Clinical trial results:
A prospective, randomised, double-blind, placebo-controlled, multicenter study with an open-label extension period to investigate the efficacy and safety of NT 201 in the simultaneous treatment of upper facial lines (horizontal forehead lines, glabellar frown lines, and lateral canthal lines)

Summary

EudraCT number	2019-004113-13
Trial protocol	DE
Global end of trial date	08 July 2022

Results information

Result version number	v1 (current)
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	M602011070

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04622254
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, Aesthetic.Trials@merz.com
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, Aesthetic.Trials@merz.com

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	08 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to investigate the safety and efficacy of NT 201 (active ingredient: Botulinum (neuro)toxin type A, free from complexing proteins) in the combined treatment of wrinkles in the upper face (upper facial lines [UFL]): Horizontal Forehead Lines [HFL], Glabellar Frown Lines [GFL], and Lateral Canthal Lines [LCL]). It is a prospective, randomised, double-blind, placebo-controlled, multicenter study with a placebo-control main period (MP) followed by an open-label extension (OLEX) period.

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	12 November 2020
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: 368
Worldwide total number of subjects	368
EEA total number of subjects	368

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)	356
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 12 investigational sites in Germany.

Pre-assignment

Screening details:

Of the 395 screened subjects, 27 subjects exited as screen failures and 368 subjects were randomised and enrolled to receive a treatment with NT 201 or placebo in the main period of the study. Out of 358 subjects who completed the main period, 346 subjects received treatment in the OLEX period of the study.

Period 1

Period 1 title	Main Period (Up to 22 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Main Period: Placebo (Group P)

Arm description:

Subjects received placebo injection in all three upper facial lines (UFL): (glabellar frown lines [GFL], horizontal forehead lines [HFL] and lateral canthal lines [LCL]) on Day 1 of main period.

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

Dosage and administration details:

Subjects received placebo, solution for injection, intramuscularly in HFL, GFL and LCL areas on Day 1 of main period.

Arm title	Main Period: NT 201 (Group U)

Arm description:

Subjects received a total of 64 Units (U) of NT 201: 20 U of NT 201 injection both in the GFL area and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, Clostridium Botulinum neurotoxin type A, Xeomin, Bocouture, Xeomin Cosmetic and Xeomeen
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received NT 201, 64 U, powder for solution for injection, intramuscularly in HFL, GFL, and LCL areas on Day 1 of main period.

Arm title	Main Period: NT 201 and Placebo (Group L)

Arm description:

Subjects received a total of 24 U NT 201: placebo injection both in the GFL and HFL area, and 24 U NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.

Arm type	Experimental

Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, Clostridium Botulinum neurotoxin type A, Xeomin, Bocouture, Xeomin Cosmetic and Xeomeen
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received NT 201, 24 U, powder for solution for injection, intramuscularly in LCL area on Day 1 of main period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received placebo, solution for injection, intramuscularly in HFL, GFL areas on Day 1 of main period.

Number of subjects in period 1	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)
Started	94	184	90
Completed	91	180	87
Not completed	3	4	3
Consent withdrawn by subject	-	1	2
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	2	1
Protocol deviation	1	-	-
Withdrawal by subject	2	-	-

Period 2

Period 2 title	OLEX Period (Up to 39 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	OLEX: NT 201 (Main Period: Group P)

Arm description:

Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.

Arm type	Experimental

Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, Clostridium Botulinum neurotoxin type A, Xeomin, Bocouture, Xeomin Cosmetic and Xeomeen
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received NT 201, 64 U, powder for solution for injection, intramuscularly in HFL, GFL, LCL areas on Day 1 (Visit 8) and Visit 13 of OLEX period.

Arm title	OLEX: NT 201 (Main Period: Group U)

Arm description:

Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, Clostridium Botulinum neurotoxin type A, Xeomin, Bocouture, Xeomin Cosmetic and Xeomeen
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received NT 201, 64 U, powder for solution for injection, intramuscularly in HFL, GFL, LCL areas on Day 1 (Visit 8) and Visit 13 of OLEX period.

Arm title	OLEX: NT 201 (Main Period: Group L)

Arm description:

Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, Clostridium Botulinum neurotoxin type A, Xeomin, Bocouture, Xeomin Cosmetic and Xeomeen
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received NT 201, 64 U, powder for solution for injection, intramuscularly in HFL, GFL, LCL areas on Day 1 (Visit 8) and Visit 13 of OLEX period.

Number of subjects in period 2[1]	OLEX: NT 201 (Main Period: Group P)	OLEX: NT 201 (Main Period: Group U)	OLEX: NT 201 (Main Period: Group L)
Started	89	170	87
Completed	81	156	76
Not completed	8	14	11
Adverse event, non-fatal	1	-	-
Other	-	-	2
Pregnancy	1	-	-
Lost to follow-up	3	-	2

Other eligibility criteria for reinjection not met	1	-	-
No need for re-injection	1	9	3
Withdrawal by subject	1	5	4

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: Several subjects who completed MP did not receive treatment in the OLEX period due to non-eligibility or other reasons.

Baseline characteristics

Reporting groups	
Reporting group title	Main Period: Placebo (Group P)
Reporting group description:	
Subjects received placebo injection in all three upper facial lines (UFL): (glabellar frown lines [GFL], horizontal forehead lines [HFL] and lateral canthal lines [LCL]) on Day 1 of main period.	
Reporting group title	Main Period: NT 201 (Group U)
Reporting group description:	
Subjects received a total of 64 Units (U) of NT 201: 20 U of NT 201 injection both in the GFL area and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.	
Reporting group title	Main Period: NT 201 and Placebo (Group L)
Reporting group description:	
Subjects received a total of 24 U NT 201: placebo injection both in the GFL and HFL area, and 24 U NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.	

Reporting group values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)
Number of subjects	94	184	90
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)	94	177	85
From 65-84 years	0	7	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.8	46.0	45.9
standard deviation	± 9.15	± 9.92	± 9.88
Gender categorical Units: Subjects			
Female	84	147	72
Male	10	37	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	2
Not Hispanic or Latino	93	182	88
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	0	0	1
White	94	182	89
Black or African American	0	1	0

Reporting group values	Total		
Number of subjects	368		
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)	356		
From 65-84 years	12		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	303		
Male	65		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	363		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	1		
White	365		
Black or African American	1		

End points

End points reporting groups

Reporting group title	Main Period: Placebo (Group P)
Reporting group description:	
Subjects received placebo injection in all three upper facial lines (UFL): (glabellar frown lines [GFL], horizontal forehead lines [HFL] and lateral canthal lines [LCL]) on Day 1 of main period.	
Reporting group title	Main Period: NT 201 (Group U)
Reporting group description:	
Subjects received a total of 64 Units (U) of NT 201: 20 U of NT 201 injection both in the GFL area and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.	
Reporting group title	Main Period: NT 201 and Placebo (Group L)
Reporting group description:	
Subjects received a total of 24 U NT 201: placebo injection both in the GFL and HFL area, and 24 U NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.	
Reporting group title	OLEX: NT 201 (Main Period: Group P)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.	
Reporting group title	OLEX: NT 201 (Main Period: Group U)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.	
Reporting group title	OLEX: NT 201 (Main Period: Group L)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.	

Primary: Main Period: Percentage of Glabellar Frown Line (GFL) Responders at Day 30

End point title	Main Period: Percentage of Glabellar Frown Line (GFL) Responders at Day 30[1]
End point description:	
MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. GFL response was score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for GFL at maximum contraction as assessed by investigator and subject. MAS for GFL ranged as 0 to 4, where 0 is "No glabellar lines", 1 is "Mild glabellar lines", 2 is "Moderate glabellar lines", 3 is "Severe glabellar lines" and 4 is "Very severe glabellar lines". Target population of main primary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.	
End point type	Primary
End point timeframe:	
Day 30	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main primary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	0	49.5		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Primary: Main Period: Percentage of Horizontal Forehead Lines (HFL) Responders at Day 30

End point title	Main Period: Percentage of Horizontal Forehead Lines (HFL) Responders at Day 30[2]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. HFL-response was defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for HFL at maximum contraction as assessed by both the investigator and the subject. MAS for HFL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". Target population of main primary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Primary

End point timeframe:

Day 30

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main primary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	0	57.7		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Primary: Main Period: Percentage of Lateral Canthal Lines (LCL) Responders at Day 30

End point title	Main Period: Percentage of Lateral Canthal Lines (LCL) Responders at Day 30[3]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. LCL-response was defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for both left and right LCL at maximum contraction as assessed by both the investigator and the subject. MAS for LCL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". Target population of main primary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Primary

End point timeframe:

Day 30

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main primary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	0	32.4		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for GFL at Maximum Contraction as Assessed by the Investigator at Day 30

End point title	Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for GFL at Maximum Contraction as Assessed by the Investigator at Day 30[4]

End point description:

MAS : 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for GFL ranged as 0 to 4, where 0 is "No glabellar lines", 1 is "Mild glabellar lines", 2 is "Moderate glabellar lines", 3 is "Severe glabellar lines" and 4 is "Very severe glabellar lines". Target population of main key secondary estimand included subjects with HFL, GFL, and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	0	86.8		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for HFL at Maximum Contraction as Assessed by the Investigator at Day 30

End point title	Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for HFL at Maximum Contraction as Assessed by the Investigator at Day 30[5]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for HFL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". Target population of main key secondary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	1.1	86.3		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild)

on MAS for Both Left and Right LCL at Maximum Contraction as Assessed by the Investigator at Day 30

End point title	Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for Both Left and Right LCL at Maximum Contraction as Assessed by the Investigator at Day 30[6]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for LCL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". Target population of main key secondary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	2.1	75.8		

Statistical analyses

Statistical analysis title	Main Period: NT 201 (Group P), Main Period: NT 201
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for GFL at Maximum Contraction as Assessed by the Subject at Day 30

End point title	Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for GFL at Maximum Contraction as Assessed by the Subject at Day 30[7]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for GFL ranged as 0 to 4, where 0 is "No glabellar lines", 1 is "Mild glabellar lines", 2 is "Moderate glabellar lines", 3 is "Severe glabellar lines" and 4 is "Very severe glabellar lines". Target population of main key secondary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum

contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	1.1	73.6		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for HFL at Maximum Contraction as Assessed by the Subject at Day 30

End point title	Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for HFL at Maximum Contraction as Assessed by the Subject at Day 30[8]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for HFL ranged as 0 to 4 where 0 is “No lines”, 1 is “Mild lines”, 2 is “Moderate lines”, 3 is “Severe lines” and 4 is “Very severe lines”. Target population of main key secondary estimand subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	2.1	79.1		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for Both Left and Right LCL at Maximum Contraction as Assessed by the Subject at Day 30

End point title	Main Period: Percentage of Subjects With a Score of 0 (no) or 1 (Mild) on MAS for Both Left and Right LCL at Maximum Contraction as Assessed by the Subject at Day 30[9]

End point description:

MAS: 5-point scale used to identify responders in clinical context and validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for LCL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". Target population of main key secondary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: percentage of subjects				
number (not applicable)	3.2	65.4		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Global Aesthetic Improvement Scale (GAIS) at Day 30 as Assessed by the Subjects

End point title	Main Period: Global Aesthetic Improvement Scale (GAIS) at Day 30 as Assessed by the Subjects[10]

End point description:

The GAIS is a 7-point Likert scale capturing the global aesthetic improvement ranging from +3 (very much improved); +2 (much improved); +1 (improved); 0 (no change); -1 (worse); -2 (much worse); -3 (very much worse), as assessed by the subject. GAIS as assessed by the subject at Day 30 was analysed using an ANCOVA model. Target population of main key secondary estimand included subjects with HFL, GFL and LCL of moderate to severe intensity at maximum contraction as assessed by investigator and subject according to MAS, as randomised in this study: Subset of subjects randomised to UFL (Group U) or to placebo (Group P) groups, grouped by randomised treatment assignment.

End point type	Secondary

End point timeframe:

Day 30

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis population for the endpoint is the target population of main key secondary estimand, which only includes subjects randomized to Group U and Group P.

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	182		
Units: score on a scale				
least squares mean (confidence interval 95%)	0.02 (-0.11 to 0.15)	2.00 (1.90 to 2.09)		

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Main Period: Percentage of Subjects With at Least One-grade Improvement From Baseline to Day 30 of MP on MAS for GFL at Maximum Contraction as Assessed by the Investigator

End point title	Main Period: Percentage of Subjects With at Least One-grade Improvement From Baseline to Day 30 of MP on MAS for GFL at Maximum Contraction as Assessed by the Investigator

End point description:

MAS are 5-point scales used to identify responders in a clinical context. They are validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for GFL ranged as 0 to 4 where 0 is "No glabellar lines", 1 is "Mild glabellar lines", 2 is "Moderate glabellar lines", 3 is "Severe glabellar lines" and 4 is "Very severe glabellar lines". The full analysis set (FAS) consisted of all randomised subjects. Here "number of subjects analysed" were subjects who had non-missing data for this endpoint.

End point type	Secondary

End point timeframe:

Day 30

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	181	88	
Units: percentage of subjects				
number (not applicable)	5.5	96.7	4.5	

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: NT 201 (Group U) v Main Period: Placebo (Group P)
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With at Least One-grade Improvement From Baseline to Day 30 of MP on MAS for HFL at Maximum Contraction as Assessed by the Investigator

End point title	Main Period: Percentage of Subjects With at Least One-grade Improvement From Baseline to Day 30 of MP on MAS for HFL at Maximum Contraction as Assessed by the Investigator

End point description:

MAS are 5-point scales used to identify responders in a clinical context. They are validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for HFL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". FAS. Here "number of subjects analysed" were subjects who had non-missing data for this endpoint.

End point type	Secondary

End point timeframe:

Day 30

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	181	88	
Units: percentage of subjects				
number (not applicable)	3.3	96.1	3.4	

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Percentage of Subjects With at Least One-grade Improvement From Baseline to Day 30 of MP on MAS for Both Left and Right LCL at Maximum Contraction as Assessed by the Investigator

End point title	Main Period: Percentage of Subjects With at Least One-grade Improvement From Baseline to Day 30 of MP on MAS for Both Left and Right LCL at Maximum Contraction as Assessed by the Investigator

End point description:

MAS are 5-point scales used to identify responders in a clinical context. They are validated photograph-based outcome instruments designed specifically for assessment of each upper facial area. MAS for LCL ranged as 0 to 4 where 0 is "No lines", 1 is "Mild lines", 2 is "Moderate lines", 3 is "Severe lines" and 4 is "Very severe lines". FAS. Here "overall number of subjects analysed" were subjects who had non-missing data for this endpoint.

End point type	Secondary

End point timeframe:

Day 30

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	181	88	
Units: percentage of subjects				
number (not applicable)	8.8	91.7	68.2	

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 (Group U)
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Statistical analysis title	Main Period: NT 201 Group P Versus Group L
Comparison groups	Main Period: NT 201 and Placebo (Group L) v Main Period: Placebo (Group P)
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel

Secondary: Main Period: Global Aesthetic Improvement Scale (GAIS) at Day 30 as Assessed by the Investigator

End point title	Main Period: Global Aesthetic Improvement Scale (GAIS) at Day 30 as Assessed by the Investigator

End point description:

The GAIS is a 7-point Likert scale capturing the global aesthetic improvement ranging from +3 (very much improved); +2 (much improved); +1 (improved); 0 (no change); -1 (worse); -2 (much worse); -3 (very much worse), as assessed by the investigator. GAIS as assessed by the investigator at Day 30 was analysed using an ANCOVA model. FAS. Here "number of subjects analysed" were subjects who had non-missing data for this endpoint.

End point type	Secondary

End point timeframe:

Day 30

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	181	88	
Units: score on a scale				
least squares mean (confidence interval 95%)	0.03 (-0.09 to 0.14)	2.23 (2.14 to 2.31)	0.68 (0.56 to 0.80)	

Statistical analyses

Statistical analysis title	Main Period: NT 201 Group P Versus Group U
Comparison groups	Main Period: NT 201 (Group U) v Main Period: Placebo (Group P)
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Main Period: NT 201 Group P Versus Group L
Comparison groups	Main Period: Placebo (Group P) v Main Period: NT 201 and Placebo (Group L)
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Main Period: Number of Subjects With Related Treatment-Emergent Adverse Events (TEAEs)

End point title	Main Period: Number of Subjects With Related Treatment-Emergent Adverse Events (TEAEs)

End point description:

TEAEs during the Main Period are defined as adverse events (AEs) with onset or worsening on or after date and time of first dose of study treatment and before date and time of first administration of study treatment in the OLEX period or the final study visit, if subject was not treated in the OLEX period. An AE is considered to be related if a causal relationship between study treatment and the AE is at least reasonably possible. The Safety Evaluation Set (SES) included all subjects treated.

End point type	Secondary

End point timeframe:

Up to 22 weeks

End point values	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	184	90	
Units: subjects	12	35	10	

Statistical analyses

No statistical analyses for this end point

Secondary: OLEX: Number of Subjects With Related TEAEs

End point title	OLEX: Number of Subjects With Related TEAEs

End point description:

TEAEs of the OLEX period are defined as AEs with onset or worsening on or after date and time of first dose of study treatment in the OLEX period up to and including the final study visit. An AE is considered to be related if a causal relationship between study treatment and the AE is at least reasonably possible. SES.

End point type	Secondary

End point timeframe:

Up to 39 weeks

End point values	OLEX: NT 201 (Main Period: Group P)	OLEX: NT 201 (Main Period: Group U)	OLEX: NT 201 (Main Period: Group L)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	170	87	
Units: subjects	18	32	12	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Main Period: Up to 22 weeks; OLEX Period: Up to 39 weeks	
Adverse event reporting additional description:	
SES. The investigator reported AEs systematically at each visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Main Period: Placebo (Group P)
Reporting group description:	
Subjects received placebo injection in all three UFL: GFL, HFL and LCL on Day 1 of main period.	
Reporting group title	Main Period: NT 201 (Group U)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL area and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.	
Reporting group title	Main Period: NT 201 and Placebo (Group L)
Reporting group description:	
Subjects received a total of 24 U NT 201: placebo injection both in the GFL and HFL area, and 24 U NT 201 injection in the LCL area (12 U per side) on Day 1 of main period.	
Reporting group title	OLEX: NT 201 (Main Period: Group P)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.	
Reporting group title	OLEX: NT 201 (Main Period: Group U)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.	
Reporting group title	OLEX: NT 201 (Main Period: Group L)
Reporting group description:	
Subjects received a total of 64 U of NT 201: 20 U of NT 201 injection both in the GFL and in the HFL area, and 24 U of NT 201 injection in the LCL area (12 U per side) on Day 1 (Visit 8) and Visit 13 of OLEX period.	

Serious adverse events	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 94 (4.26%)	1 / 184 (0.54%)	2 / 90 (2.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			

subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leiomyoma			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 94 (0.00%)	1 / 184 (0.54%)	0 / 90 (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
Intracranial hypotension			
subjects affected / exposed	0 / 94 (0.00%)	1 / 184 (0.54%)	0 / 90 (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
Sciatica			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 94 (0.00%)	1 / 184 (0.54%)	0 / 90 (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
Inguinal hernia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 184 (0.00%)	0 / 90 (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
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	1 / 90 (1.11%)
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 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid mass			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 94 (1.06%)	0 / 184 (0.00%)	0 / 90 (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
Osteoarthritis			

subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 94 (0.00%)	0 / 184 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-acute COVID-19 syndrome			
subjects affected / exposed	1 / 94 (1.06%)	0 / 184 (0.00%)	0 / 90 (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
Meningitis viral			
subjects affected / exposed	0 / 94 (0.00%)	1 / 184 (0.54%)	0 / 90 (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: NT 201 (Main Period: Group P)	OLEX: NT 201 (Main Period: Group U)	OLEX: NT 201 (Main Period: Group L)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 89 (2.25%)	6 / 170 (3.53%)	3 / 87 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leiomyoma			
subjects affected / exposed	0 / 89 (0.00%)	1 / 170 (0.59%)	0 / 87 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hypotension			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 89 (1.12%)	0 / 170 (0.00%)	0 / 87 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	1 / 87 (1.15%)
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			
Abdominal pain			
subjects affected / exposed	0 / 89 (0.00%)	1 / 170 (0.59%)	0 / 87 (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
Inguinal hernia			

subjects affected / exposed	1 / 89 (1.12%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 89 (1.12%)	1 / 170 (0.59%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid mass			
subjects affected / exposed	0 / 89 (0.00%)	1 / 170 (0.59%)	0 / 87 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			

subjects affected / exposed	0 / 89 (0.00%)	1 / 170 (0.59%)	0 / 87 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 170 (0.59%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 170 (0.59%)	0 / 87 (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
Post-acute COVID-19 syndrome			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	0 / 89 (0.00%)	0 / 170 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Main Period: Placebo (Group P)	Main Period: NT 201 (Group U)	Main Period: NT 201 and Placebo (Group L)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 94 (24.47%)	43 / 184 (23.37%)	23 / 90 (25.56%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 94 (8.51%)	18 / 184 (9.78%)	7 / 90 (7.78%)
occurrences (all)	8	23	7
General disorders and administration site conditions			
Injection site haematoma			
subjects affected / exposed	8 / 94 (8.51%)	15 / 184 (8.15%)	9 / 90 (10.00%)
occurrences (all)	8	17	10

Immune system disorders			
Immunisation reaction			
subjects affected / exposed	2 / 94 (2.13%)	10 / 184 (5.43%)	9 / 90 (10.00%)
occurrences (all)	2	20	12
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 94 (4.26%)	2 / 184 (1.09%)	0 / 90 (0.00%)
occurrences (all)	4	2	0
Nasopharyngitis			
subjects affected / exposed	4 / 94 (4.26%)	3 / 184 (1.63%)	3 / 90 (3.33%)
occurrences (all)	4	3	3

Non-serious adverse events	OLEX: NT 201 (Main Period: Group P)	OLEX: NT 201 (Main Period: Group U)	OLEX: NT 201 (Main Period: Group L)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 89 (43.82%)	74 / 170 (43.53%)	29 / 87 (33.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 89 (10.11%)	9 / 170 (5.29%)	2 / 87 (2.30%)
occurrences (all)	11	11	3
General disorders and administration site conditions			
Injection site haematoma			
subjects affected / exposed	11 / 89 (12.36%)	22 / 170 (12.94%)	9 / 87 (10.34%)
occurrences (all)	12	29	11
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	4 / 89 (4.49%)	8 / 170 (4.71%)	8 / 87 (9.20%)
occurrences (all)	5	14	12
Infections and infestations			
COVID-19			
subjects affected / exposed	13 / 89 (14.61%)	33 / 170 (19.41%)	12 / 87 (13.79%)
occurrences (all)	13	34	12
Nasopharyngitis			
subjects affected / exposed	9 / 89 (10.11%)	22 / 170 (12.94%)	11 / 87 (12.64%)
occurrences (all)	10	22	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2020	The first Amendment occurred before first subject first visit. The amendment was due to new government regulations and restrictions caused by the COVID-19 pandemic and due to the advice/deficiency letters issued respectively by the Food and drug administration (FDA) and The federal institute for drug and medical devices (BfArM). The purpose of this amendment was to assure subjects' safety and mitigate the impact on assessments of AEs and on assessments of efficacy parameters which were based on subjects' self-assessment in case subjects could not attend on-site visits during the pandemic.
02 September 2020	The second amendment also occurred before first subject first visit. In addition to minor formatting changes, this amendment was issued to implement measures that might had to be taken in case of a second outbreak of a pandemic leading to a public health emergency, and, as requested by the Ethics Committee (EC) Hamburg, to specify who would inform the subject in case of pathological laboratory values and to inform the subject that the improvement of wrinkles following treatment with NT 201 would only be temporary.
24 June 2021	The third protocol amendment occurred after first subject first visit. This amendment was made due to the advice/information request letter issued to study protocol M602011071 by the FDA on 06-JAN-2021 and the meeting request/written responses issued by the FDA on 30-APR-2021. In addition to minor formatting/spelling changes and administrative changes were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported