units per kilogram (U/kg) body weight onabotulinumtoxin A (Botox)	

Reporting group values	IncobotulinumtoxinA (Xeomin)	Onabotulinumtoxin A (Botox)	Total
Number of subjects	32	32	64
Age categorical Units: Subjects			
Age 2 to 12 years	32	32	64
Age continuous Units: years			
arithmetic mean	4.9	4.5	
standard deviation	± 2.6	± 2.37	-
Gender categorical Units: Subjects			
Female	14	15	29
Male	18	17	35

End points

End points reporting groups

Reporting group title	IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 4 (8) units per kilogram (U/kg) body weight incobotulinumtoxinA (Xeomin)	
Reporting group title	Onabotulinumtoxin A (Botox)
Reporting group description:	
Subjects received 4 (6) units per kilogram (U/kg) body weight onabotulinumtoxin A (Botox)	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS was a subgroup of subjects in the safety evaluation set (SES) group for whom an assessment of primary efficacy criteria was possible (that is all subjects who had initial indicators and at least one of the subsequent indicators for efficacy assessment).	
Subject analysis set title	Safety Evaluation Set (SES)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SES was defined as a group of the subjects who have signed an informed consent and who had been administered the study products (Xeomin and Botox).	

Primary: Change From Baseline (Day 0) in the Degree of Spasticity in Gastrocnemius According to Modified Ashworth Scale (MAS) at Visit 2 (Day 30)

End point title	Change From Baseline (Day 0) in the Degree of Spasticity in Gastrocnemius According to Modified Ashworth Scale (MAS) at Visit 2 (Day 30)
End point description:	
The MAS 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 6-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension) and includes intermediate scores of 1, 1+, 2, and 3.	
End point type	Primary
End point timeframe:	
Baseline to Visit 2 (Day 30)	

End point values	IncobotulinumtoxinA (Xeomin)	Onabotulinumtoxin A (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[1]	31[2]		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.9 (± 0.43)	-0.8 (± 0.31)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Comparison of mean changes from baseline.
The actual pre-specified primary efficacy analysis was a comparison of pre- and post treatment values within each reporting group:

IncobotulinumtoxinA: one-sample Wilcoxon test, p = 0.000004
OnabotulinumtoxinA: one-sample Wilcoxon test, p = 0.000002

Comparison groups	Onabotulinumtoxin A (Botox) v IncobotulinumtoxinA (Xeomin)
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.443
Method	Wilcoxon (Mann-Whitney)

Secondary: Change From Baseline (Day 0) in the Degree of Spasticity in Gastrocnemius According to MAS at Visit 3 (Day 60) and Visit 4 (Day 90)

End point title	Change From Baseline (Day 0) in the Degree of Spasticity in Gastrocnemius According to MAS at Visit 3 (Day 60) and Visit 4 (Day 90)

End point description:

The MAS 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 6-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension) and includes intermediate scores of 1, 1+, 2, and 3.

End point type	Secondary

End point timeframe:

Baseline to Visit 3 (Day 60) and Visit 4 (Day 90)

End point values	IncobotulinumtoxinA (Xeomin)	Onabotulinumtoxin A (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[3]	31[4]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Visit 3	-0.9 (± 0.43)	-0.8 (± 0.31)		
Visit 4	-0.9 (± 0.41)	-0.7 (± 0.38)		

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subjects Percentage in Groups by the Degree of Gastrocnemius Spasticity According to MAS at Visit 2 (Day 30), Visit 3 (Day 60) and Visit 4 (Day 90)

End point title	Change From Baseline in Subjects Percentage in Groups by the Degree of Gastrocnemius Spasticity According to MAS at Visit 2 (Day 30), Visit 3 (Day 60) and Visit 4 (Day 90)

End point description:

The MAS is a well known and commonly used scale in clinical trials with spasticity. In spasticmuscles the resistance to passive movement is assessed. It is a 6-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension) and includes intermediate scores of 1, 1+, 2, and 3.

End point type	Secondary

End point timeframe:

Baseline to Visit 2 (Day 30), Visit 3 (Day 60) and Visit 4 (Day 90)

End point values	Incobotulinumtoxin A (Xeomin)	Onabotulinumtoxin A (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[5]	31[6]		
Units: percentage of subjects				
number (not applicable)				
MAS score 1, visit 2	16.1	19.4		
MAS score 1+, visit 2	29	41.9		
MAS score 2, visit 2	9.7	-25.8		
MAS score 3, visit 2	-54.8	-32.3		
MAS score 4, visit 2	0	-3.2		
MAS score 1, visit 3	19.4	19.4		
MAS score 1+, visit 3	25.8	41.9		
MAS score 2, visit 3	9.7	-25.8		
MAS score 3, visit 3	-54.8	-32.3		
MAS score 4, visit 3	0	-3.2		
MAS score 1, visit 4	19.4	16.1		
MAS score 1+, visit 4	22.6	35.5		
MAS score 2, visit 4	12.9	-16.1		
MAS score 3, visit 4	-54.8	-32.3		
MAS score 4, visit 4	0	-3.2		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Decrease in M-response Magnitude and Area Recorded From the Lateral and Medial Gastrocnemius Heads at Visit 2 (Day 30) and Visit 4 (Day 90) From Baseline Values

End point title	Percentage of Decrease in M-response Magnitude and Area Recorded From the Lateral and Medial Gastrocnemius Heads at Visit 2 (Day 30) and Visit 4 (Day 90) From Baseline Values

End point description:

EMG is performed using an electromyograph designed to perform electrical stimulation of peripheral nerves with single rectangular pulses and to record muscle responses. The amplitude of a compound muscle action potential (M-wave) is recorded in millivolts (mV) and the duration is recorded in milliseconds (ms). The measurements include the M-wave amplitude and the negative peak area under the curve of the M-wave. Values given are percentage decreases from baseline for the following muscles: LGH = Lateral gastrocnemius heads and MGH = Medial gastrocnemius heads.

End point type	Secondary

End point timeframe:

Baseline to Visit 2 (Day 30) and Visit 4 (Day 90)

End point values	IncobotulinumtoxinA (Xeomin)	OnabotulinumtoxinA (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[7]	31[8]		
Units: percentage of decrease				
number (not applicable)				
M-response magnitude, LGH, visit 2	33.4	50.6		
M-response magnitude, LGH, visit 4	31.7	35.8		
M-response magnitude, MGH, visit 2	44.9	42.8		
M-response magnitude, MGH, visit 4	20.7	34		
M-response area LGH, visit 2	42.3	54.7		
M-response area LGH, visit 4	36.2	42.8		
M-response area MGH, visit 2	51.9	35.8		
M-response area MGH, visit 4	35.9	44		

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Ratio of M-response Magnitude Recorded From the Lateral and Medial Gastrocnemius Heads and From Tibialis Anterior at Visit 2 (Day 30) and Visit 4 (Day 90)

End point title	Change From Baseline in the Ratio of M-response Magnitude Recorded From the Lateral and Medial Gastrocnemius Heads and From Tibialis Anterior at Visit 2 (Day 30) and Visit 4 (Day 90)

End point description:

EMG is performed using an electromyograph designed to perform electrical stimulation of peripheral nerves with single rectangular pulses and to record muscle responses. The M-wave is recorded in mV, the duration in ms. A ratio of the M-wave amplitude between injected muscles (LGH, MGH) and a non-injected muscle tibialis anterior.
(TA) is calculated. Values given are changes in M-wave amplitude ratios from baseline. LGH = Lateral gastrocnemius heads; MGH = Medial gastrocnemius heads.

End point type	Secondary

End point timeframe:

Baseline to Visit 2 (Day 30) and Visit 4 (Day 90)

End point values	IncobotulinumtoxinA (Xeomin)	OnabotulinumtoxinA (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[9]	31[10]		
Units: ratio				
number (not applicable)				
Ratio LGH - TA, visit 2	-0.3	-0.4		
Ratio LGH - TA, visit 4	-0.4	-0.4		
Ratio MGH - TA, visit 2	-0.5	-0.3		
Ratio MGH - TA, visit 4	-0.2	-0.5		

Notes:
[9] - FAS
[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Angles and Angle Ratio of Ankle Joints at Passive and Voluntary Extension at Visit 2 (Day 30), Visit 3 (Day 60), and Visit 4 (Day 90)

End point title	Change From Baseline in Angles and Angle Ratio of Ankle Joints at Passive and Voluntary Extension at Visit 2 (Day 30), Visit 3 (Day 60), and Visit 4 (Day 90)

End point description:

Using a goniometer the movement amplitude (angle) of the ankle extension was measured for the following conditions:
1) Knee flexion and extension – muscles relaxed (passive function) (subject supine);
2) Knee extension – voluntary muscle contraction (active function) (subject supine).
The ratio of the angles in passive ankle extension (knee flexion and extension) and the ratio of the angles in passive and active ankle extension (knee extension) was also calculated.
Values given are decreases from baseline in angles and ratios.

End point type	Secondary

End point timeframe:

Baseline to Visit 2 (Day 30), Visit 3 (Day 60), and Visit 4 (Day 90)

End point values	Incobotulinumtoxin A (Xeomin)	Onabotulinumtoxin A (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[11]	31[12]		
Units: angle [°] and angle ratio				
arithmetic mean (standard deviation)				
Knee flexion, passive, visit 2	9.2 (± 6.66)	12.6 (± 9.57)		
Knee flexion, passive, visit 3	10 (± 7.5)	14.1 (± 12.45)		
Knee flexion, passive, visit 4	8.3 (± 8.45)	13.1 (± 11.5)		
Knee extension, passive, visit 2	11.5 (± 7.99)	12.2 (± 7.5)		
Knee extension, passive, visit 3	13.1 (± 8.68)	12.9 (± 9.58)		
Knee extension, passive, visit 4	10.9 (± 7.76)	11.8 (± 9.91)		
Knee extension, voluntary, visit 2	9.5 (± 7.05)	9.8 (± 6.88)		
Knee extension, voluntary, visit 3	11.8 (± 8.32)	11.1 (± 8.36)		
Knee extension, voluntary, visit 4	10 (± 7.88)	9.5 (± 8.21)		
Ratio flexion vs. extension, voluntary, visit 2	0.01 (± 0.06)	0.04 (± 0.08)		
Ratio flexion vs. extension, voluntary, visit 3	-0.01 (± 0.07)	0.05 (± 0.1)		
Ratio flexion vs. extension, voluntary, visit 4	0.01 (± 0.08)	0.05 (± 0.1)		

Notes:

[11] - FAS

[12] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Motor Activity According to Gross Motor Function Classification Systems (GMFCS) Criteria

End point title	Change From Baseline in Motor Activity According to Gross Motor Function Classification Systems (GMFCS) Criteria

End point description:

The GMFCS is a system to classify gross motor function in children of different age groups with cerebral palsy. Five levels are defined, with Level 1 describing the best and Level 5 the worst functional level. Values given are score changes from baseline.

End point type	Secondary

End point timeframe:

Baseline to Visit 2 (Day 30), Visit 3 (Day 60), and Visit 4 (Day 90)

End point values	Incobotulinumtoxin A (Xeomin)	Onabotulinumtoxin A (Botox)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[13]	31[14]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Visit 2	-0.5 (± 0.51)	-0.3 (± 0.48)		
Visit 3	-0.5 (± 0.51)	-0.4 (± 0.49)		
Visit 4	-0.5 (± 0.51)	-0.4 (± 0.49)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From time point of first injection (Day 0) up to Day 90	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	IncobotulinumtoxinA (Xeomin)
Reporting group description:	
Subjects received 4 (8) U/kg body weight incobotulinumtoxinA (Xeomin)	
Reporting group title	OnabotulinumtoxinA (Botox)
Reporting group description:	
Subjects received 4 (6) U/kg body weight onabotulinumtoxin A (Botox)	

Serious adverse events	IncobotulinumtoxinA (Xeomin)	OnabotulinumtoxinA (Botox)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	IncobotulinumtoxinA (Xeomin)	OnabotulinumtoxinA (Botox)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	2 / 32 (6.25%)	
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pain in Injection Site			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Rash papular subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 32 (0.00%) 0	
Infections and infestations Respiratory tract infection viral subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 32 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 32 (3.13%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported