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 upper limb

Summary

EudraCT number	2010-023043-15
Trial protocol	DE HU CZ
Global end of trial date	13 February 2014

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	MRZ 60201/SP/3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01392300
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merz Pharmaceuticals GmbH
Sponsor organisation address	Eckenheimer Landstrasse 100, Frankfurt/Main, Germany, 60318
Public contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, clinicaltrials@merz.de
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, 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	20 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2013
Global end of trial reached?	Yes
Global end of trial date	13 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether injections of Botulinum toxin type A into muscles of the upper limb are effective in treating spasticity in patients after stroke.

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:

Physiotherapy, occupational therapy, and other rehabilitation measures to treat spasticity.

Evidence for comparator: -

Actual start date of recruitment	02 September 2011
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: 104
Country: Number of subjects enrolled	Czech Republic: 71
Country: Number of subjects enrolled	India: 39
Country: Number of subjects enrolled	United States: 38
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	317
EEA total number of subjects	208

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)	237
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

349 subjects were screened, of whom 26 did not meet study entry criteria, and 6 withdrew their consent

Period 1

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

Arms

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

Arm description:

IncobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA (400 U)
Investigational medicinal product code	NT 201
Other name	Xeomin, Bocouture, Botulinum toxin type A (150 kiloDalton) free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

400 U total dose per injection session, to be administered by guided (EMG, E-Stim) intramuscular injections. In the double-blind period, a primary target clinical pattern (PTCP, flexed elbow, flexed wrist or clenched fist) was selected for each patient by the investigator and treated with a predefined fixed dose (flexed elbow, 200 U; flexed wrist, 150 U; or clenched fist, 100 U). Doses and injection sites for other muscles were flexible within pre-defined ranges, based on patients' individual conditions, and on approved (in the EU) dose ranges for individual muscles.

Arm title	Double-blind Placebo Comparator

Arm description:

Placebo to incobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment

Arm type	Placebo
Investigational medicinal product name	Placebo to incobotulinumtoxinA (Xeomin) powder for solution for injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Volume equivalent to 400 U total dose per injection session, to be administered by guided (EMG, E-Stim) intramuscular injections. In the double-blind period, a primary target clinical pattern (PTCP, flexed elbow, flexed wrist or clenched fist) was selected for each patient by the investigator and treated with a predefined fixed dose (flexed elbow, 200 U; flexed wrist, 150 U; or clenched fist, 100 U). Doses and injection sites for other muscles were flexible within pre-defined ranges, based on patients' individual conditions, and on approved (in the EU) dose ranges for individual muscles.

Number of subjects in period 1	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator
Started	210	107
Completed	199	100
Not completed	11	7
Consent withdrawn by subject	5	1
Non-compliance	1	-
Lost to follow-up	3	3
Predefined discontinuation criteria	2	3

Period 2

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

Arms

Arm title	OLEX IncobotulinumtoxinA (Xeomin) (400 units, 3 Injections)

Arm description:

IncobotulinumtoxinA (Xeomin) (400 Units): OLEX period, three injection sessions - open-label treatment assignment

Arm type	Experimental
Investigational medicinal product name	IncobotulinumtoxinA (400 U)
Investigational medicinal product code	NT 201
Other name	Xeomin, Bocouture, Botulinum toxin type A (150 kiloDalton) free from complexing proteins
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

400 U total dose per injection session, to be administered by guided (EMG, E-Stim) intramuscular injections to elbow flexor, forearm pronator, wrist flexor, finger flexor and thumb flexor muscles. In the open-label extension period, doses and injection sites were flexible within pre-defined ranges, based on patients' individual condition and on approved (in the EU) dose ranges for individual muscles.

Number of subjects in period 2	OLEX IncobotulinumtoxinA (Xeomin) (400 units, 3 Injections)
Started	299
Week 24	283
Week 36	259
Completed	248
Not completed	51
Adverse event, serious fatal	4
Consent withdrawn by subject	17
Adverse event, non-fatal	7
Non-compliance	1
Lost to follow-up	6
Protocol deviation	13
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)
Reporting group description:	
IncobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment	
Reporting group title	Double-blind Placebo Comparator
Reporting group description:	
Placebo to incobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment	

Reporting group values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator	Total
Number of subjects	210	107	317
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)	162	75	237
From 65-84 years	48	32	80
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	55.3	57.8	
standard deviation	± 11.9	± 10.9	-
Gender, Male/Female Units: participants			
Female	120	61	181
Male	90	46	136
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	0	4
Not Hispanic or Latino	22	12	34
Unknown or Not Reported	184	95	279
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	27	13	40
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	6	3	9
White	175	91	266
More than one race	0	0	0

Unknown or Not Reported	1	0	1
Region of Enrollment Units: Subjects			
United States	26	12	38
Czech Republic	46	25	71
Hungary	23	9	32
Poland	66	38	104
Russian Federation	22	10	32
Germany	1	0	1
India	26	13	39

End points

End points reporting groups

Reporting group title	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)
Reporting group description:	
IncobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment	
Reporting group title	Double-blind Placebo Comparator
Reporting group description:	
Placebo to incobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment	
Reporting group title	OLEX IncobotulinumtoxinA (Xeomin) (400 units, 3 Injections)
Reporting group description:	
IncobotulinumtoxinA (Xeomin) (400 Units): OLEX period, three injection sessions - open-label treatment assignment	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who were randomized after the Amended Protocol Version 3.0 (dated 11-MAY-2012) became effective, who were treated, and for whom at least an AS baseline value for the primary target clinical pattern was given.	

Primary: Change from baseline in Ashworth Scale (AS) Score of primary target clinical pattern

End point title	Change from baseline in Ashworth Scale (AS) Score of primary target clinical pattern
End point description:	
Primary target clinical pattern was defined by investigator for each subject at baseline visit and was either flexed wrist or clenched fist or flexed elbow. The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).	
End point type	Primary
End point timeframe:	
Week 4	

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.9 (± 0.06)	-0.5 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v

	Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.1

Primary: Investigator's Global Impression of Change

End point title	Investigator's Global Impression of Change

End point description:

This is the co-primary outcome measure.
The Global Impression of Change Scale [GICS] is used to measure the investigator's impression of change due to treatment. The response option is a common 7-point Likert scale that ranges from -3 = very much worse to +3 = very much improved.

End point type	Primary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	1.2 (± 0.07)	0.9 (± 0.09)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.11

Secondary: Response rates on the Ashworth Scale at week 4 calculated for the primary target clinical pattern

End point title	Response rates on the Ashworth Scale at week 4 calculated for the primary target clinical pattern

End point description:

Primary target clinical pattern was defined by investigator for each subject at baseline visit and was either flexed wrist or clenched fist or flexed elbow. Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	119	33		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.43
upper limit	7.52

Secondary: Response rates on the Ashworth Scale at week 8 calculated for the primary target clinical pattern

End point title	Response rates on the Ashworth Scale at week 8 calculated for the primary target clinical pattern

End point description:

Primary target clinical pattern was defined by investigator for each subject at baseline visit and was either flexed wrist or clenched fist or flexed elbow. Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	104	34		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	4.63

Secondary: Response rates on the Ashworth Scale at week 12 calculated for the primary target clinical pattern

End point title	Response rates on the Ashworth Scale at week 12 calculated for the primary target clinical pattern

End point description:

Primary target clinical pattern was defined by investigator for each subject at baseline visit and was either flexed wrist or clenched fist or flexed elbow. Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	68	22		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	4.61

Secondary: Response rates on the Ashworth Scale at week 4 calculated for the muscle group flexed wrist

End point title	Response rates on the Ashworth Scale at week 4 calculated for the muscle group flexed wrist

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	102	31		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.76
upper limit	5.57

Secondary: Response rates on the Ashworth Scale at week 8 calculated for the muscle group flexed wrist

End point title	Response rates on the Ashworth Scale at week 8 calculated for

	the muscle group flexed wrist

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	90	33		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.34

Secondary: Response rates on the Ashworth Scale at week 12 calculated for the muscle group flexed wrist

End point title	Response rates on the Ashworth Scale at week 12 calculated for the muscle group flexed wrist

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	59	17		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	5.05

Secondary: Response rates on the Ashworth Scale at week 4 calculated for the muscle group flexed elbow

End point title	Response rates on the Ashworth Scale at week 4 calculated for the muscle group flexed elbow

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	99	28		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.06
upper limit	6.72

Secondary: Response rates on the Ashworth Scale at week 8 calculated for the muscle group flexed elbow

End point title	Response rates on the Ashworth Scale at week 8 calculated for the muscle group flexed elbow

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				

number (not applicable)	85	28		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	4.46

Secondary: Response rates on the Ashworth Scale at week 12 calculated for the muscle group flexed elbow

End point title	Response rates on the Ashworth Scale at week 12 calculated for the muscle group flexed elbow

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	52	21		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.22

Secondary: Response rates on the Ashworth Scale at week 4 calculated for the muscle group clenched fist

End point title	Response rates on the Ashworth Scale at week 4 calculated for the muscle group clenched fist

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	90	26		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	5.23

Secondary: Response rates on the Ashworth Scale at week 8 calculated for the muscle group clenched fist

End point title	Response rates on the Ashworth Scale at week 8 calculated for the muscle group clenched fist

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	82	27		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	4.41

Secondary: Response rates on the Ashworth Scale at week 12 calculated for the muscle group clenched fist

End point title	Response rates on the Ashworth Scale at week 12 calculated for the muscle group clenched fist

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	49	19		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	3.69

Secondary: Response rates on the Ashworth Scale at week 4 calculated for the muscle group thumb-in-palm

End point title	Response rates on the Ashworth Scale at week 4 calculated for the muscle group thumb-in-palm

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	56	21		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	4

Secondary: Response rates on the Ashworth Scale at week 8 calculated for the muscle group thumb-in-palm

End point title	Response rates on the Ashworth Scale at week 8 calculated for the muscle group thumb-in-palm

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	52	23		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	3.16

Secondary: Response rates on the Ashworth Scale at week 12 calculated for the muscle group thumb-in-palm

End point title	Response rates on the Ashworth Scale at week 12 calculated for the muscle group thumb-in-palm

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	35	20		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.18

Secondary: Response rates on the Ashworth Scale at week 4 calculated for the muscle group pronated forearm

End point title	Response rates on the Ashworth Scale at week 4 calculated for the muscle group pronated forearm

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	73	19		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.83
upper limit	6.91

Secondary: Response rates on the Ashworth Scale at week 8 calculated for the muscle group pronated forearm

End point title	Response rates on the Ashworth Scale at week 8 calculated for the muscle group pronated forearm

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	64	20		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	4.56

Secondary: Response rates on the Ashworth Scale at week 12 calculated for the muscle group pronated forearm

End point title	Response rates on the Ashworth Scale at week 12 calculated for the muscle group pronated forearm

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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). Subjects with a reduction of one point were defined as responder for the aim of the efficacy analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: participants				
number (not applicable)	51	15		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	4.41

Secondary: Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group flexed wrist.

End point title	Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group flexed wrist.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.8 (± 0.06)	-0.5 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group flexed wrist.

End point title	Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group flexed wrist.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.6 (± 0.06)	-0.4 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1

Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group flexed wrist.

End point title	Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group flexed wrist.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.05)	-0.1 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group flexed elbow.

End point title	Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group flexed elbow.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.7 (± 0.05)	-0.3 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group flexed elbow.

End point title	Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group flexed elbow.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.6 (± 0.05)	-0.3 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group flexed elbow.

End point title	Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group flexed elbow.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind Incobotulinumtoxin A (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group clenched fist.

End point title	Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group clenched fist.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind Incobotulinumtoxin A (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.7 (± 0.06)	-0.3 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group clenched fist.

End point title	Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group clenched fist.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.6 (± 0.05)	-0.4 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group clenched fist.

End point title	Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group clenched fist.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.05)	-0.1 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group thumb-in-palm.

End point title	Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group thumb-in-palm.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group thumb-in-palm.

End point title	Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group thumb-in-palm.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.05)	-0.2 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group thumb-in-palm.

End point title	Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group thumb-in-palm.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.2 (± 0.05)	-0.1 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.714
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group pronated forearm.

End point title	Changes from baseline to week 4 in Ashworth Scale Score for treated muscle group pronated forearm.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.5 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group pronated forearm.

End point title	Changes from baseline to week 8 in Ashworth Scale Score for treated muscle group pronated forearm.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group pronated forearm.

End point title	Changes from baseline to week 12 in Ashworth Scale Score for treated muscle group pronated forearm.

End point description:

The Ashworth Scale is well known and commonly used in clinical trials with spasticity. It was used to categorize 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).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.05)	-0.1 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 4 in Disability Assessment Scale - principal therapeutic target domain

End point title	Changes from baseline to Week 4 in Disability Assessment Scale - principal therapeutic target domain

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.5 (± 0.05)	-0.3 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 8 in Disability Assessment Scale - principal therapeutic target domain

End point title	Changes from baseline to Week 8 in Disability Assessment Scale - principal therapeutic target domain

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.5 (± 0.05)	-0.3 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 12 in Disability Assessment Scale - principal therapeutic target domain

End point title	Changes from baseline to Week 12 in Disability Assessment Scale - principal therapeutic target domain

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.4 (± 0.06)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.416
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 4 in Disability Assessment Scale - domain hygiene

End point title	Changes from baseline to Week 4 in Disability Assessment Scale - domain hygiene

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.1 (± 0.06)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Secondary: Changes from baseline to Week 8 in Disability Assessment Scale - domain hygiene

End point title	Changes from baseline to Week 8 in Disability Assessment Scale - domain hygiene

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 12 in Disability Assessment Scale - domain hygiene

End point title	Changes from baseline to Week 12 in Disability Assessment Scale - domain hygiene

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.05)	-0.1 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 4 in Disability Assessment Scale - domain dressing

End point title	Changes from baseline to Week 4 in Disability Assessment Scale - domain dressing

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.06)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Secondary: Changes from baseline to Week 8 in Disability Assessment Scale - domain dressing

End point title	Changes from baseline to Week 8 in Disability Assessment Scale - domain dressing

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 12 in Disability Assessment Scale - domain dressing

End point title	Changes from baseline to Week 12 in Disability Assessment Scale - domain dressing

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.04)	-0.1 (± 0.06)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.07

Secondary: Changes from baseline to Week 4 in Disability Assessment Scale - domain limb position

End point title	Changes from baseline to Week 4 in Disability Assessment Scale - domain limb position

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.5 (± 0.05)	-0.3 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 8 in Disability Assessment Scale - domain limb position

End point title	Changes from baseline to Week 8 in Disability Assessment Scale - domain limb position

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.2 (± 0.07)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Changes from baseline to Week 12 in Disability Assessment Scale - domain limb position

End point title	Changes from baseline to Week 12 in Disability Assessment Scale - domain limb position

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.05)	-0.3 (± 0.06)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Secondary: Changes from baseline to Week 4 in Disability Assessment Scale - domain pain

End point title	Changes from baseline to Week 4 in Disability Assessment Scale - domain pain

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 4

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.2 (± 0.06)	-0.2 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.429
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to Week 8 in Disability Assessment Scale - domain pain

End point title	Changes from baseline to Week 8 in Disability Assessment Scale - domain pain

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.2 (± 0.06)	-0.2 (± 0.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.884
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Changes from baseline to Week 12 in Disability Assessment Scale - domain pain

End point title	Changes from baseline to Week 12 in Disability Assessment Scale - domain pain

End point description:

The Disability Assessment Scale consists of the four domains hygiene, dressing, limb position, and pain which were assessed on a 4-point scale with the values 0 (=no disability), 1 (=mild disability), 2 (=moderate disability), and 3 (=severe disability).

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	88		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.06)	-0.2 (± 0.09)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units) v Double-blind Placebo Comparator
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.844
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the timepoint of first injection until 12 weeks +/- 3 days after last injection	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)
Reporting group description:	
IncobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment	
Reporting group title	Double-blind Placebo Comparator
Reporting group description:	
Placebo to incobotulinumtoxinA (Xeomin) (400 Units): Main period, one injection session - double-blind, randomized treatment assignment	
Reporting group title	OLEX IncobotulinumtoxinA (Xeomin) (400 Units, 3 injections)
Reporting group description:	
IncobotulinumtoxinA (Xeomin) (400 Units): OLEX period, three injection sessions - open-label treatment assignment	

Serious adverse events	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator	OLEX IncobotulinumtoxinA (Xeomin) (400 Units, 3 injections)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 210 (3.33%)	2 / 107 (1.87%)	22 / 296 (7.43%)
number of deaths (all causes)	0	0	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	0 / 210 (0.00%)	1 / 107 (0.93%)	0 / 296 (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
Ovarian adenoma			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral ischaemia			

subjects affected / exposed	2 / 210 (0.95%)	0 / 107 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
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			
Cardiac death			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
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	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
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 / 210 (0.48%)	0 / 107 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudobulbar palsy			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatic enlargement			
subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	0 / 296 (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
Abdominal pain			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
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			
Biliary colic			
subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	0 / 296 (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
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 210 (0.00%)	1 / 107 (0.93%)	0 / 296 (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
Dysuria			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
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 failure			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	0 / 296 (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
Cellulitis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endocarditis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 210 (0.00%)	0 / 107 (0.00%)	1 / 296 (0.34%)
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	Double-blind IncobotulinumtoxinA (Xeomin) (400 Units)	Double-blind Placebo Comparator	OLEX IncobotulinumtoxinA (Xeomin) (400 Units, 3 injections)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 210 (2.86%)	4 / 107 (3.74%)	32 / 296 (10.81%)
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	8 / 296 (2.70%)
occurrences (all)	1	0	9
International normalised ratio increased			
subjects affected / exposed	1 / 210 (0.48%)	0 / 107 (0.00%)	8 / 296 (2.70%)
occurrences (all)	1	0	10
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 210 (0.00%)	1 / 107 (0.93%)	7 / 296 (2.36%)
occurrences (all)	0	1	9
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 210 (0.48%)	3 / 107 (2.80%)	3 / 296 (1.01%)
occurrences (all)	1	6	6
Epilepsy			
subjects affected / exposed	5 / 210 (2.38%)	0 / 107 (0.00%)	6 / 296 (2.03%)
occurrences (all)	6	0	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2012	The amendment specified changes in the study inclusion criteria, selection of primary target pattern, instructions for administration and dosing of NT 201, study assessments and co-primary endpoint and statistical methods to reflect FDA comments and to demonstrate the improvement of spasticity throughout the upper limb with NT 201 treatment accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 January 2012	The original protocol was altered by a single major amendment, prompted by comments received in January 2012 from the US Food and Drug Administration following a special protocol assessment. As patient recruitment for this study had already started (in September 2011) and 58 subjects had already been enrolled, recruitment of further patients was set on temporary hold to allow implementation of the comments into the study protocol.	17 April 2012

Notes:

Limitations and caveats

None reported