Clinical trial results:
Prospective, double-blind, placebo-controlled, randomized, parallel-group, multi-center study with an open-label extension period to investigate the efficacy and safety of two different doses of NT 201 in Botulinum toxin treatment-naïve subjects with blepharospasm

Summary

EudraCT number	2012-004821-26
Trial protocol	GR
Global end of trial date	10 November 2016

Results information

Result version number	v1
This version publication date	23 November 2017
First version publication date	23 November 2017

Trial information

Trial identification

Sponsor protocol code	MRZ60201_3074_1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01896895
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merz Pharmaceuticals GmbH
Sponsor organisation address	Eckenheimer Landstrasse 100, Frankfurt/M, Germany, 60318
Public contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.de
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to investigate the efficacy and safety of two different doses of IncobotulinumtoxinA (NT 201) compared to placebo in one double-blind cycle Main Period (MP) with one subsequent open-label treatment cycle Open label Extension (OLEX period) in botulinum toxin [BTX] treatment-naïve subjects with benign essential blepharospasm (BEB) using a dose of 12.5 or 25 units IncobotulinumtoxinA per eye (total dose of 25 or 50 units IncobotulinumtoxinA for both eyes) in the MP and a single dose of up to 35 units IncobotulinumtoxinA per eye in the OLEX period (total dose of up to 70 units IncobotulinumtoxinA for both eyes), each followed by 6 to 20 weeks observation.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Malaysia: 17
Country: Number of subjects enrolled	Sri Lanka: 30
Country: Number of subjects enrolled	Greece: 14
Worldwide total number of subjects	61
EEA total number of subjects	14

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)	44
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The clinical study was conducted at 5 sites in Malaysia, 4 sites in Sri Lanka and 3 sites in Greece from 21 January 2014 to 10 November 2016.

Pre-assignment

Screening details:

A total of 68 subjects were screened, 61 were enrolled and treated of which 55 completed the double-blind MP. 39 subjects from the double-blind MP entered the OLEX period and completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind MP: Placebo

Arm description:

Subjects received 1.0 milliliter (mL) placebo.

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

Dosage and administration details:

Subjects received 1.0 mL placebo matched to the volume of incobotulinumtoxinA doses per injection session via intramuscular injections into orbicular oculi muscles on Day 1 in the double-blind MP.

Arm title	Double-blind MP: IncobotulinumtoxinA 25 Units

Arm description:

Subjects received 1.0 mL of incobotulinumtoxinA containing 25 units per injection session.

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

Dosage and administration details:

Subjects received 1.0 mL of incobotulinumtoxinA containing 25 units per injection session (12.5 units per eye) via intramuscular injections into orbicular oculi muscles on Day 1 in the double-blind MP.

Arm title	Double-blind MP: IncobotulinumtoxinA 50 Units

Arm description:

Subjects received 1.0 mL of incobotulinumtoxinA containing 50 units per injection session.

Arm type	Experimental

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

Dosage and administration details:

Subjects received 1.0 mL of incobotulinumtoxinA containing 50 units per injection session (25 units per eye) via intramuscular injections into orbicular oculi muscles on Day 1 in the double-blind MP.

Number of subjects in period 1	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units
Started	20	22	19
Completed	19	20	16
Not completed	1	2	3
Consent withdrawn by subject	-	2	1
Physician decision	-	-	1
Lost to follow-up	1	-	1

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 70 Units

Arm description:

Subjects received up to 1.4 mL of incobotulinumtoxinA containing up to 70 units per injection session.

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

Dosage and administration details:

Subjects received up to 1.4 mL of incobotulinumtoxinA containing up to 70 units per injection session (up to 35 units per eye) via intramuscular injections into orbicular oculi muscles on Day 1 in the OLEX Period.

Number of subjects in period 2[1]	OLEX: IncobotulinumtoxinA 70 Units
Started	39
Completed	39

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects who completed the double-blind MP fulfilled the eligibility criteria for inclusion into the OLEX period.

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind MP: Placebo
Reporting group description:	
Subjects received 1.0 milliliter (mL) placebo.	
Reporting group title	Double-blind MP: IncobotulinumtoxinA 25 Units
Reporting group description:	
Subjects received 1.0 mL of incobotulinumtoxinA containing 25 units per injection session.	
Reporting group title	Double-blind MP: IncobotulinumtoxinA 50 Units
Reporting group description:	
Subjects received 1.0 mL of incobotulinumtoxinA containing 50 units per injection session.	

Reporting group values	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units
Number of subjects	20	22	19
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)	17	13	14
From 65-84 years	3	9	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.4	55.8	53.5
standard deviation	± 12.01	± 15.70	± 13.82
Gender categorical Units: Subjects			
Female	12	11	13
Male	8	11	6
Race Units: Subjects			
White	4	6	4
Asian	16	16	15
Height Units: centimeter (cm)			
arithmetic mean	160.9	159.6	158.6
standard deviation	± 9.79	± 12.00	± 6.74
Weight Units: kilogram (kg)			
arithmetic mean	61.6	61.0	63.1
standard deviation	± 16.20	± 18.45	± 8.70

Body mass index (BMI)			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	23.6	23.6	25.2
standard deviation	± 5.03	± 5.27	± 3.33

Reporting group values	Total		
Number of subjects	61		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	44		
From 65-84 years	17		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	36		
Male	25		
Race			
Units: Subjects			
White	14		
Asian	47		
Height			
Units: centimeter (cm)			
arithmetic mean			
standard deviation	-		
Weight			
Units: kilogram (kg)			
arithmetic mean			
standard deviation	-		
Body mass index (BMI)			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Double-blind MP: Placebo
Reporting group description:	
Subjects received 1.0 milliliter (mL) placebo.	
Reporting group title	Double-blind MP: IncobotulinumtoxinA 25 Units
Reporting group description:	
Subjects received 1.0 mL of incobotulinumtoxinA containing 25 units per injection session.	
Reporting group title	Double-blind MP: IncobotulinumtoxinA 50 Units
Reporting group description:	
Subjects received 1.0 mL of incobotulinumtoxinA containing 50 units per injection session.	
Reporting group title	OLEX: IncobotulinumtoxinA 70 Units
Reporting group description:	
Subjects received up to 1.4 mL of incobotulinumtoxinA containing up to 70 units per injection session.	
Subject analysis set title	Full Analysis Set (FAS) of Double-blind MP
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS) is the subset of subjects in the safety evaluation set (SES) of the double-blind MP for whom at least a baseline value of the Jankovic Rating Scale (JRS) severity subscore is available.	

Primary: Double-blind MP: Change from Baseline in JRS Severity Subscore at Day 43 (Visit 4)

End point title	Double-blind MP: Change from Baseline in JRS Severity Subscore at Day 43 (Visit 4)
End point description:	
JRS severity subscore was used for the classification of the subject's individual symptoms of blepharospasm and for the determination of the therapeutic efficacy of the study drug. The JRS severity subscore ranges from 0 to 4, where 0: None; 1: increased blinking present only with external stimuli; 2: Mild but spontaneous eyelid fluttering (without actual spasm), definitely noticeable, possibly embarrassing, but not functionally disabling, 3: Moderate, very noticeable spasm of eyelids only, mildly incapacitating, 4: Severe, incapacitating spasm of eyelids and possibly other facial muscles. Values represent least square (LS) mean differences between baseline and visit 4 resulting from an analysis of covariance (ANCOVA) with treatment group, pooled site, and gender as fixed factors and baseline JRS severity subscore and age as covariates and missings replaced using the last observation carried forward method (LOCF).	
End point type	Primary
End point timeframe:	
Baseline, Day 43 (Visit 4)	

End point values	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[1]	22[2]	19[3]	
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.6 (-1.0 to -0.1)	-1.0 (-1.5 to -0.6)	-1.8 (-2.3 to -1.3)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Visit 4: IncobotulinumtoxinA 50 Units Vs Placebo

Statistical analysis description:

The difference in change of JRS severity subscore between treatment groups was analyzed by an ANCOVA according to a hierarchical test procedure. First step of hierarchy is hypothesis of superiority of 50 unit dose group NT 201 compared to placebo. This was tested confirmatory (α=0.05, 2-sided) by an ANCOVA with treatment group, pooled site, and gender as fixed factors and baseline JRS severity subscore and age as covariates based on LS means comparison. Missing values were imputed by LOCF.

Comparison groups	Double-blind MP: IncobotulinumtoxinA 50 Units v Double-blind MP: Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.6

Statistical analysis title	Visit 4: IncobotulinumtoxinA 25 Units Vs Placebo

Statistical analysis description:

The difference in change of JRS severity subscore between treatment groups was analyzed by an ANCOVA according to a hierarchical test procedure. Second step of hierarchy is hypothesis of superiority of 25 unit dose group NT 201 compared to placebo. This was tested confirmatory (α=0.05, 2-sided) by an ANCOVA with treatment group, pooled site, and gender as fixed factors and baseline JRS severity subscore and age as covariates based on LS means comparison. Missing values were imputed by LOCF.

Comparison groups	Double-blind MP: IncobotulinumtoxinA 25 Units v Double-blind MP: Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1452
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.2

Secondary: Double-blind MP: Change from Baseline in Blepharospasm Disability Index (BSDI) at Day 43 (Visit 4)

End point title	Double-blind MP: Change from Baseline in Blepharospasm Disability Index (BSDI) at Day 43 (Visit 4)

End point description:

BSDI is a scale for the assessment of impairment of specific activities of daily living caused by blepharospasm. The BSDI consists of six items (driving a vehicle; reading; watching TV; shopping; getting about on foot (walking); doing everyday activities), with each ranging from 0 (=no impairment) to 4 (=no longer possible due to illness).

End point type	Secondary

End point timeframe:

Baseline, Day 43 (Visit 4)

End point values	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[4]	22[5]	19[6]	
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.4 (-0.8 to 0.0)	-0.5 (-0.9 to -0.2)	-0.7 (-1.1 to -0.3)	

Notes:

[4] - FAS

[5] - FAS

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind MP: Patient Evaluation of Global Response (PEGR) at Final Visit (Day 43-Day 141)

End point title	Double-blind MP: Patient Evaluation of Global Response (PEGR) at Final Visit (Day 43-Day 141)

End point description:

PEGR scale is a descriptive subjective 9-point response self-rating scale ranging from "complete abolishment of signs and symptoms" (value=+4) down to "very marked worsening" (value=-4).

End point type	Secondary

End point timeframe:

Baseline, Final Visit (Day 43-Day 141)

End point values	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[7]	22[8]	19[9]	
Units: score on a scale				
least squares mean (confidence interval 95%)	1.3 (0.7 to 1.9)	1.8 (1.2 to 2.4)	2.2 (1.5 to 2.8)	

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind MP: From the time point of first injection up to final visit (Day 43 to 141); OLEX Period: From the time point of first injection up to end of study visit (Day 43 to 141)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Double-blind MP: Placebo

Reporting group description:

Subjects received 1.0 mL placebo matched to incobotulinumtoxinA doses per injection session via intramuscular injections into orbicular muscles on Day 1 in the double-blind MP.

Reporting group title	Double-blind MP: IncobotulinumtoxinA 25 Units

Reporting group description:

Subjects received 1.0 mL of incobotulinumtoxinA containing 25 units per injection session (12.5 units per eye) via intramuscular injections into orbicular oculi muscles on Day 1 in the double-blind MP.

Reporting group title	Double-blind MP: IncobotulinumtoxinA 50 Units

Reporting group description:

Subjects received 1.0 mL of incobotulinumtoxinA containing 50 units per injection session (25 units per eye) via intramuscular injections into orbicular oculi muscles on Day 1 in the double-blind MP.

Reporting group title	OLEX: IncobotulinumtoxinA 70 Units

Reporting group description:

Subjects received up to 1.4 mL of incobotulinumtoxinA containing up to 70 units per injection session (35 units per eye) via intramuscular injections into orbicular oculi muscles on Day 1 in the OLEX Period.

Serious adverse events	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	2 / 22 (9.09%)	1 / 19 (5.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (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

Serious adverse events	OLEX: IncobotulinumtoxinA 70 Units		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.5 %

Non-serious adverse events	Double-blind MP: Placebo	Double-blind MP: IncobotulinumtoxinA 25 Units	Double-blind MP: IncobotulinumtoxinA 50 Units
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	7 / 22 (31.82%)	7 / 19 (36.84%)
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0

Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injection site swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 22 (9.09%)	3 / 19 (15.79%)
occurrences (all)	0	2	3
Blepharospasm			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eye irritation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Eye swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eyelid disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Eyelid function disorder			
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Ocular hyperaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blepharitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	2 / 20 (10.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Periorbital oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hepatic steatosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pruritus generalised			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Muscular weakness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	0 / 19 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	OLEX: IncobotulinumtoxinA 70 Units		

Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 39 (10.26%)		
Investigations Blood creatine increased subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0		
Nervous system disorders Hypoaesthesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0 0 / 39 (0.00%) 0		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all) Injection site swelling subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0		
Eye disorders Eyelid ptosis subjects affected / exposed occurrences (all) Blepharospasm subjects affected / exposed occurrences (all) Eye irritation subjects affected / exposed occurrences (all) Eye pruritus subjects affected / exposed occurrences (all) Eye swelling	2 / 39 (5.13%) 2 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0		

subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Eyelid disorder			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Eyelid function disorder			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Ocular hyperaemia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Blepharitis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Periorbital oedema			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Hepatic steatosis			

subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Pruritus generalised			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		

Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all)	 0 / 39 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2014	1) Change in safety information: Due to the global harmonization of the Company Core Safety Information (CCSI) which is included as RSI within the investigator's brochure (IB) new safety information have been included for the indication blepharospasm. Common AEs related to NT 201 in the indication BEB were updated. 2) Updates in the current approval status and external responsibilities implemented.
04 May 2015	1) Addition of a new safety assessment to prospectively monitor suicidality in order to comply with FDA guidance on suicidality testing in all clinical trials investigating neurological indications: Columbia Suicide Severity Rating Scale (C-SSRS). 2) Addition of a new safety variable (classified as other safety variable) based on the results of the C-SSRS. 3) Addition of an exclusion criterion specifying that subjects with significant risk of suicidality at the baseline assessment were to be excluded. 4) Addition of a new eligibility criterion for injection in the OLEX period: no significant risk of suicidality since last injection based on the investigator's judgement, or if appropriate, as indicated of "no" to questions 4 or 5 in the suicidal ideation section of the C-SSRS, or no non suicidal self-injurious behavior, or no suicidal behavior. 5) Addition of a new discontinuation criterion: subjects were to be discontinued if there was a positive report on suicidality based on the C-SSRS. 6) Modification of data management procedures clarifying documentation of the C-SSRS results. 7) Modification of the definition of SAEs further specifying suicidal ideation (a response of “yes” to questions 4 or 5) or any suicidal behavior as “medically important condition”. 8) Description of the analysis of C-SSRS data. 9) New data added to the risk-benefit assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported