Clinical trial results:
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of MT10109L (NivobotulinumtoxinA) for the Treatment of Glabellar Lines With or Without Concurrent Treatment of Lateral Canthal Lines

Summary

EudraCT number	2014-005301-21
Trial protocol	GB DE
Global end of trial date	22 January 2021

Results information

Result version number	v1 (current)
This version publication date	15 February 2024
First version publication date	15 February 2024

Trial information

Trial identification

Sponsor protocol code	MT10109L-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03721016
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 121473

Notes:

Sponsors

Sponsor organisation name	Medytox Inc
Sponsor organisation address	78, Gangni 1-gil, Ochang-eup, Cheongwon-gu,, Cheongju-si, Korea, Republic of, 28126
Public contact	Young Ryu, Medytox Inc, +82 2-69015424,
Scientific contact	Gyungjin Heo, Medytox Inc, +82 2-6901-5839, gjheo@medytox.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	29 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2020
Global end of trial reached?	Yes
Global end of trial date	22 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy between 20 U MT10109L and placebo for the treatment of GL (with or without concurrent 24 U treatment of LCL) in participants with moderate to severe GL and LCL.

The total global enrollment (as presented in the "Population of Trial Subjects" below was 415, which included the Intent-To-Treat population. However, all primary and secondary efficacy analyses for EU regulatory endpoints reported here are using the mITT population that included a total of 356 participants (USA -240; Germany - 47, United-Kingdom - 20 and Canada - 49).

Protection of trial subjects:

The study protocol, all study protocol amendments, written study participant information, informed consent form (ICF), Investigator's Brochure (IB) and any other relevant documents were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) at each study center.
The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and other Guidelines, and applicable laws and regulations.
An ICF approved by each study center's IEC/IRB was signed by the participant or their legally authorized representative and the authorized person obtaining the ICF before the participant was entered in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2018
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	United Kingdom: 23
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	United States: 271
Country: Number of subjects enrolled	Canada: 57
Worldwide total number of subjects	415
EEA total number of subjects	64

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)	394
From 65 to 84 years	20
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were screened and recruited at sites in US, UK, Germany and Canada.
The data described here is for the ITT population. The ITT population consisted of all randomized participants.

Pre-assignment

Screening details:

505 patients were screened and 415 met the incusion/exclusion criteria and were randomized.

Period 1

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

Blinding implementation details:

Randomization and double blinding were used to minimize bias arising from the assignment of participants to treatment groups and the expectations of participants, investigators and individuals collecting data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo was injected into the Glabellar Lines (GL) and latheral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving the placebo in GL & LCL areas as defined in the protocol.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate, Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - Placebo 0U per 0.1mL/injection
Administration details - 11 injection sites (Placebo in 5 GL sites + Placebo in 6 LCL sites)

Arm title	MT10109L 20U in GL + Placebo in LCL

Arm description:

MT10109L 20U was injected into the Glabellar Lines (GL) and Placebo into the Lateral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving the MT10109L in GL & Placebo in LCL areas as defined in the protocol.

Arm type	Experimental
Investigational medicinal product name	MT10109L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - MT10109L 4 U/0.1 mL/injection;
Administration - MT10109L in 5 GL sites; 0.1 mL/injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - Placebo 0 U/0.1 mL/injection
Administration - Placebo in 6 LCL sites; 0.1 mL/injection.

Arm title	MT10109L 20U GL + MT10109L 24 U LCL

Arm description:

MT10109L 20U was injected into the Glabellar Lines (GL) and MT10109L 24U injected into Lateral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving MT10109L in GL & LCL areas as defined in the protocol.

Arm type	Experimental
Investigational medicinal product name	MT10109L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - MT10109L 4 U/0.1 mL/injection;
Administration details - 11 injection sites (MT10109L in 5 GL sites + MT10109L in 6 LCL sites)

Number of subjects in period 1	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL
Started	82	173	160
Completed	69	148	141
Not completed	13	25	19
Consent withdrawn by subject	7	10	8
Physician decision	-	1	1
site terminated by Sponsor	3	7	6
Adverse event, non-fatal	-	1	1
other	1	-	-
Lost to follow-up	2	6	3

Period 2

Period 2 title	Retreatment 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator

Blinding implementation details:

Randomization and double-blinding were used to minimize bias arising from the assignment of participants to treatment group and the expectations of participants, investigators and individuals collecting data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Retreatment 1 for Placebo arm

Arm description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - Placebo 0U per 0.1mL/injection
Administration details - 11 injection sites (Placebo in 5 GL sites + Placebo in 6 LCL sites)

Arm title	MT10109L 20U in GL + Placebo in LCL retreatment 1

Arm description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Arm type	Experimental
Investigational medicinal product name	MT10109L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - MT10109L 4 U/0.1 mL/injection;
Administration - MT10109L in 5 GL sites; 0.1 mL/injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - Placebo 0 U/0.1 mL/injection
Administration - Placebo in 6 LCL sites; 0.1 mL/injection.

Arm title	MT10109L 20U GL + MT10109L 24 U LCL retreatment 1

Arm description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Arm type	Experimental

Investigational medicinal product name	MT10109L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - MT10109L 4 U/0.1 mL/injection;
Administration details - 11 injection sites (MT10109L in 5 GL sites + MT10109L in 6 LCL sites)

Number of subjects in period 2[1]	Retreatment 1 for Placebo arm	MT10109L 20U in GL + Placebo in LCL retreatment 1	MT10109L 20U GL + MT10109L 24 U LCL retreatment 1
Started	64	145	137
Completed	62	139	130
Not completed	2	6	7
Consent withdrawn by subject	-	6	5
Lost to follow-up	2	-	2

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: Only participants from period 1 (first treatment), who met the protocol-defined retreatment criteria, were eligible to enter period 2 (Retreatment 1)

Period 3

Period 3 title	Retreatment 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomization and double blinding weere used to minimize bias arising from the assignment of participants to treatment groups and the expectations of participants, investigators and individuals collecting data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo retreatment 2

Arm description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - Placebo 0U per 0.1mL/injection

Arm title	MT10109L 20U in GL + Placebo in LCL retreatment 2

Arm description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Arm type	Experimental
Investigational medicinal product name	MT10109L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - MT10109L 4 U/0.1 mL/injection;
Administration - MT10109L in 5 GL sites; 0.1 mL/injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - Placebo 0 U/0.1 mL/injection
Administration - Placebo in 6 LCL sites; 0.1 mL/injection.

Arm title	MT10109L 20U GL + MT10109L 24 U LCL retreatment2

Arm description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Arm type	Experimental
Investigational medicinal product name	MT10109L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Sterile concentrate
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage - MT10109L 4 U/0.1 mL/injection;
Administration details - 11 injection sites (MT10109L in 5 GL sites + MT10109L in 6 LCL sites)

Number of subjects in period 3[2]	Placebo retreatment 2	MT10109L 20U in GL + Placebo in LCL retreatment 2	MT10109L 20U GL + MT10109L 24 U LCL retreatment2
Started	47	95	91
Completed	46	94	90
Not completed	1	1	1
Consent withdrawn by subject	1	-	-
Physician decision	-	-	1
Protocol deviation	-	1	-

Notes:

[2] - 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: Only participants from period 2 (Retreatment1), who met the protocol-defined retreatment criteria, were eligible to enter period 3 (Retreatment 2)

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Placebo was injected into the Glabellar Lines (GL) and latheral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving the placebo in GL & LCL areas as defined in the protocol.

Reporting group title	MT10109L 20U in GL + Placebo in LCL

Reporting group description:

MT10109L 20U was injected into the Glabellar Lines (GL) and Placebo into the Lateral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving the MT10109L in GL & Placebo in LCL areas as defined in the protocol.

Reporting group title	MT10109L 20U GL + MT10109L 24 U LCL

Reporting group description:

MT10109L 20U was injected into the Glabellar Lines (GL) and MT10109L 24U injected into Lateral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving MT10109L in GL & LCL areas as defined in the protocol.

Reporting group values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL
Number of subjects	82	173	160
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)	78	160	156
From 65-84 years	4	12	4
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	47.6	47.5	46.2
standard deviation	± 10.91	± 11.49	± 11.15
Gender categorical Units: Subjects			
Female	72	148	143
Male	10	25	17

Reporting group values	Total		
Number of subjects	415		
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)	394		
From 65-84 years	20		
85 years and over	1		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	363		
Male	52		

Subject analysis sets

Subject analysis set title	Demographic and other Baseline Characteristics - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

82 participants in the placebo group
173 participants in the MT10109L 20 U group
160 participants in the MT10109L 44 U group

Subject analysis set title	Demographic and other Baseline Characteristics -mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

67 participants in the placebo group
155 participants in the MT10109L 20U group
134 participants in the MTL10109L 44U group

Reporting group values	Demographic and other Baseline Characteristics - ITT	Demographic and other Baseline Characteristics - mITT	
Number of subjects	415	356	
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)	394	338	
From 65-84 years	20	17	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	47.0	47.7	
standard deviation	± 11.23	± 10.83	

Gender categorical Units: Subjects			
Female	363	324	
Male	52	32	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo was injected into the Glabellar Lines (GL) and latheral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving the placebo in GL & LCL areas as defined in the protocol.

Reporting group title	MT10109L 20U in GL + Placebo in LCL

Reporting group description:

MT10109L 20U was injected into the Glabellar Lines (GL) and Placebo into the Lateral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving the MT10109L in GL & Placebo in LCL areas as defined in the protocol.

Reporting group title	MT10109L 20U GL + MT10109L 24 U LCL

Reporting group description:

MT10109L 20U was injected into the Glabellar Lines (GL) and MT10109L 24U injected into Lateral Canthal Lines (LCL): initial double-blind treatment on Day 1. This arm describes the data for participants receiving MT10109L in GL & LCL areas as defined in the protocol.

Reporting group title	Retreatment 1 for Placebo arm

Reporting group description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Reporting group title	MT10109L 20U in GL + Placebo in LCL retreatment 1

Reporting group description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Reporting group title	MT10109L 20U GL + MT10109L 24 U LCL retreatment 1

Reporting group description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Reporting group title	Placebo retreatment 2

Reporting group description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Reporting group title	MT10109L 20U in GL + Placebo in LCL retreatment 2

Reporting group description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Reporting group title	MT10109L 20U GL + MT10109L 24 U LCL retreatment2

Reporting group description:

During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria received up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 20 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

Subject analysis set title	Demographic and other Baseline Characteristics - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

82 participants in the placebo group
173 participants in the MT10109L 20 U group
160 participants in the MT10109L 44 U group

Subject analysis set title	Demographic and other Baseline Characteristics -mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

67 participants in the placebo group
155 participants in the MT10109L 20U group
134 participants in the MTL10109L 44U group

Primary: 1.1 Co-primary Efficacy Endpoint: The Percentage of Participants Achieving None or Mild on the FWS According to Investigator Assessment of GL Severity at Maximum Frown at Day 30 of Treatment Cycle 1

End point title	1.1 Co-primary Efficacy Endpoint: The Percentage of Participants Achieving None or Mild on the FWS According to Investigator Assessment of GL Severity at Maximum Frown at Day 30 of Treatment Cycle 1

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50. The data here presents the percentage of participants who had GL severity at maximum frown of none or mild based on investigator FWS rating at Cycle 1 Day 30.
FWS is 4-point grading scale, where 0=none, 1=mild, 2=moderate, and 3=severe.

End point type	Primary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	155	134	
Units: Participants				
number (not applicable)	3	115	99	

Statistical analyses

Statistical analysis title	Placebo VS MT10109L in GL + Placebo in LCL
Comparison groups	MT10109L 20U in GL + Placebo in LCL v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	MT10109L in GL plus MT10109L in LCL VS Placebo

Comparison groups	MT10109L 20U GL + MT10109L 24 U LCL v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Primary: 1.2 Co-primary Efficacy Endpoint:The Percentage of Participants Achieving None or Mild on the FWS according to Participant assessment in GL Severity at Maximum Frown at Day 30 of Treatment Cycle 1

End point title	1.2 Co-primary Efficacy Endpoint:The Percentage of Participants Achieving None or Mild on the FWS according to Participant assessment in GL Severity at Maximum Frown at Day 30 of Treatment Cycle 1

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50. The data here presents the percentage of participants who had GL severity at maximum frown of none or mild based on participant FWS rating at Cycle 1 Day 30.
FWS is 4-point grading scale, where 0=none, 1=mild, 2=moderate, and 3=severe.

End point type	Primary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	155	134	
Units: Participants				
number (not applicable)	2	107	82	

Statistical analyses

Statistical analysis title	Placebo VS MT10109L in GL + Placebo in LCL
Comparison groups	Placebo v MT10109L 20U in GL + Placebo in LCL
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	MT10109L in GL plus MT10109L in LCL VS Placebo

Comparison groups	Placebo v MT10109L 20U GL + MT10109L 24 U LCL
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: 2.1 The Duration of GL Treatment Effect Estimated as the Median Time to Return to Moderate or Severe GL at Maximum Frown in Participants Who Achieved a Rating of None or Mild GL Severity at Maximum Frown at Day 30 According to Inv Assessment

End point title	2.1 The Duration of GL Treatment Effect Estimated as the Median Time to Return to Moderate or Severe GL at Maximum Frown in Participants Who Achieved a Rating of None or Mild GL Severity at Maximum Frown at Day 30 According to Inv Assessment

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The investigator evaluates the participant's GL severity using a 4-grade FWS scale (0 to 3) where 0=none and 3 = severe. The outcome is measured as median time to loss of treatment effect (i.e., return to moderate or severe GL severity at maximum frown using the FWS).

End point type	Secondary

End point timeframe:

Day 1 (first treatment) to Day 180

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	109	96	
Units: day				
median (inter-quartile range (Q1-Q3))	157.0 (114 to 216)	116.0 (85 to 149)	97.0 (67 to 147)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.2 Sec Eff Endpoint: The Percentage of Participants Reporting Mostly Satisfied/Very Satisfied on a 5-point Scale of Very Dissatisfied to Very Satisfied at Day 60 on the FLSQ Follow-up Version Item 5 for GL

End point title	2.2 Sec Eff Endpoint: The Percentage of Participants Reporting Mostly Satisfied/Very Satisfied on a 5-point Scale of Very Dissatisfied to Very Satisfied at Day 60 on the FLSQ Follow-up Version Item 5 for GL

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The Satisfaction Question 5, grades facial line treatment satisfaction on a 5-point scale (-2 to 2) where -2=Very dissatisfied and 2=Very satisfied.

End point type	Secondary

End point timeframe:

Day 60

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	141	125	
Units: Participants				
number (not applicable)	4	101	96	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.3 Sec Eff Endpoint: The Percentage of Participants with ≥20-point Improvement from Baseline at Day 30 on the FLSQ Impact Domain for GL

End point title	2.3 Sec Eff Endpoint: The Percentage of Participants with ≥20-point Improvement from Baseline at Day 30 on the FLSQ Impact Domain for GL

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The percentage of participants who achieved a ≥20-point improvement from baseline on the FLSQ impact domain (eg, reported a good improvement of the facial lines negative impact) are presented here.

End point type	Secondary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	146	129	
Units: Participants				
number (not applicable)	14	106	88	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.4 Sec Eff Endpoint: The Percentage of Responders for Investigator Assessments of GL Severity at Rest Using the FWS Among Participants Who were Rated At least Mild at Rest at Baseline, Where a Responder was Defined as Achieving ≥1-grade Improvement

End point title	2.4 Sec Eff Endpoint: The Percentage of Responders for Investigator Assessments of GL Severity at Rest Using the FWS Among Participants Who were Rated At least Mild at Rest at Baseline, Where a Responder was Defined as Achieving ≥1-grade Improvement

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The percentage of participants who achieved a ≥1-grade improvement from baseline GL severity at rest based on participant FWS rating is presented here. FWS is a 4-grade scale (0 to 3) where 0 = none and 3 = severe.

End point type	Secondary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	137	122	
Units: Participants				
number (not applicable)	8	75	89	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.5 Sec Eff Endpoint: The Percentage of Responders for Participant Assessments of GL Severity at Rest Using the FWS Among Participants Who were Rated At least Mild at Rest at Baseline, where a Responder was defined as Achieving ≥1-grade Improvement

End point title	2.5 Sec Eff Endpoint: The Percentage of Responders for Participant Assessments of GL Severity at Rest Using the FWS Among Participants Who were Rated At least Mild at Rest at Baseline, where a Responder was defined as Achieving ≥1-

	grade Improvement

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The percentage of participants who achieved a ≥1-grade improvement from baseline GL severity at rest based on participant FWS rating is presented here. FWS is a 4-grade scale (0 to 3) where 0 = none and 3 = severe.

End point type	Secondary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	140	122	
Units: Participants				
number (not applicable)	6	85	89	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.6 Sec Eff Endpoint: The Percentage of Participants with a ≥20-point Improvement from Baseline at Day 30 on the FLO-11 Questionnaire Total Score for GL

End point title	2.6 Sec Eff Endpoint: The Percentage of Participants with a ≥20-point Improvement from Baseline at Day 30 on the FLO-11 Questionnaire Total Score for GL

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The percentage of participants who achieved a ≥20-point improvement from baseline on the FLO-11 questionnaire for GL (eg, reported less emotional and appearance-related impacts of upper-facial lines) is presented here.

End point type	Secondary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	147	129	
Units: Participants				
number (not applicable)	9	107	95	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.7 Sec Eff Endpoint: The Percentage of Participants with a ≥4-point Improvement from Baseline at Day 30 on the FLO-11 Questionnaire Item 2 for GL

End point title	2.7 Sec Eff Endpoint: The Percentage of Participants with a ≥4-point Improvement from Baseline at Day 30 on the FLO-11 Questionnaire Item 2 for GL

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The percentage of participants who achieved a ≥4-point improvement from baseline on the FLO-11 questionnaire item 2 for GL (eg, reported good improvement in the appearance of skin age) is presented here.

End point type	Secondary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	146	127	
Units: Participants				
number (not applicable)	8	96	79	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.8 Sec Eff Endpoint: The Percentage of Participants with a ≥4-point Improvement from Baseline at Day 30 on the FLO-11 Questionnaire Item 5 for GL

End point title	2.8 Sec Eff Endpoint: The Percentage of Participants with a ≥4-point Improvement from Baseline at Day 30 on the FLO-11 Questionnaire Item 5 for GL

End point description:

All primary and secondary efficacy analyses for EU regulatory endpoints were carried out using the mITT population, which consisted of all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50.
The percentage of participants who achieved a ≥4-point improvement from baseline on the FLO-11 questionnaire item 5 for GL (eg, reported good improvement in attractiveness) is presented here.

End point type	Secondary

End point timeframe:

Day 30

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	141	126	
Units: Participants				
number (not applicable)	5	87	71	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.9 Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Systolic Blood Pressure (BP)

End point title	2.9 Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Systolic Blood Pressure (BP)

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	151	135	
Units: mm Hg				
arithmetic mean (standard deviation)	2.5 (± 12.81)	0.0 (± 12.33)	-1.7 (± 12.26)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.10: Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Diastolic Blood Pressure (BP)

End point title	2.10: Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Diastolic Blood Pressure (BP)

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	151	135	
Units: mm Hg				
arithmetic mean (standard deviation)	-1.4 (± 7.81)	-0.9 (± 10.07)	-0.8 (± 8.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.11 Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Respiratory rate

End point title	2.11 Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Respiratory rate

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	151	135	
Units: breath/min				
arithmetic mean (standard deviation)	0.0 (± 2.13)	0.1 (± 2.28)	-0.2 (± 2.21)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.12 Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Pulse Rate

End point title	2.12 Secondary Safety Endpoint: Mean Change From Baseline in Vital Signs - Pulse Rate

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	151	135	
Units: beats/min				
arithmetic mean (standard deviation)	-1.7 (± 11.25)	-1.0 (± 10.30)	-1.0 (± 8.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.13 Secondary Safety endpoint: Mean Change From Baseline in Electrocardiogram (ECG) Parameters - Heart Rate

End point title	2.13 Secondary Safety endpoint: Mean Change From Baseline in Electrocardiogram (ECG) Parameters - Heart Rate

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	134	
Units: beats/min				
arithmetic mean (standard deviation)	3.6 (± 9.79)	2.4 (± 8.41)	3.4 (± 9.51)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.14 Secondary Safety endpoint: Mean Change From Baseline in Electrocardiogram (ECG) Parameters - PR Interval

End point title	2.14 Secondary Safety endpoint: Mean Change From Baseline in Electrocardiogram (ECG) Parameters - PR Interval

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	133	
Units: milliseconds				
arithmetic mean (standard deviation)	-3.2 (± 14.41)	-0.5 (± 12.41)	-0.7 (± 11.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.15 Secondary Safety Endpoint Mean Change From Baseline in

Electrocardiogram (ECG) Parameters - QRS Duration

End point title	2.15 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QRS Duration

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	134	
Units: milliseconds				
arithmetic mean (standard deviation)	0.9 (± 5.78)	1.1 (± 6.08)	0.8 (± 6.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.16 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QT Interval

End point title	2.16 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QT Interval

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	134	
Units: milliseconds				
arithmetic mean (standard deviation)	-10.4 (± 23.88)	-5.6 (± 21.00)	-8.0 (± 22.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.17 Secondary Safety Endpoint: Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QTcB Interval

End point title	2.17 Secondary Safety Endpoint: Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QTcB Interval

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	134	
Units: milliseconds				
arithmetic mean (standard deviation)	0.1 (± 15.50)	1.2 (± 18.92)	1.7 (± 17.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.18 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QTcF Interval

End point title	2.18 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - QTcF Interval

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	134	
Units: milliseconds				
arithmetic mean (standard deviation)	-3.5 (± 14.19)	-1.2 (± 15.91)	-1.8 (± 14.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.19 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - RR Interval

End point title	2.19 Secondary Safety Endpoint Mean Change From Baseline in Electrocardiogram (ECG) Parameters - RR Interval

End point description:

Change from baseline at study exit.
All safety analyses were carried out using Safety Population which includes all subjects who received at least 1 study treatment injection.

End point type	Secondary

End point timeframe:

Day 360 (Study exit) or Early exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	152	134	
Units: milliseconds				
arithmetic mean (standard deviation)	-46.0 (± 113.98)	-31.0 (± 113.11)	-44.6 (± 122.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.20 Secondary Safety Endpoint Number of Participants With Binding and Neutralizing Antibodies

End point title	2.20 Secondary Safety Endpoint Number of Participants With Binding and Neutralizing Antibodies

End point description:

Only samples that tested positive in the binding antibody confirmatory assay were evaluated for neutralizing antibodies. The participants with positive neutralizing antibodies are only shown.

End point type	Secondary

End point timeframe:

Baseline to Study Exit

End point values	Placebo	MT10109L 20U in GL + Placebo in LCL	MT10109L 20U GL + MT10109L 24 U LCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	173	160	
Units: Participants				
number (not applicable)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The timeframe for AEs is from the first dose on Day 1 and up to 30 days after their last visit or study exit (Day 360 or early exit)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo in both GL & LCL	
Reporting group title	MT10109L 20 U
Reporting group description:	
GL: MT10109L 20U + LCL: Placebo	
Reporting group title	MT10109L 44 U
Reporting group description:	
GL: MT10109L 20U + LCL: MT10109L 24U	

Serious adverse events	Placebo	MT10109L 20 U	MT10109L 44 U
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 82 (2.44%)	3 / 174 (1.72%)	5 / 159 (3.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 174 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 82 (0.00%)	0 / 174 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 174 (0.57%)	0 / 159 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 82 (0.00%)	0 / 174 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 174 (0.00%)	1 / 159 (0.63%)
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			
Diarrhea			
subjects affected / exposed	0 / 82 (0.00%)	0 / 174 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 174 (0.57%)	0 / 159 (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			
Osteoarthritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 174 (0.57%)	0 / 159 (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			
Diverticulitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 174 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 174 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Appendicitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 174 (0.00%)	0 / 159 (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

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

Non-serious adverse events	Placebo	MT10109L 20 U	MT10109L 44 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 82 (9.76%)	23 / 174 (13.22%)	13 / 159 (8.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 82 (4.88%)	14 / 174 (8.05%)	6 / 159 (3.77%)
occurrences (all)	4	14	6
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	4 / 82 (4.88%)	9 / 174 (5.17%)	7 / 159 (4.40%)
occurrences (all)	4	9	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2019	Substantial, made to integrate feedback and recommendations from health authorities and improve clarity of study processes: • Clarified the primary objective and endpoint, added secondary objectives and efficacy and safety endpoints. • Added vital sign measurements, ECG assessments, and collection of blood samples for hematology and chemistry testing for Days 30 and 120. Vital sign measurements were added for 30 days after each retreatment; ECG assessments were added for the days of Retreatments 1 and 2 and 30 days after each retreatment. • Added text to clarify that collection of AEs at follow-up visits only applies to participants who received study intervention, added a new section related to which type of AESI were selected for this study, revised the timeframe for which to report nonserious AESIs, revised the duration after which an AE would not be counted as a TEAE, and added a paragraph describing analysis of TEAEs related to PDSOT and monitoring of PDSOT. • Revised the description of which pregnancy outcomes were considered SAEs. • Added statement in primary analyses describing the condition under which MT10109L 44 U was to be tested, added text describing imputation methods, replaced site with baseline GL severity at maximum frown as assessed by the clinician (investigator or subinvestigator) as stratification factors, added text to describe the methods of sensitivity analyses, provided details on the ranking order for hierarchical testing of MT10109L 20 U and MT10109L 44 U versus placebo for secondary analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported