# 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<br>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<br>Units: years | | | |
| arithmetic mean | 49.6 | | |
| standard deviation | ± 9.8 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 127 | 127 | |
| Male | 13 | 13 | |
| Race<br>Units: Subjects | | | |
| White | 140 | 140 | |
| Black or African American | 0 | 0 | |
| Asian | 0 | 0 | |
| Other | 0 | 0 | |
| Height<br>Units: centimeter (cm) | | | |
| arithmetic mean | 169.1 | | |
| standard deviation | ± 6.4 | - | |
| Weight<br>Units: kilogram (kg) | | | |
| arithmetic mean | 66.4 | | |
| standard deviation | ± 10.2 | - | |
| Body mass index (BMI)<br>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