Clinical trial results:
Prospective, randomized, double-blind, placebo-controlled, parallel-group multicenter study, with an extension period of dose-blinded active treatment, to investigate the efficacy and safety of two dose levels of NT 201 in treating chronic troublesome sialorrhea in various neurological conditions

Summary

EudraCT number	2012-005539-10
Trial protocol	DE
Global end of trial date	09 November 2016

Results information

Result version number	v3 (current)
This version publication date	21 April 2018
First version publication date	14 December 2017
Version creation reason	• Correction of full data set Minor editorial changes to make it match with CTgov entries

Trial information

Trial identification

Sponsor protocol code	MRZ60201_3090_1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02091739
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	01 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to investigate the efficacy and safety of two different dose levels of NT 201 (75 units or 100 units per cycle), compared with placebo, in reducing the salivary flow rate, and the severity and frequency of chronic troublesome sialorrhea with Parkinson's disease or atypical parkinsonism (multiple system atrophy, corticobasal degeneration, or progressive supranuclear palsy) or after stroke or traumatic brain injury.

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	11 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Poland: 131
Worldwide total number of subjects	184
EEA total number of subjects	184

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)	77
From 65 to 84 years	107

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 12 sites in Poland and Germany.

Pre-assignment

Screening details:

A total of 216 subjects were screened for the study, of which 184 subjects were randomized and treated in the Main Period (MP) of the study. A total of 173 subjects who completed the MP, entered the 2 treatment arms of the Extension Period (EP) of the study.

Period 1

Period 1 title	MP: 16 Weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MP: Placebo

Arm description:

Subjects received 2.0 milliliter (mL) placebo.

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

Dosage and administration details:

Subjects received one injection session of overall 2.0 mL placebo matched to the volume of incobotulinumtoxinA via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 in the MP.

Arm title	MP: IncobotulinumtoxinA (Xeomin) (75 units)

Arm description:

Subjects received 2.0 mL incobotulinumtoxinA containing 75 units.

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	Intraglandular use

Dosage and administration details:

Subjects received one injection session of overall 2.0 mL incobotulinumtoxinA containing 75 units via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 in the MP.

Arm title	MP: IncobotulinumtoxinA (Xeomin) (100 units)

Arm description:

Subjects received 2.0 mL incobotulinumtoxinA containing 100 units.

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	Intraglandular use

Dosage and administration details:

Subjects received one injection session of overall 2.0 mL incobotulinumtoxinA containing 100 units via bilateral intraglandular injection into the parotid and submandibular glands on Day 1 in the MP.

Number of subjects in period 1	MP: Placebo	MP: IncobotulinumtoxinA (Xeomin) (75 units)	MP: IncobotulinumtoxinA (Xeomin) (100 units)
Started	36	74	74
Completed	32	69	72
Not completed	4	5	2
Consent withdrawn by subject	3	4	-
Lost to follow-up	-	-	1
Adverse event, non-fatal	1	1	1

Period 2

Period 2 title	EP: 48 Weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	EP: IncobotulinumtoxinA (Xeomin) (75 units)

Arm description:

Subjects received 2.0 mL incobotulinumtoxinA containing 75 units at each of the three EP injection sessions.

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	Intraglandular use

Dosage and administration details:

Subjects received overall 2.0 mL incobotulinumtoxinA containing 75 units via bilateral intraglandular injection into the parotid and submandibular glands at each of the three injection sessions in the EP.

Arm title	EP: IncobotulinumtoxinA (Xeomin) (100 units)

Arm description:

Subjects received 2.0 mL incobotulinumtoxinA containing 100 units at each of the three EP injection sessions

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	Intraglandular use

Dosage and administration details:

Subjects received overall 2.0 mL incobotulinumtoxinA containing 100 units via bilateral intraglandular injection into the parotid and submandibular glands at each of the three injection sessions in the EP.

Number of subjects in period 2	EP: IncobotulinumtoxinA (Xeomin) (75 units)	EP: IncobotulinumtoxinA (Xeomin) (100 units)
Started	84	89
Completed	76	75
Not completed	8	14
Adverse event, serious fatal	3	2
Consent withdrawn by subject	2	6
Adverse event, non-fatal	2	6
Other	1	-

Baseline characteristics

Reporting groups	
Reporting group title	MP: Placebo
Reporting group description:	
Subjects received 2.0 milliliter (mL) placebo.	

Reporting group title	MP: IncobotulinumtoxinA (Xeomin) (75 units)
Reporting group description:	
Subjects received 2.0 mL incobotulinumtoxinA containing 75 units.	
Reporting group title	MP: IncobotulinumtoxinA (Xeomin) (100 units)
Reporting group description:	
Subjects received 2.0 mL incobotulinumtoxinA containing 100 units.	

Reporting group values	MP: Placebo	MP: IncobotulinumtoxinA (Xeomin) (75 units)	MP: IncobotulinumtoxinA (Xeomin) (100 units)
Number of subjects	36	74	74
Age categorical Units: Subjects			
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)	19	30	28
From 65-84 years	17	44	46
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	24	22
Male	28	50	52
Race Units: Subjects			
White	36	74	73
Asian	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	36	74	73
Weight Units: kilogram (kg)			
arithmetic mean	80.6	78.4	79.8
standard deviation	± 16.4	± 17.1	± 14
Body Mass Index (BMI) Units: kilogram per square meter (kg/m^2)			
arithmetic mean	28.5	26.7	27.7
standard deviation	± 6	± 5.2	± 3.8

Reporting group values	Total		
Number of subjects	184		
Age categorical Units: Subjects			
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)	77		
From 65-84 years	107		
85 years and over	0		
Gender categorical Units: Subjects			
Female	54		
Male	130		
Race Units: Subjects			
White	183		
Asian	1		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	183		
Weight Units: kilogram (kg)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI) Units: kilogram per square meter (kg/m^2)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	MP: Placebo
Reporting group description:	
Subjects received 2.0 milliliter (mL) placebo.	

Reporting group title	MP: IncobotulinumtoxinA (Xeomin) (75 units)
Reporting group description:	
Subjects received 2.0 mL incobotulinumtoxinA containing 75 units.	
Reporting group title	MP: IncobotulinumtoxinA (Xeomin) (100 units)
Reporting group description:	
Subjects received 2.0 mL incobotulinumtoxinA containing 100 units.	
Reporting group title	EP: IncobotulinumtoxinA (Xeomin) (75 units)
Reporting group description:	
Subjects received 2.0 mL incobotulinumtoxinA containing 75 units at each of the three EP injection sessions.	
Reporting group title	EP: IncobotulinumtoxinA (Xeomin) (100 units)
Reporting group description:	
Subjects received 2.0 mL incobotulinumtoxinA containing 100 units at each of the three EP injection sessions	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS is the subset of subjects who were treated and had at least the baseline value of unstimulated salivary flow (uSFR).	

Primary: MP: Change From Baseline in Unstimulated Salivary Flow (uSFR) Rate at Week 4

End point title	MP: Change From Baseline in Unstimulated Salivary Flow (uSFR) Rate at Week 4
End point description:	
uSFR was assessed by weighing of dental rolls soaked with saliva over 5 minutes and then procedure was repeated after 30 minutes and the average of the 2 results for flow rate was calculated.	
End point type	Primary
End point timeframe:	
Baseline and Week 4	

End point values	MP: Placebo	MP: IncobotulinumtoxinA (Xeomin) (75 units)	MP: IncobotulinumtoxinA (Xeomin) (100 units)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36[1]	73[2]	73[3]	
Units: gram per minute (g/min)				
least squares mean (standard error)	-0.04 (± 0.033)	-0.06 (± 0.027)	-0.13 (± 0.026)	

Notes:
[1] - FAS
[2] - FAS
[3] - FAS

Statistical analyses

Statistical analysis title	Week 4: IncobotulinumtoxinA 100 units v Placebo

Statistical analysis description:

A fixed sequence test procedure was used for the confirmatory analysis of the co-primary endpoints by comparing the least square (LS) means estimates of an mixed model repeated measurement (MMRM) model (2-sided, significance level alpha=0.05) between treatment groups in the following order:
1) IncobotulinumtoxinA 100 units versus (v) Placebo
2) IncobotulinumtoxinA 75 units v Placebo

Comparison groups	MP: IncobotulinumtoxinA (Xeomin) (100 units) v MP: Placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.031

Statistical analysis title	Week 4: IncobotulinumtoxinA 75 units v Placebo

Statistical analysis description:

A fixed sequence test procedure was used for the confirmatory analysis of the co-primary endpoints by comparing the least square means estimates of an MMRM model (2-sided, significance level alpha=0.05) between treatment groups in the following order:
1) IncobotulinumtoxinA 100 units versus (v) Placebo
2) IncobotulinumtoxinA 75 units v Placebo

Comparison groups	MP: Placebo v MP: IncobotulinumtoxinA (Xeomin) (75 units)
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.542
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.03

Primary: MP: Subjects's Global Impression of Change Scale (GICS) at Week 4

End point title	MP: Subjects's Global Impression of Change Scale (GICS) at Week 4

End point description:

The GICS was used to measure the impression of change due to treatment. The response option was a common 7-point Likert scale that ranged from -3 = very much worse to +3 = very much improved and was applicable for subject and caregiver. If the subject was not able to answer then carer's rating was to be recorded instead of subject's rating and the subject's rating was left blank.

End point type	Primary

End point timeframe:

Week 4

End point values	MP: Placebo	MP: IncobotulinumtoxinA (Xeomin) (75 units)	MP: IncobotulinumtoxinA (Xeomin) (100 units)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36[4]	74[5]	74[6]	
Units: units on scale				
least squares mean (standard error)	0.67 (± 0.186)	1.02 (± 0.148)	1.25 (± 0.144)	

Notes:

[4] - FAS

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Week 4: IncobotulinumtoxinA 100 units v Placebo

Statistical analysis description:

A fixed sequence test procedure was used for the confirmatory analysis of the co-primary endpoints by comparing the least square means estimates of an MMRM model (2-sided, significance level alpha=0.05) between treatment groups in the following order:
1) IncobotulinumtoxinA 100 units versus (v) Placebo
2) IncobotulinumtoxinA 75 Units v Placebo

Comparison groups	MP: Placebo v MP: IncobotulinumtoxinA (Xeomin) (100 units)

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.94
Variability estimate	Standard error of the mean
Dispersion value	0.183

Statistical analysis title	Week 4: IncobotulinumtoxinA 75 units v Placebo

Statistical analysis description:

A fixed sequence test procedure was used for the confirmatory analysis of the co-primary endpoints by comparing the least square means estimates of an MMRM model (2-sided, significance level alpha=0.05) between treatment groups in the following order:
1) IncobotulinumtoxinA 100 units versus (v) Placebo
2) IncobotulinumtoxinA 75 units v Placebo

Comparison groups	MP: Placebo v MP: IncobotulinumtoxinA (Xeomin) (75 units)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.71
Variability estimate	Standard error of the mean
Dispersion value	0.181

Secondary: MP: Change From Baseline in uSFR Rate at Week 8 and 12

End point title	MP: Change From Baseline in uSFR Rate at Week 8 and 12

End point description:

uSFR was assessed by weighing of dental rolls soaked with saliva over 5 minutes and then procedure was repeated after 30 minutes and the average of the 2 results for flow rate was calculated.

End point type	Secondary

End point timeframe:

Baseline, Week 8 and 12

End point values	MP: Placebo	MP: Incobotulinumtoxin A (Xeomin) (75 units)	MP: Incobotulinumtoxin A (Xeomin) (100 units)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36[7]	73[8]	73[9]	
Units: g/min				
least squares mean (standard error)				
Week 8	-0.02 (± 0.033)	-0.08 (± 0.027)	-0.13 (± 0.026)	
Week 12	-0.03 (± 0.033)	-0.1 (± 0.027)	-0.12 (± 0.026)	

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: MP: Global Impression of Change Scale (GICS) at Week 1, 2, 8 and 12

End point title	MP: Global Impression of Change Scale (GICS) at Week 1, 2, 8 and 12

End point description:

The GICS was used to measure the investigator's impression of change due to treatment. The response option was a common 7-point Likert scale that ranged from -3 = very much worse to +3 = very much improved and was applicable for subject and caregiver. If the subject was not able to answer then carer's rating was to be recorded instead of subject's rating and the subject's rating was left blank.

End point type	Secondary

End point timeframe:

Week 1, 2, 8, and 12

End point values	MP: Placebo	MP: Incobotulinumtoxin A (Xeomin) (75 units)	MP: Incobotulinumtoxin A (Xeomin) (100 units)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36[10]	74[11]	74[12]	
Units: units on scale				
least squares mean (standard error)				
Week 1	0.67 (± 0.17)	0.73 (± 0.138)	0.96 (± 0.133)	
Week 2	0.83 (± 0.178)	0.91 (± 0.143)	1.11 (± 0.139)	
Week 8	0.47 (± 0.192)	1.07 (± 0.151)	1.3 (± 0.148)	
Week 12	0.56 (± 0.197)	0.98 (± 0.156)	1.21 (± 0.152)	

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

MP: From first injection up to first injection in EP (week 16).
EP: From first injection in EP (week 16) up to end of study (week 64).

Adverse event reporting additional description:

The investigator asked the subject for adverse events systematically at each visit. Two subjects received the wrong or no dose in single EP cycles due to procedural reasons and hence were not included in the safety analyses that cover the complete EP: IncobotulinumtoxinA (Xeomin) (75 Units) arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	MP: Placebo

Reporting group description:

Subjects received 2.0 mL placebo.

Reporting group title	MP: IncobotulinumtoxinA (Xeomin) (75 units)

Reporting group description:

Subjects received 2.0 mL incobotulinumtoxinA containing 75 units.

Reporting group title	MP: IncobotulinumtoxinA (Xeomin) (100 units)

Reporting group description:

Subjects received 2.0 mL incobotulinumtoxinA containing 100 units.

Reporting group title	EP: IncobotulinumtoxinA (Xeomin) (75 units)

Reporting group description:

Subjects received 2.0 mL incobotulinumtoxinA containing 75 units at each of the three EP injection sessions.

Reporting group title	EP: IncobotulinumtoxinA (Xeomin) (100 units)

Reporting group description:

Subjects received 2.0 mL incobotulinumtoxinA containing 100 units at each of the three EP injection sessions.

Serious adverse events	MP: Placebo	MP: IncobotulinumtoxinA (Xeomin) (75 units)	MP: IncobotulinumtoxinA (Xeomin) (100 units)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 36 (8.33%)	6 / 74 (8.11%)	9 / 74 (12.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 36 (2.78%)	0 / 74 (0.00%)	0 / 74 (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
Hypertensive crisis			

subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Medical device battery replacement			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device change			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
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 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioplasty			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicectomy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterostomy			

subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Explorative laparotomy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laparotomy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrectomy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal stone removal			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureter dilation procedure			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral stent insertion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
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 physical health deterioration			

subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Pulmonary embolism			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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

Delusion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dopamine dysregulation syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 36 (2.78%)	0 / 74 (0.00%)	0 / 74 (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
Investigations			
Angiogram			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Femur fracture			

subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin abrasion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			

subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Cardiac failure			
subjects affected / exposed	1 / 36 (2.78%)	0 / 74 (0.00%)	0 / 74 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Parkinson's disease			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drop attacks			

subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Freezing phenomenon			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Akinesia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Movement disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic intolerance			

subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 36 (2.78%)	0 / 74 (0.00%)	0 / 74 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastritis erosive			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Gastrointestinal obstruction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Volvulus			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal vomiting			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Giant cell epulis			

subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Megacolon			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal food impaction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
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			
Hydronephrosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 74 (0.00%)	0 / 74 (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
Urethral stenosis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Extravasation of urine			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Pyuria			
subjects affected / exposed	1 / 36 (2.78%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	EP: IncobotulinumtoxinA (Xeomin) (75 units)	EP: IncobotulinumtoxinA (Xeomin) (100 units)	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 82 (18.29%)	14 / 89 (15.73%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device battery replacement			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device change			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			

subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioplasty			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicectomy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterostomy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Explorative laparotomy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparotomy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal stone removal			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureter dilation procedure			

subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral stent insertion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	1 / 82 (1.22%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dopamine dysregulation syndrome			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Angiogram			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 82 (1.22%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laceration			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Parkinson's disease			
subjects affected / exposed	6 / 82 (7.32%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drop attacks			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Freezing phenomenon			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Akinesia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 82 (1.22%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	2 / 82 (2.44%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal vomiting			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			

subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell epulis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal food impaction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 82 (0.00%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation of urine			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyuria			
subjects affected / exposed	0 / 82 (0.00%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MP: Placebo	MP: IncobotulinumtoxinA (Xeomin) (75 units)	MP: IncobotulinumtoxinA (Xeomin) (100 units)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)	14 / 74 (18.92%)	10 / 74 (13.51%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 36 (0.00%)	6 / 74 (8.11%)	2 / 74 (2.70%)
occurrences (all)	0	8	5
Contusion			
subjects affected / exposed	0 / 36 (0.00%)	4 / 74 (5.41%)	0 / 74 (0.00%)
occurrences (all)	0	5	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 36 (2.78%)	2 / 74 (2.70%)	3 / 74 (4.05%)
occurrences (all)	1	2	3
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 74 (0.00%)	4 / 74 (5.41%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 36 (0.00%)	4 / 74 (5.41%)	3 / 74 (4.05%)
occurrences (all)	0	5	3
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	1 / 36 (2.78%)	2 / 74 (2.70%)	2 / 74 (2.70%)
occurrences (all)	1	2	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	2 / 74 (2.70%)	0 / 74 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	EP: IncobotulinumtoxinA (Xeomin) (75 units)	EP: IncobotulinumtoxinA (Xeomin) (100 units)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 82 (26.83%)	22 / 89 (24.72%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 82 (6.10%)	4 / 89 (4.49%)	
occurrences (all)	9	5	
Contusion			
subjects affected / exposed	3 / 82 (3.66%)	1 / 89 (1.12%)	
occurrences (all)	3	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 82 (6.10%)	2 / 89 (2.25%)	
occurrences (all)	5	2	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	3 / 82 (3.66%)	4 / 89 (4.49%)	
occurrences (all)	4	5	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	3 / 82 (3.66%)	10 / 89 (11.24%)	
occurrences (all)	4	13	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 82 (1.22%)	6 / 89 (6.74%)	
occurrences (all)	1	6	
Upper respiratory tract infection			
subjects affected / exposed	5 / 82 (6.10%)	0 / 89 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2014	Main Changes: 1. Addition of a new safety assessment to prospectively monitor suicidality in order to comply with FDA guidance on suicidality testing in all clinical trials investigating neurological indications: Columbia Suicide Severity Rating Scale (C-SSRS). 2. Addition of detailed immunogenicity assessment. 3. Addition of dental examination by a dentist at week 32 4. Legally acceptable representative was replaced by impartial witness 5. Dental examinations and mROAG assessment concerning AE reporting were explicitly explained.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported