Clinical trial results:
Prospective, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study With an Open-Label Extension Period to Investigate the Efficacy and Safety of NT 201 in the Treatment of Post-Stroke Spasticity of the Lower Limb

Summary

EudraCT number	2010-024579-23
Trial protocol	DE AT CZ ES PL IT HU
Global end of trial date	04 January 2016

Results information

Result version number	v1 (current)
This version publication date	19 May 2016
First version publication date	19 May 2016

Trial information

Trial identification

Sponsor protocol code	MRZ 60201/SP/3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01464307
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to investigate the efficacy and safety of 400 units NT 201 compared with placebo in the first double-blind treatment cycle, and to investigate the safety of 400 units NT 201 administered in three subsequent open-label treatment cycles.

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	01 February 2012
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: 111
Country: Number of subjects enrolled	Russian Federation: 43
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	France: 3
Worldwide total number of subjects	289
EEA total number of subjects	201

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	203
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 331 individuals suffering from post-stroke lower-limb spasticity were screened and 290 were included in study at 51 sites. One ineligible subject was randomized to placebo but withdrawn from study prior to first treatment with study medication. For purpose of study analysis overall number of subjects enrolled is therefore considered 289.

Pre-assignment

Screening details:

A total of 289 subjects were enrolled in main period. All of the 269 subjects who completed the main period of the study entered the open-label extension period.

Period 1

Period 1 title	Main Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	IncobotulinumtoxinA (Xeomin) 400 Units

Arm description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): Main period: One injection session of solution, prepared by reconstitution of powder with 0.9 percent (%) Sodium Chloride (NaCl), 400 units, total volume 8.0 milliliter (mL); Mode of administration: intramuscular injection.

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	NT 201
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received IncobotulinumtoxinA (400 Units) one intramuscular injection session of solution, prepared by reconstitution of powder with 0.9% NaCl, 400 units, total volume 8.0 ml.

Arm title	Placebo

Arm description:

Placebo to incobotulinumtoxinA (Xeomin) powder for solution for injection.

Placebo Comparator: Main period: one injection session of solution, prepared by reconstitution of powder with 0.9% NaCl, corresponding total placebo volume 8.0 mL; Mode of administration: intramuscular injection

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

Dosage and administration details:

Subjects received Placebo to IncobotulinumtoxinA one intramuscular injection session of solution,

prepared by reconstitution of powder with 0.9% NaCl, 400 units, total volume 8.0 mL.

Number of subjects in period 1	IncobotulinumtoxinA (Xeomin) 400 Units	Placebo
Started	144	145
Treated	144	145
Completed	129	140
Not completed	15	5
Adverse event, serious fatal	-	1
Consent withdrawn by subject	5	2
Adverse event, non-fatal	6	1
Lack of efficacy	2	-
Predefined discontinuation criteria	2	1

Period 2

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

Arms

Arm title	IncobotulinumtoxinA (Xeomin) 400 Units

Arm description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): All subjects receive three injection sessions of solution, prepared by reconstitution of powder with 0.9% NaCl, 400 units, total volume 8.0 mL; Mode of administration: intramuscular injection.

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	NT 201
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received IncobotulinumtoxinA (400 Units) three intramuscular injection sessions of solution, prepared by reconstitution of powder with 0.9% NaCl, 400 units, total volume 8.0 ml.

Number of subjects in period 2	IncobotulinumtoxinA (Xeomin) 400 Units
Started	269
Treated	269
Completed	218
Not completed	51
Adverse event, serious fatal	1
Consent withdrawn by subject	14
Adverse event, non-fatal	15
Non-compliance	9
Lost to follow-up	1
Lack of efficacy	5
Predefined discontinuation criteria	6

Baseline characteristics

Reporting groups

Reporting group title	IncobotulinumtoxinA (Xeomin) 400 Units

Reporting group description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): Main period: One injection session of solution, prepared by reconstitution of powder with 0.9 percent (%) Sodium Chloride (NaCl), 400 units, total volume 8.0 milliliter (mL); Mode of administration: intramuscular injection.

Reporting group title	Placebo

Reporting group description:

Placebo to incobotulinumtoxinA (Xeomin) powder for solution for injection.

Placebo Comparator: Main period: one injection session of solution, prepared by reconstitution of powder with 0.9% NaCl, corresponding total placebo volume 8.0 mL; Mode of administration: intramuscular injection

Reporting group values	IncobotulinumtoxinA (Xeomin) 400 Units	Placebo	Total
Number of subjects	144	145	289
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	100	103	203
From 65-84 years	44	42	86
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.3	57	
standard deviation	± 11.2	± 13	-
Gender, Male/Female Units: participants			
Female	40	55	95
Male	104	90	194

End points

End points reporting groups

Reporting group title	IncobotulinumtoxinA (Xeomin) 400 Units

Reporting group description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): Main period: One injection session of solution, prepared by reconstitution of powder with 0.9 percent (%) Sodium Chloride (NaCl), 400 units, total volume 8.0 milliliter (mL); Mode of administration: intramuscular injection.

Reporting group title	Placebo

Reporting group description:

Placebo to incobotulinumtoxinA (Xeomin) powder for solution for injection.

Placebo Comparator: Main period: one injection session of solution, prepared by reconstitution of powder with 0.9% NaCl, corresponding total placebo volume 8.0 mL; Mode of administration: intramuscular injection

Reporting group title	IncobotulinumtoxinA (Xeomin) 400 Units

Reporting group description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): All subjects receive three injection sessions of solution, prepared by reconstitution of powder with 0.9% NaCl, 400 units, total volume 8.0 mL; Mode of administration: intramuscular injection.

Primary: Change from Baseline in Ashworth Scale (AS) for Plantar Flexors at Week 4

End point title	Change from Baseline in Ashworth Scale (AS) for Plantar Flexors at Week 4

End point description:

The AS is a well known and commonly used scale in clinical trials with spasticity. It was considered to be the best clinical tool for measuring resistance to movement. It was used to categorize the severity of spasticity by judging resistance to passive movement. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension).
Full Analysis Set: Subset of subjects in the Safety Evaluation Set (SES) of the main period for whom the primary efficacy variable was available, whereby SES is the subset of all subjects who were exposed to IP in the main period at least once.

End point type	Primary

End point timeframe:

Baseline and Week 4

End point values	IncobotulinumtoxinA (Xeomin) 400 Units	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	145		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	2.8 (± 0.7)	2.8 (± 0.7)		

Change at Week 4	-0.4 (± 0.7)	-0.4 (± 0.7)		

Statistical analyses

Statistical analysis title	IncobotulinumtoxinA (Xeomin) Vs Placebo

Statistical analysis description:

The number of subjects included in the MMRM analysis was only 286 because a covariate was missing for 3 subjects.

Comparison groups	IncobotulinumtoxinA (Xeomin) 400 Units v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.777
Method	Mixed-Model Repeated Measures
Parameter estimate	Least Square Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Primary: Co-primary variable: Investigator's Global Assessment of Efficacy at Week 12

End point title	Co-primary variable: Investigator's Global Assessment of Efficacy at Week 12

End point description:

A 4-point Likert scale was used with the ratings 1 = very good, 2 = good, 3 = moderate, and 4 = poor. Investigator's Global Assessment of Efficacy at Week 12 was co-primary outcome measure to fulfill post marketing commitments for U.S. regulatory authorities only. Elsewhere, it would be a secondary outcome measure.
Full Analysis Set: Subset of subjects in the Safety Evaluation Set (SES) of the main period for whom the primary efficacy variable was available, whereby SES is the subset of all subjects who were exposed to IP in the main period at least once.

End point type	Primary

End point timeframe:

Baseline to Week 12

End point values	IncobotulinumtoxinA (Xeomin) 400 Units	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	145		
Units: Percentage of Participants				
number (not applicable)				

Very good	3.5	4.8		
Good	28.5	22.8		
Moderate	22.2	26.9		
Poor	45.8	45.5		

Statistical analyses

Statistical analysis title	IncobotulinumtoxinA (Xeomin) Vs Placebo
Comparison groups	IncobotulinumtoxinA (Xeomin) 400 Units v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.804 [1]
Method	Wilcoxon's Rank-Sum Test

Notes:

[1] - worst-case analysis.

Secondary: Response Rate for Plantar Flexors at all Post-Baseline Visits for Subjects With an Improvement (Reduction) of at Least 1 Point From Baseline in the Ashworth Scale (AS)

End point title	Response Rate for Plantar Flexors at all Post-Baseline Visits for Subjects With an Improvement (Reduction) of at Least 1 Point From Baseline in the Ashworth Scale (AS)

End point description:

Response is defined as an improvement (reduction) of the plantar flexor Ashworth Score by at least one score point. The AS is a well known and commonly used scale in clinical trials with spasticity. It was considered to be the best clinical tool for measuring resistance to movement. It was used to categorize the severity of spasticity by judging resistance to passive movement. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension). Here, 'n' specifies those subjects who were evaluated for this outcome measure at given time point.
Full Analysis Set: Subset of subjects in the Safety Evaluation Set (SES) of the main period for whom the primary efficacy variable was available, whereby SES is the subset of all subjects who were exposed to IP in the main period at least once.

End point type	Secondary

End point timeframe:

Week 4, 8, and 12

End point values	IncobotulinumtoxinA (Xeomin) 400 Units	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	144		
Units: Percentage of Participants				
number (not applicable)				
Week 4 (n=142, 144)	37.3	35.4		
Week 8 (n=140, 142)	39.3	33.8		
Week 12 (n=135, 141)	20	17		

Statistical analyses

Statistical analysis title	IncobotulinumtoxinA (Xeomin) Vs Placebo

Statistical analysis description:

Week 4. Number of subjects included in analysis was three less than the observed cases because of a missing covariate for the logistic regression analysis, that is, n=283 for week 4.

Comparison groups	IncobotulinumtoxinA (Xeomin) 400 Units v Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.74

Notes:

[2] - observed cases analysis.

Statistical analysis title	IncobotulinumtoxinA (Xeomin) Vs Placebo

Statistical analysis description:

Week 8. Number of subjects included in analysis was three less than the observed cases because of a missing covariate for the logistic regression analysis, that is, n=279 for week 8.

Comparison groups	IncobotulinumtoxinA (Xeomin) 400 Units v Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.04

Notes:

[3] - observed cases analysis.

Statistical analysis title	IncobotulinumtoxinA (Xeomin) Vs Placebo

Statistical analysis description:

Week 12. Number of subjects included in analysis was three less than the observed cases because of a

missing covariate for the logistic regression analysis, that is, n=273 for week 12.

Comparison groups	IncobotulinumtoxinA (Xeomin) 400 Units v Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.698 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.21

Notes:

[4] - observed cases analysis.

Secondary: Ashworth Scale (AS) for Plantar Flexors at all Post-Baseline Visits

End point title	Ashworth Scale (AS) for Plantar Flexors at all Post-Baseline Visits

End point description:

The AS is a well known and commonly used scale in clinical trials with spasticity. It was considered to be the best clinical tool for measuring resistance to movement. It was used to categorize the severity of spasticity by judging resistance to passive movement. It is a 5-point scale that ranges from 0 (=no increase in tone) to 4 (=limb rigid in flexion or extension). Here, 'n' specifies those subjects who were evaluated for this outcome measure at given time point.
Full Analysis Set: Subset of subjects in the Safety Evaluation Set (SES) of the main period for whom the primary efficacy variable was available, whereby SES is the subset of all subjects who were exposed to IP in the main period at least once.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, and 12

End point values	IncobotulinumtoxinA (Xeomin) 400 Units	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	145		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=144, 145)	2.8 (± 0.7)	2.8 (± 0.7)		
Week 4 (n= 142, 144)	2.4 (± 0.9)	2.4 (± 0.8)		
Week 8 (n=140, 142)	2.4 (± 0.9)	2.5 (± 0.7)		
Week 12 (n= 135, 141)	2.7 (± 0.8)	2.7 (± 0.7)		

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 until 120 +/- 7 days after last administration of injection

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Main Period: IncobotulinumtoxinA (Xeomin) 400 Units

Reporting group description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): Main period: One injection session of solution, prepared by reconstitution of powder with 0.9% Sodium Chloride (NaCl), 400 units, total volume 8.0 mL; Mode of administration: intramuscular injection.

Reporting group title	Main Period: Placebo

Reporting group description:

Placebo to incobotulinumtoxinA (Xeomin) powder for solution for injection.

Placebo Comparator: Main period: one injection session of solution, prepared by reconstitution of powder with 0.9% NaCl,
corresponding total placebo volume 8.0 mL; Mode of administration: intramuscular injection

Reporting group title	Open-Label Extension: IncobotulinumtoxinA (Xeomin) 400 Units

Reporting group description:

IncobotulinumtoxinA (Xeomin, also known as "NT 201" or "Botulinum toxin type A (150 kiloDalton), free from complexing proteins") (active ingredient: Clostridium Botulinum neurotoxin Type A free from complexing proteins) powder for solution for injection.

IncobotulinumtoxinA (400 Units): Open-Label Extension Period: All subjects receive three injection session of solution, prepared by reconstitution of powder with 0.9% Sodium Chloride (NaCl), 400 units, total volume 8.0 mL; Mode of administration: intramuscular injection.

Serious adverse events	Main Period: IncobotulinumtoxinA (Xeomin) 400 Units	Main Period: Placebo	Open-Label Extension: IncobotulinumtoxinA (Xeomin) 400 Units
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 144 (4.17%)	5 / 145 (3.45%)	22 / 269 (8.18%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neoplasm			

subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Desmoid tumour			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cranioplasty			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical induction of coma			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin lesion excision			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy			

subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Limb operation			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Immobile			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Personality disorder			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Head injury			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper-limb fracture			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	2 / 269 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial haematoma			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebrovascular accident			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Mobility decreased			

subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 269 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			

subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Main Period: IncobotulinumtoxinA (Xeomin) 400 Units	Main Period: Placebo	Open-Label Extension: IncobotulinumtoxinA (Xeomin) 400 Units
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 144 (9.03%)	13 / 145 (8.97%)	31 / 269 (11.52%)
Investigations			
γ-glutamyltransferase increased			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	7 / 269 (2.60%)
occurrences (all)	0	0	7
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 144 (0.00%)	2 / 145 (1.38%)	11 / 269 (4.09%)
occurrences (all)	0	3	12
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 144 (0.69%)	3 / 145 (2.07%)	2 / 269 (0.74%)
occurrences (all)	1	4	2
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 144 (0.00%)	3 / 145 (2.07%)	3 / 269 (1.12%)
occurrences (all)	0	3	3
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 144 (2.08%)	0 / 145 (0.00%)	1 / 269 (0.37%)
occurrences (all)	4	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	7 / 144 (4.86%)	7 / 145 (4.83%)	10 / 269 (3.72%)
occurrences (all)	8	9	10
Back pain			

subjects affected / exposed occurrences (all)	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0	6 / 269 (2.23%) 6
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 144 (2.08%) 3	1 / 145 (0.69%) 1	4 / 269 (1.49%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2011	The overall reason for the amendment was to fulfil a post marketing commitment (PMC) for Xeomin in the United States. A co-primary endpoint was added, the 'Investigator's Global Assessment of Efficacy'. This scale had been part of the Study Protocol as tertiary outcome measure before. Accordingly, details on the analyses of the primary endpoint(s) were updated. The Ashworth Scale (AS) and the co-primary endpoint were only to be co-analyzed for United States submission and both had to show significant treatment differences.
16 May 2014	The overall reason for the amendment was to implement a revision of sample-size calculation and to implement current updates of approval status, safety information and statistical methods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported