Clinical trial results:
A prospective, open-label, multi-center, repeat-dose study to investigate the safety and efficacy of NT 201 (incobotulinumtoxinA) in the combined treatment of upper facial lines (horizontal forehead lines, glabellar frown lines, and lateral periorbital lines)

Summary

EudraCT number	2014-003770-16
Trial protocol	DE
Global end of trial date	08 December 2016

Results information

Result version number	v1 (current)
This version publication date	03 January 2018
First version publication date	03 January 2018

Trial information

Trial identification

Sponsor protocol code	MRZ60201_3100_1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	02 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to investigate the safety and tolerability of 54 to 64 Units of NT 201 intramuscularly administered in subjects with moderate to severe upper facial lines (UFL) during repeat-dose treatment of these lines.

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	30 April 2015
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	Germany: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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)	131
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The clinical study was conducted at 10 sites in Germany from 30 April 2015 to 08 December 2016.

Pre-assignment

Screening details:

Subjects with moderate to severe lines (horizontal forehead lines [HFL], glabellar frown lines [GFL], and lateral periorbital lines [LPL]) at maximum contraction were enrolled. Total 145 subjects were screened, of which 140 subjects were enrolled and treated with 54 to 64 Units of IncobotulinumtoxinA, and of these 125 subjects completed the study.

Period 1

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

Arms

Arm title	IncobotulinumtoxinA 54 to 64 Units

Arm description:

Subjects received a total volume of 1.35 to 1.6 milliliter (mL) of incobotulinumtoxinA (Xeomin) with a maximum of 54 to 64 units per injection treatment via intramuscular injection into the 3 facial areas (HFL, GFL and LPL) on Day 1 of each treatment cycle for up to a maximum of 4 treatment cycles.

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 a total volume of 1.35 to 1.6 mL of incobotulinumtoxinA with a maximum of 54 to 64 units per injection treatment via intramuscular injection into the 3 facial areas (HFL, GFL and LPL) on Day 1 of each treatment cycle for up to a maximum of 4 treatment cycles.

Number of subjects in period 1	IncobotulinumtoxinA 54 to 64 Units
Started	140
Completed	125
Not completed	15
Consent withdrawn by subject	6
Physician decision	1
Adverse event, non-fatal	3
Pregnancy	1
Unspecified	4

Baseline characteristics

Reporting groups	
Reporting group title	IncobotulinumtoxinA 54 to 64 Units
Reporting group description:	
Subjects received a total volume of 1.35 to 1.6 milliliter (mL) of incobotulinumtoxinA (Xeomin) with a maximum of 54 to 64 units per injection treatment via intramuscular injection into the 3 facial areas (HFL, GFL and LPL) on Day 1 of each treatment cycle for up to a maximum of 4 treatment cycles.	

Reporting group values	IncobotulinumtoxinA 54 to 64 Units	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	131	131	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	49.6		
standard deviation	± 9.8	-	
Gender categorical Units: Subjects			
Female	127	127	
Male	13	13	
Race Units: Subjects			
White	140	140	
Black or African American	0	0	
Asian	0	0	
Other	0	0	
Height Units: centimeter (cm)			
arithmetic mean	169.1		
standard deviation	± 6.4	-	
Weight Units: kilogram (kg)			
arithmetic mean	66.4		
standard deviation	± 10.2	-	
Body mass index (BMI) Units: kilogram per square meter (kg/m^2)			
arithmetic mean	23.2		

standard deviation	± 3.1	-	

End points

End points reporting groups

Reporting group title	IncobotulinumtoxinA 54 to 64 Units
Reporting group description:	
Subjects received a total volume of 1.35 to 1.6 milliliter (mL) of incobotulinumtoxinA (Xeomin) with a maximum of 54 to 64 units per injection treatment via intramuscular injection into the 3 facial areas (HFL, GFL and LPL) on Day 1 of each treatment cycle for up to a maximum of 4 treatment cycles.	
Subject analysis set title	Safety Evaluation Set (SES)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The SES included all subjects who were exposed to study medication at least once.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all subjects in the SES with at least one post-injection efficacy assessment.	

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs)[1]
End point description:	
TEAEs were defined as adverse events (AEs) with onset or worsening or change to serious during or after 1st injection of study medication up to and including the end of study visit. Values reported here refer to the number of overall subjects affected.	
End point type	Primary
End point timeframe:	
From the time point of first injection up to end of study visit (Day 480)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	IncobotulinumtoxinA 54 to 64 Units			
Subject group type	Reporting group			
Number of subjects analysed	140[2]			
Units: subjects	100			

Notes:

[2] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with TEAEs per Treatment Cycle

End point title	Number of Subjects with TEAEs per Treatment Cycle
End point description:	
TEAEs were defined as AEs with onset or worsening or change to serious during or after 1st injection of study medication up to and including the end of study visit. Values reported here refer to the number of subjects affected per treatment cycle. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.	
End point type	Secondary

End point timeframe:

From the time point of first injection up to end of study visit (Day 480)

End point values	IncobotulinumtoxinA 54 to 64 Units			
Subject group type	Reporting group			
Number of subjects analysed	140[3]			
Units: subjects				
1st Injection Cycle (n=140)	55			
2nd Injection Cycle (n=132)	53			
3rd Injection Cycle (n=127)	33			
4th Injection Cycle (n=126)	23			

Notes:

[3] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events of Special Interest (TEAESIs) Overall and per Injection Cycle

End point title	Number of Subjects with Treatment Emergent Adverse Events of Special Interest (TEAESIs) Overall and per Injection Cycle

End point description:

TEAEs were defined as AEs with onset or worsening or change to serious during or after 1st injection of study medication up to and including the end of study visit. AEs occurring after treatment that were thought to possibly indicate toxin spread were defined as adverse events of special interests (AESIs). Values reported here refer to the number of subjects affected per treatment cycle.

End point type	Secondary

End point timeframe:

From the time point of first injection until end of study visit (Day 480)

End point values	IncobotulinumtoxinA 54 to 64 Units			
Subject group type	Reporting group			
Number of subjects analysed	140[4]			
Units: subjects				
1st Injection Cycle (n=140)	5			
2nd Injection Cycle (n=132)	3			
3rd Injection Cycle (n=127)	2			
4th Injection Cycle (n=126)	0			
Overall Period (n=140)	9			

Notes:

[4] - SES

Statistical analyses

No statistical analyses for this end point

Secondary: Responders Rate at Maximum Contraction for GFL, HFL, and LPL as Assessed by the Investigator

End point title	Responders Rate at Maximum Contraction for GFL, HFL, and LPL as Assessed by the Investigator

End point description:

Response at maximum contraction was defined as a score of 0 or 1 on the Merz Aesthetics Scale (MAS) as assessed by the investigator. MAS is a validated 5-point scale for the treated areas. The five points of the scales show the evident severity of aging processes of the aesthetic lines. The severity grades of the scale are 0 for none, 1 for mild, 2 for moderate, 3 for severe, and 4 for very severe lines. Here, 'n' indicated number of subjects for which the variable was assessed at each of the injection cycles.

End point type	Secondary

End point timeframe:

Day 30 of each injection cycle

End point values	IncobotulinumtoxinA 54 to 64 Units			
Subject group type	Reporting group			
Number of subjects analysed	140[5]			
Units: percentage of subjects				
number (not applicable)				
GFL 1st injection cycle (n=140)	80.7			
GFL 2nd injection cycle (n=131)	87.8			
GFL 3rd injection cycle (n=127)	87.4			
GFL 4th injection cycle (n=126)	81.7			
HFL 1st injection cycle (n=140)	72.9			
HFL 2nd injection cycle (n=131)	87.0			
HFL 3rd injection cycle (n=127)	85.8			
HFL 4th injection cycle (n=126)	83.3			
LPL 1st injection cycle (n=140)	71.4			
LPL 2nd injection cycle (n=131)	77.1			
LPL 3rd injection cycle (n=127)	81.9			
LPL 4th injection cycle (n=126)	84.1			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Responders Rate for Overall Upper Face Appearance as Assessed by the Subject

End point title	Responders Rate for Overall Upper Face Appearance as Assessed by the Subject

End point description:

Response was defined as a score of much improved (+2) or very much improved (+3) on the Global impression of change scale (GICS) as assessed by the subject. GICS is a 7-point likert scale that range from -3, very much worse to +3, very much improved. Here, 'n' indicated number of subjects for which

the variable was assessed at each of the injection cycles.

End point type	Secondary

End point timeframe:

Day 30 of each injection cycle

End point values	IncobotulinumtoxinA 54 to 64 Units			
Subject group type	Reporting group			
Number of subjects analysed	140[6]			
Units: percentage of subjects				
number (not applicable)				
1st injection cycle (n=140)	81.4			
2nd injection cycle (n=130)	78.5			
3rd injection cycle (n=127)	83.5			
4th injection cycle (n=126)	84.1			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the time point of first injection up to end of study visit (Day 480)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	IncobotulinumtoxinA 54 to 64 Units

Reporting group description:

Subjects received a total volume of 1.35 to 1.6 mL of incobotulinumtoxinA with a maximum of 54 to 64 units per injection treatment via intramuscular injection into the 3 facial areas (HFL, GFL and LPL) on Day 1 of each treatment cycle for up to a maximum of 4 treatment cycles.

Serious adverse events	IncobotulinumtoxinA 54 to 64 Units		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 140 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Myomectomy			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hypertrophic scar			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	IncobotulinumtoxinA 54 to 64 Units		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 140 (41.43%)		
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 140 (10.71%)		
occurrences (all)	18		
General disorders and administration site conditions			
Injection site haematoma			
subjects affected / exposed	6 / 140 (4.29%)		
occurrences (all)	7		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	41 / 140 (29.29%)		
occurrences (all)	54		
Bronchitis			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported