Clinical trial results:
Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study of BOTOX (Botulinum Toxin Type A) for the Prevention of Migraine in Subjects With Episodic Migraine

Summary

EudraCT number	2021-001979-16
Trial protocol	CZ ES SE PL
Global end of trial date	06 November 2024

Results information

Result version number	v1 (current)
This version publication date	12 November 2025
First version publication date	12 November 2025

Trial information

Trial identification

Sponsor protocol code	M21-307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05028569
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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	06 November 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Migraine is a neurological disease characterized by moderate or severe headache, associated with nausea, vomiting, and/or sensitivity to light and sound (International Classification of Headache Disorders, 2018). Migraine can be further categorized according to the frequency of attacks as episodic migraine (EM) or chronic migraine (CM).

This study will assess the effects of BOTOX in preventing migraine in adult participants with EM. BOTOX is being developed for the prevention of migraine in adults with episodic migraine (EM). Participants will be enrolled in 3 different treatment groups. There is 1 in 3 chance that participants will be assigned to receive placebo. Approximately 777 adult participants with EM will be enrolled in approximately 125 sites across the world.

Participants will receive intramuscular injections (injected into the muscle) of BOTOX or Placebo on Day 1 and Week 12. Eligible participants will receive BOTOX on Week 24 and Week 36.

Protection of trial subjects:

Subjects must voluntarily sign and date an informed consent approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2021
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	Canada: 36
Country: Number of subjects enrolled	Czechia: 66
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Poland: 124
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	United States: 387
Worldwide total number of subjects	775
EEA total number of subjects	308

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)	770
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a 4-week Screening/Baseline Phase.

Period 1

Period 1 title	Screening/Baseline Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Screening/Baseline Phase

Arm description:

Participants with 6 to 14 migraine days and < 15 headache days per month in each of the 3 months prior to the screening visit (Visit 1) and during the 4-week Screening/Baseline Phase were randomized in this study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Screening/Baseline Phase
Started	775
Completed	775

Period 2

Period 2 title	Double-Blind Phase
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Double-Blind Phase: Placebo

Arm description:

Participants randomized to receive placebo intramuscular injections in the head/neck muscles for BOTOX on Day 1 and Week 12.

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

Dosage and administration details:

Intramuscular Injection

Arm title	Double-Blind Phase: BOTOX 155 U

Arm description:

Participants randomized to receive intramuscular injections in the head/neck muscles of BOTOX 155 U on Day 1 and Week 12.

Arm type	Experimental
Investigational medicinal product name	BOTOX
Investigational medicinal product code	
Other name	Botulinum Toxin Type A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular Injection

Arm title	Double-Blind Phase: BOTOX 195 U

Arm description:

Participants randomized to receive intramuscular injections in the head/neck muscles of BOTOX 195 U on Day 1 and Week 12.

Arm type	Experimental
Investigational medicinal product name	BOTOX
Investigational medicinal product code	
Other name	Botulinum Toxin Type A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular Injection

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The Double-Blind Phase is the baseline period in this study.

Number of subjects in period 2	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U
Started	257	257	261
Completed	217	230	223
Not completed	40	27	38
Death	-	-	1
Other, not specified	5	4	6
Lost to follow-up	6	3	9
Protocol deviation	2	-	-
Withdrawal by subject	27	20	22

Period 3

Period 3 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Phase: Placebo/Open-Label Phase: BOTOX 195 U

Arm description:

Participants randomized to receive placebo for BOTOX intramuscular injections in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.

Arm type	Experimental
Investigational medicinal product name	BOTOX
Investigational medicinal product code	
Other name	Botulinum Toxin Type A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular Injection

Arm title	Double-Blind Phase: BOTOX 155 U/ Open-Label Phase: BOTOX 195 U

Arm description:

Participants randomized to receive intramuscular injections of BOTOX 155 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.

Arm type	Experimental
Investigational medicinal product name	BOTOX
Investigational medicinal product code	
Other name	Botulinum Toxin Type A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular Injection

Arm title	Double-Blind Phase: BOTOX 195 U/Open-Label Phase: BOTOX 195 U

Arm description:

Participants randomized to receive intramuscular injections of BOTOX 195 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.

Arm type	Experimental

Investigational medicinal product name	BOTOX
Investigational medicinal product code	
Other name	Botulinum Toxin Type A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular Injection

Number of subjects in period 3	Double-Blind Phase: Placebo/Open-Label Phase: BOTOX 195 U	Double-Blind Phase: BOTOX 155 U/ Open-Label Phase: BOTOX 195 U	Double-Blind Phase: BOTOX 195 U/Open-Label Phase: BOTOX 195 U
Started	217	230	223
Completed	186	199	192
Not completed	31	31	31
Completed DB Phase, then withdrew b/c of pregnancy	-	-	1
Study Terminated By Sponsor	4	10	5
Death	-	-	1
Other, not specified	6	5	7
Pregnancy	-	1	-
Completed DB Phase and then withdrew from study	-	2	-
Lost to follow-up	5	5	4
Withdrawal by subject	15	8	13
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Phase: Placebo
Reporting group description:	
Participants randomized to receive placebo intramuscular injections in the head/neck muscles for BOTOX on Day 1 and Week 12.	
Reporting group title	Double-Blind Phase: BOTOX 155 U
Reporting group description:	
Participants randomized to receive intramuscular injections in the head/neck muscles of BOTOX 155 U on Day 1 and Week 12.	
Reporting group title	Double-Blind Phase: BOTOX 195 U
Reporting group description:	
Participants randomized to receive intramuscular injections in the head/neck muscles of BOTOX 195 U on Day 1 and Week 12.	

Reporting group values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U
Number of subjects	257	257	261
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.3	41.1	41.1
standard deviation	± 11.12	± 10.37	± 10.76
Gender categorical Units: Subjects			
Female	231	227	224
Male	26	30	37
Ethnicity Units: Subjects			
Hispanic or Latino	24	30	37
Not Hispanic or Latino	233	227	224
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	3	3	7
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	23	12	14
White	229	240	237
More than one race	2	0	2
Unknown or Not Reported	0	0	1

Reporting group values	Total		
Number of subjects	775		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	682		
Male	93		
Ethnicity Units: Subjects			
Hispanic or Latino	91		
Not Hispanic or Latino	684		
Unknown or Not Reported	0		
Race Units: Subjects			
American Indian or Alaska Native	1		
Asian	13		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	49		
White	706		
More than one race	4		
Unknown or Not Reported	1		

Subject analysis sets

Subject analysis set title	Double-Blind Phase: Placebo (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo intramuscular injections in the head/neck muscles for BOTOX on Day 1 and Week 12. Participants were analyzed according to the treatment received.

Subject analysis set title	Double-Blind Phase: BOTOX 155 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received intramuscular injections in the head/neck muscles of BOTOX 155 U on Day 1 and Week 12. Participants were analyzed according to the treatment received.

Subject analysis set title	Double-Blind Phase: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received intramuscular injections in the head/neck muscles of BOTOX 195 U on Day 1 and Week 12. Participants were analyzed according to the treatment received.

Subject analysis set title	DB Phase: Placebo/OL Phase: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received placebo for BOTOX intramuscular injections in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase. Participants were analyzed according to the treatment received.

Subject analysis set title	DB: BOTOX 155 U/OL: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received intramuscular injections of BOTOX 155 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase. Participants were analyzed according to the treatment received.

Subject analysis set title	DB: BOTOX 195 U/OL: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received intramuscular injections of BOTOX 195 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase. Participants were analyzed according to the treatment received.

Reporting group values	Double-Blind Phase: Placebo (Safety Analysis Set)	Double-Blind Phase: BOTOX 155 U (Safety Analysis Set)	Double-Blind Phase: BOTOX 195 U (Safety Analysis Set)
Number of subjects	257	255	262
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.3	41.1	41.1
standard deviation	± 11.12	± 10.41	± 10.73
Gender categorical Units: Subjects			
Female	231	225	225
Male	26	30	37
Ethnicity Units: Subjects			
Hispanic or Latino	233	225	225
Not Hispanic or Latino	24	30	37
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	3	3	7
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	23	12	14
White	229	238	238
More than one race	2	0	2
Unknown or Not Reported	0	0	1

Reporting group values	DB Phase: Placebo/OL Phase: BOTOX 195 U (Safety Analysis Set)	DB: BOTOX 155 U/OL: BOTOX 195 U (Safety Analysis Set)	DB: BOTOX 195 U/OL: BOTOX 195 U (Safety Analysis Set)
Number of subjects	217	225	223
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	40.2	41.2	41.1
standard deviation	± 10.83	± 10.46	± 10.29
Gender categorical Units: Subjects			
Female	196	196	189
Male	21	29	34
Ethnicity Units: Subjects			
Hispanic or Latino	199	200	197
Not Hispanic or Latino	18	25	26
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	1	3	7
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	19	8	8
White	195	212	205
More than one race	2	0	2
Unknown or Not Reported	0	0	1

End points

End points reporting groups

Reporting group title	Screening/Baseline Phase
Reporting group description:	
Participants with 6 to 14 migraine days and < 15 headache days per month in each of the 3 months prior to the screening visit (Visit 1) and during the 4-week Screening/Baseline Phase were randomized in this study.	
Reporting group title	Double-Blind Phase: Placebo
Reporting group description:	
Participants randomized to receive placebo intramuscular injections in the head/neck muscles for BOTOX on Day 1 and Week 12.	
Reporting group title	Double-Blind Phase: BOTOX 155 U
Reporting group description:	
Participants randomized to receive intramuscular injections in the head/neck muscles of BOTOX 155 U on Day 1 and Week 12.	
Reporting group title	Double-Blind Phase: BOTOX 195 U
Reporting group description:	
Participants randomized to receive intramuscular injections in the head/neck muscles of BOTOX 195 U on Day 1 and Week 12.	
Reporting group title	Double-Blind Phase: Placebo/Open-Label Phase: BOTOX 195 U
Reporting group description:	
Participants randomized to receive placebo for BOTOX intramuscular injections in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.	
Reporting group title	Double-Blind Phase: BOTOX 155 U/ Open-Label Phase: BOTOX 195 U
Reporting group description:	
Participants randomized to receive intramuscular injections of BOTOX 155 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.	
Reporting group title	Double-Blind Phase: BOTOX 195 U/Open-Label Phase: BOTOX 195 U
Reporting group description:	
Participants randomized to receive intramuscular injections of BOTOX 195 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.	
Subject analysis set title	Double-Blind Phase: Placebo (Safety Analysis Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo intramuscular injections in the head/neck muscles for BOTOX on Day 1 and Week 12. Participants were analyzed according to the treatment received.	
Subject analysis set title	Double-Blind Phase: BOTOX 155 U (Safety Analysis Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received intramuscular injections in the head/neck muscles of BOTOX 155 U on Day 1 and Week 12. Participants were analyzed according to the treatment received.	
Subject analysis set title	Double-Blind Phase: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received intramuscular injections in the head/neck muscles of BOTOX 195 U on Day 1 and Week 12. Participants were analyzed according to the treatment received.	
Subject analysis set title	DB Phase: Placebo/OL Phase: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received placebo for BOTOX intramuscular injections in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase. Participants were analyzed according to the treatment received.

Subject analysis set title	DB: BOTOX 155 U/OL: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received intramuscular injections of BOTOX 155 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase. Participants were analyzed according to the treatment received.

Subject analysis set title	DB: BOTOX 195 U/OL: BOTOX 195 U (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received intramuscular injections of BOTOX 195 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase. Participants were analyzed according to the treatment received.

Primary: Change From Baseline in the Frequency of Monthly Migraine Days Across Months 5 and 6

End point title	Change From Baseline in the Frequency of Monthly Migraine Days Across Months 5 and 6

End point description:

The frequency of monthly migraine days across Months 5 and 6 is calculated from the 28-day daily diary periods ending with Days 56 and 84 after the second study treatment intervention day with BOTOX or placebo injections. Negative changes from Baseline indicate improvement.

Analysis population: Intent-to-Treat Population (as Randomized); data used are "observed data"(without imputation for missing values)

End point type	Primary

End point timeframe:

Baseline, Months 5-6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	227	234	227	
Units: monthly migraine days				
least squares mean (confidence interval 95%)	-3.0 (-3.55 to -2.46)	-3.1 (-3.65 to -2.57)	-3.0 (-3.51 to -2.43)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with Baseline monthly migraine days as covariate, included as a continuous variable rather than the binomial stratification variable. Subject/residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 195 U
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.914 [1]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.69
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[1] - LS Mean Difference = BOTOX 195 U - Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with Baseline monthly migraine days as covariate, included as a continuous variable rather than the binomial stratification variable. Subject/residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155 U
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.745 [2]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[2] - LS Mean Difference = BOTOX 155 U - Placebo

Primary: Number of Participants With Treatment-Emergent Adverse Events (AEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (AEs)[3]

End point description:

An adverse event (AE): any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. Investigator assesses the relationship of each event to the use of study drug. Serious adverse event (SAE): an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an

important medical event that, based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Treatment-emergent adverse events/treatment-emergent serious adverse events (TEAEs/TESAEs) are defined as any event that began or worsened in severity on or after the first dose of study drug.

Analysis population: Safety Analysis Set: all subjects who received any amount of study Tx; analyzed as Tx actually rcvd

End point type	Primary

End point timeframe:

Double-Blind Phase (Week 0-24); Open-Label Phase (Week 24-48)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive data are summarized for this end point per protocol.

End point values	Double-Blind Phase: Placebo (Safety Analysis Set)	Double-Blind Phase: BOTOX 155 U (Safety Analysis Set)	Double-Blind Phase: BOTOX 195 U (Safety Analysis Set)	DB Phase: Placebo/OL Phase: BOTOX 195 U (Safety Analysis Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	257	255	262	217
Units: participants				
Any TEAE	106	117	120	76
TESAE	6	3	6	2

End point values	DB: BOTOX 155 U/OL: BOTOX 195 U (Safety Analysis Set)	DB: BOTOX 195 U/OL: BOTOX 195 U (Safety Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	225	223		
Units: participants				
Any TEAE	75	80		
TESAE	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Frequency of Monthly Headache Days Across Months 5 and 6

End point title	Change From Baseline in the Frequency of Monthly Headache Days Across Months 5 and 6

End point description:

The frequency of monthly headache days across Months 5 and 6 is calculated from the 28-day daily diary periods ending with Days 56 and 84 after the second study treatment intervention day with BOTOX or placebo injections. Negative changes from Baseline indicate improvement.

Analysis population: Intent-to-Treat Population (as Randomized); data used are "observed data"(without imputation for missing values)

End point type	Secondary

End point timeframe:

Baseline, Months 5-6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	227	234	227	
Units: monthly headache days				
least squares mean (confidence interval 95%)	-3.2 (-3.77 to -2.59)	-3.1 (-3.71 to -2.54)	-2.9 (-3.46 to -2.29)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with Baseline monthly headache days as covariate, included as a continuous variable. Subject/residual errors are random effects.

Comparison groups	Double-Blind Phase: BOTOX 195 U v Double-Blind Phase: Placebo
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414 [4]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	1.01
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[4] - LS Mean Difference = BOTOX 195 U - Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with Baseline monthly headache days as covariate, included as a continuous variable. Subject/residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155 U

Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.889 [5]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.76
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[5] - LS Mean Difference = BOTOX 155 U - Placebo

Secondary: Percentage of Participants With ≥ 50% Reduction From Baseline in the Frequency of Monthly Migraine Days Across Months 5 and 6

End point title	Percentage of Participants With ≥ 50% Reduction From Baseline in the Frequency of Monthly Migraine Days Across Months 5 and 6

End point description:

The frequency of monthly migraine days across Months 5 and 6 Is calculated from the 28-day daily diary periods ending with days 56 and 84 after the second study treatment intervention day with BOTOX or placebo injections. The responder status of 50% reduction from Baseline is defined as a participant with at least a 50% reduction from Baseline in the 2-month average of monthly migraine days over Months 5 and 6.

Analysis population: Intent-to-Treat Population (as Randomized); data used are "observed data"(without imputation for missing values)

End point type	Secondary

End point timeframe:

Baseline, Months 5-6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	227	234	227	
Units: percentage of participants				
number (confidence interval 95%)	44.9 (38.35 to 51.66)	46.2 (39.64 to 52.77)	47.1 (40.50 to 53.85)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value is obtained from Logistic Regression. Model includes treatment (BOTOX 195 U, BOTOX 155 U, and placebo), country and strata of previous exposure to migraine prophylactic treatment as fixed

effects, with the Baseline monthly migraine days as a covariate, included as a continuous variable. Subject and residual errors are random effects in this by visit logistic covariate analysis of variance (ANCOVA). Confidence intervals (Clopper-Pearson) are based on binomial-distribution assumptions

Comparison groups	Double-Blind Phase: BOTOX 195 U v Double-Blind Phase: Placebo
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451 [6]
Method	Regression, Logistic
Parameter estimate	Response Rate Difference
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.08
upper limit	11.46

Notes:

[6] - Response Rate Difference = BOTOX 195 U –Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value is obtained from Logistic Regression. Model includes treatment (BOTOX 195 U, BOTOX 155 U, and placebo), country and strata of previous exposure to migraine prophylactic treatment as fixed effects, with the Baseline monthly migraine days as a covariate, included as a continuous variable. Subject and residual errors are random effects in this by visit logistic covariate analysis of variance (ANCOVA). Confidence intervals (Clopper-Pearson) are based on binomial-distribution assumptions

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155 U
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.762 [7]
Method	Regression, Logistic
Parameter estimate	Response Rate Difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.94
upper limit	10.4

Notes:

[7] - Response Rate Difference = BOTOX 155 U –Placebo

Secondary: Change From Baseline in the Frequency of Monthly Acute Headache Medication Days Across Months 5 and 6

End point title	Change From Baseline in the Frequency of Monthly Acute Headache Medication Days Across Months 5 and 6

End point description:

Monthly acute headache medication days across Months 5 and 6 is calculated from the 28-day daily diary periods ending with days 56 and 84 after the second study treatment intervention day with BOTOX or placebo injections. Negative changes from Baseline indicate improvement.

Analysis population: Intent-to-Treat Population (as Randomized); data used are "observed data"(without imputation for missing values)

End point type	Secondary

End point timeframe:

Baseline, Months 5-6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	227	234	227	
Units: Monthly Acute Headache Medication Days				
least squares mean (confidence interval 95%)	-2.0 (-2.47 to -1.47)	-1.9 (-2.44 to -1.44)	-1.8 (-2.34 to -1.35)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline monthly acute headache medication days as a covariate, included as a continuous variable. Subject and residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 195 U
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.686 [8]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[8] - LS Mean Difference = BOTOX 195 U –Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline monthly acute headache medication days as a covariate, included as a continuous variable. Subject and residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155

	U
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.913 [9]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[9] - LS Mean Difference = BOTOX 155 U –Placebo

Secondary: Change From Baseline in Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1) Role Function - Restrictive (RFR) Domain Score At Month 6

End point title	Change From Baseline in Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1) Role Function - Restrictive (RFR) Domain Score At Month 6

End point description:

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality of life impairments attributed to migraine over the past 4 weeks. It is divided into 3 domains, and the Role Function Restrictive (RFR) assesses how migraines limit one's daily social and work-related activities using a 6-point scale ranging from "none of the time" to "all of the time". Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life. Positive changes from Baseline indicate improvement.

Analysis population: Intent-to-Treat Population (as Randomized); data used are “observed data”(without imputation for missing values)

End point type	Secondary

End point timeframe:

Baseline, Month 6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	228	218	
Units: units on a scale				
least squares mean (confidence interval 95%)	18.6 (15.77 to 21.51)	19.4 (16.58 to 22.27)	19.0 (16.15 to 21.87)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the visit at Month 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline MSQ v2.1 RFR Domain Score as a covariate, included as a continuous variable. Subject and residual
errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 195 U
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.837 [10]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	3.93
Variability estimate	Standard error of the mean
Dispersion value	1.81

Notes:

[10] - LS Mean Difference = BOTOX 195 U –Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value/95% CI obtained from mixed-effects model for repeated measures (MMRM) for primary analysis of the visit at Month 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline MSQ v2.1 RFR Domain Score as a covariate, included as a continuous variable. Subject and residual
errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155 U
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.662 [11]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	4.31
Variability estimate	Standard error of the mean
Dispersion value	1.79

Notes:

[11] - LS Mean Difference = BOTOX 155 U –Placebo

Secondary: Change From Baseline in the Activity Impairment in Migraine - Diary (AIM-D) Physical Impairment Domain Score Across Months 5 and 6

End point title	Change From Baseline in the Activity Impairment in Migraine - Diary (AIM-D) Physical Impairment Domain Score Across Months 5 and 6

End point description:

The AIM–D is an 11-item patient-reported outcome instrument that assesses the impact of migraine on the performance of daily activities and physical impairment. Participants answer each question based on the level of difficulty experienced in the 24 hours prior, with "during your headache" indicated for when they reported a headache, using the following 6-point rating scale: "not difficult at all"; "a little difficult"; "somewhat difficult"; "very difficult"; "extremely difficult". AIM-D Physical Impairment domain score across Months 5 and 6 which are calculated from the 28-day daily diary periods ending with days 56 and 84 after the second study treatment intervention day with BOTOX or placebo injections. Negative changes from Baseline in the Physical Impairment domain scores indicate improvement.

Analysis population: Intent-to-Treat Population (as Randomized); data used are "observed data"(without imputation for missing values)

End point type	Secondary

End point timeframe:

Baseline, Months 5-6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	232	222	
Units: units on a scale				
least squares mean (confidence interval 95%)	-5.0 (-6.23 to -3.82)	-4.6 (-5.82 to -3.39)	-4.9 (-6.07 to -3.66)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value/95% CI are obtained from mixed-effects model for repeated measures (MMRM) analysis for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline AIM-D Physical Impairment domain score as a covariate, included as a continuous variable. Subject and residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 195 U
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.834 [12]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	1.63
Variability estimate	Standard error of the mean
Dispersion value	0.75

Notes:

[12] - LS Mean Difference = BOTOX 195 U –Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value/95% CI are obtained from mixed-effects model for repeated measures (MMRM) analysis for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline AIM-D Physical Impairment domain score as a covariate, included as a continuous variable. Subject and residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155 U
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.578 [13]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	0.75

Notes:

[13] - LS Mean Difference = BOTOX 155 U –Placebo

Secondary: Change From Baseline in the Total 6-item Headache Impact Test (HIT-6) Score Across Months 5 and 6

End point title	Change From Baseline in the Total 6-item Headache Impact Test (HIT-6) Score Across Months 5 and 6

End point description:

The HIT-6 is a 6-item assessment used to measure the impact headaches have on a participant’s ability to function on the job, at school, at home and in social situations. It assesses the effect that headaches have on normal daily life and the subject's ability to function. Responses are based on frequency using a 5-point scale ranging from "never" to "always." The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses, each of which is assigned a score ranging from 6 points (never) to 13 points (always). Negative changes from Baseline in the HIT-6 score indicate improvement.

Analysis population: Intent-to-Treat Population (as Randomized); data used are “observed data”(without imputation for missing values)

End point type	Secondary

End point timeframe:

Baseline, Months 5-6

End point values	Double-Blind Phase: Placebo	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	228	238	229	
Units: units on a scale				
least squares mean (confidence interval 95%)	-6.2 (-7.26 to -5.08)	-6.9 (-7.94 to -5.77)	-6.5 (-7.62 to -5.45)	

Statistical analyses

Statistical analysis title	BOTOX 195 U vs Placebo

Statistical analysis description:

P-value/95% CI are obtained from a mixed-effects model for repeated measures (MMRM) analysis for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline total HIT-6 score as a covariate, included as a continuous variable. Subject and residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 195 U
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.589 [14]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	0.96
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[14] - LS Mean Difference = BOTOX 195 U –Placebo

Statistical analysis title	BOTOX 155 U vs Placebo

Statistical analysis description:

P-value/95% CI are obtained from a mixed-effects model for repeated measures (MMRM) analysis for primary analysis of the 2 visits across Months 5 and 6. Tx (BOTOX 195 U, BOTOX 155 U, placebo), month (Months 1-6), country, strata of previous exposure to migraine prophylactic treatment, and Tx group-by-month interaction as fixed effects, with the Baseline total HIT-6 score as a covariate, included as a continuous variable. Subject and residual errors are random effects.

Comparison groups	Double-Blind Phase: Placebo v Double-Blind Phase: BOTOX 155 U

Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [15]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.67

Notes:

[15] - LS Mean Difference = BOTOX 155 U –Placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality/adverse event tables include events from time informed consent was signed to end of the study. Median time on follow-up was 30 days in Screening/Baseline Phase; 168 days in Double-Blind Phase; and 169 days in Open-Label Phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Screening/Baseline Phase

Reporting group description:

Participants with 6 to 14 migraine days and < 15 headache days per month in each of the 3 months prior to the screening visit (Visit 1) and during the 4-week Screening/Baseline Phase were randomized in this study.

Reporting group title	Double-Blind Phase: BOTOX 155 U

Reporting group description:

Participants received intramuscular injections in the head/neck muscles of BOTOX 155 U on Day 1 and Week 12.

Reporting group title	Double-Blind Phase: BOTOX 195 U/ Open-Label Phase: BOTOX 195 U

Reporting group description:

Participants who received intramuscular injections of BOTOX 195 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.

Reporting group title	Double-Blind Phase: Placebo/Open- Label Phase: BOTOX 195 U

Reporting group description:

Participants who received placebo for BOTOX intramuscular injections in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.

Reporting group title	Double-Blind Phase: BOTOX 155 U/ Open-Label Phase: BOTOX 195 U

Reporting group description:

Participants who received intramuscular injections of BOTOX 155 U in the head/neck muscles on Day 1 and Week 12 during the Double-Blind Phase who then received intramuscular injections of BOTOX 195 U in the head/neck muscles on Weeks 24 and 36 in the Open-Label Phase.

Reporting group title	Double-Blind Phase: Placebo

Reporting group description:

Participants received placebo intramuscular injections in the head/neck muscles for BOTOX on Day 1 and Week 12.

Reporting group title	Double-Blind Phase: BOTOX 195 U

Reporting group description:

Participants received intramuscular injections in the head/neck muscles of BOTOX 195 U on Day 1 and Week 12.

Serious adverse events	Screening/Baseline Phase	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U/ Open-Label Phase: BOTOX 195 U
Total subjects affected by serious adverse events			

subjects affected / exposed	2 / 775 (0.26%)	3 / 256 (1.17%)	1 / 223 (0.45%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LIPOSARCOMA			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 775 (0.13%)	0 / 256 (0.00%)	0 / 223 (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
LABILE BLOOD PRESSURE			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
Reproductive system and breast disorders			
BREAST HYPERPLASIA			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 775 (0.00%)	1 / 256 (0.39%)	0 / 223 (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
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			

subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
Psychiatric disorders			
COMPLETED SUICIDE			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
FALL			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
TRAUMATIC HAEMATOMA			
subjects affected / exposed	0 / 775 (0.00%)	1 / 256 (0.39%)	0 / 223 (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			
MIGRAINE			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
MIGRAINE WITH AURA			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
MYELOPATHY			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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
Blood and lymphatic system disorders			
IMMUNE THROMBOCYTOPENIA			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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			
VESTIBULAR DISORDER			
subjects affected / exposed	1 / 775 (0.13%)	0 / 256 (0.00%)	0 / 223 (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
Hepatobiliary disorders			
PORTOSPLENOMESENTERIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 775 (0.00%)	1 / 256 (0.39%)	0 / 223 (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			
STAPHYLOCOCCAL ABSCESS			
subjects affected / exposed	0 / 775 (0.00%)	0 / 256 (0.00%)	0 / 223 (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

Serious adverse events	Double-Blind Phase: Placebo/Open- Label Phase: BOTOX 195 U	Double-Blind Phase: BOTOX 155 U/ Open-Label Phase: BOTOX 195 U	Double-Blind Phase: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 217 (0.92%)	1 / 227 (0.44%)	6 / 257 (2.33%)
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)			
LIPOSARCOMA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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
LABILE BLOOD PRESSURE			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	1 / 257 (0.39%)
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			
BREAST HYPERPLASIA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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			
DYSPNOEA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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

Psychiatric disorders			
COMPLETED SUICIDE			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 217 (0.46%)	0 / 227 (0.00%)	0 / 257 (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
FALL			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC HAEMATOMA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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			
MIGRAINE			
subjects affected / exposed	1 / 217 (0.46%)	1 / 227 (0.44%)	0 / 257 (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
MIGRAINE WITH AURA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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
MYELOPATHY			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCIATICA			

subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
IMMUNE THROMBOCYTOPENIA			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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			
VESTIBULAR DISORDER			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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
Hepatobiliary disorders			
PORTOSPLENOMESENTERIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
STAPHYLOCOCCAL ABSCESS			
subjects affected / exposed	0 / 217 (0.00%)	0 / 227 (0.00%)	0 / 257 (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

Serious adverse events	Double-Blind Phase: BOTOX 195 U		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 262 (2.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LIPOSARCOMA			
subjects affected / exposed	0 / 262 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 262 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LABILE BLOOD PRESSURE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 262 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
BREAST HYPERPLASIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 262 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

COMPLETED SUICIDE				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
ANKLE FRACTURE				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FALL				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TRAUMATIC HAEMATOMA				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
MIGRAINE				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MIGRAINE WITH AURA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYELOPATHY				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SCIATICA				
subjects affected / exposed	0 / 262 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Blood and lymphatic system disorders			
IMMUNE THROMBOCYTOPENIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
VESTIBULAR DISORDER			
subjects affected / exposed	0 / 262 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
PORTOSPLENOMESENTERIC VENOUS THROMBOSIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 262 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
STAPHYLOCOCCAL ABSCESS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Screening/Baseline Phase	Double-Blind Phase: BOTOX 155 U	Double-Blind Phase: BOTOX 195 U/ Open-Label Phase: BOTOX 195 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 775 (1.81%)	35 / 256 (13.67%)	14 / 223 (6.28%)
Infections and infestations			

COVID-19			
subjects affected / exposed	4 / 775 (0.52%)	16 / 256 (6.25%)	7 / 223 (3.14%)
occurrences (all)	4	16	7
NASOPHARYNGITIS			
subjects affected / exposed	10 / 775 (1.29%)	23 / 256 (8.98%)	8 / 223 (3.59%)
occurrences (all)	10	26	8

Non-serious adverse events	Double-Blind Phase: Placebo/Open- Label Phase: BOTOX 195 U	Double-Blind Phase: BOTOX 155 U/ Open-Label Phase: BOTOX 195 U	Double-Blind Phase: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 217 (8.76%)	18 / 227 (7.93%)	21 / 257 (8.17%)
Infections and infestations			
COVID-19			
subjects affected / exposed	12 / 217 (5.53%)	9 / 227 (3.96%)	9 / 257 (3.50%)
occurrences (all)	12	9	9
NASOPHARYNGITIS			
subjects affected / exposed	7 / 217 (3.23%)	10 / 227 (4.41%)	14 / 257 (5.45%)
occurrences (all)	10	12	15

Non-serious adverse events	Double-Blind Phase: BOTOX 195 U		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 262 (8.40%)		
Infections and infestations			
COVID-19			
subjects affected / exposed	8 / 262 (3.05%)		
occurrences (all)	8		
NASOPHARYNGITIS			
subjects affected / exposed	15 / 262 (5.73%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2021	Version 2.0 Introduced new "Other" study endpoints, including evaluation of changes from Baseline in the frequency of monthly migraine attacks during Months 5 and 6, frequency of monthly migraine days across Months 4 through 6, as well as the average daily severity of headaches and all days (including headache-free days) across Months 5 and 6. Additional modifications were made to the protocol: enrollment was capped so that no more than 20% of subjects could meet criteria for acute headache medication overuse; a weekly migraine attack assessment was added; and a new eligibility criterion specified that participants cannot concurrently take part in another clinical trial. The Operations Manual (Appendix F) was updated to provide instructions for procedures affected by regulatory changes related to the COVID-19 pandemic, while Sections 3.1 and 8.2 were amended to include language on Verified Clinical Trials procedures and to define acute headache medication overuse, respectively.
16 August 2021	Version 3.0 Updated the language in the Operations Manual's sections on Biomarker Research and Biomarker Research Sampling. Additional changes include revised eligibility criteria in Section 5.1 to incorporate the C-SSRS, clarified requirements for female contraception, and updated language regarding medication overuse headache. Section 5.2 clarified that contraception requirements now extend to 90 days after the last dose of the study drug. Sections 7.4 and 7.5 were revied to include a 'medication overuse subgroup' in the analyses of both primary efficacy and key safety endpoints. In the Operations Manual, references to paper SAE forms were removed from Section 4.2, Section 6.5 specified the number of vials to be reconstituted, and language regarding the relevant time period in Section 8.2 was clarified.
11 February 2022	Version 4.0 Provided a summary of BOTOX risks and specifies that participation in biomarker sampling is now optional. Urine biomarker collection was removed in light of recent literature. The Screening/Baseline Phase may be extended for COVID-19 reasons, and visit windows were aligned with Appendix D. Subjects who have failed 2 to 4 preventive treatments will receive continued monitoring, and new language addressed enrollment criteria for those with medication overuse; details were added regarding potential enrollment restrictions and the re-screening process. Reference to legally authorized representatives was removed, and eligibility criteria were updated, correcting an error regarding thyroid status and clarifying the requirement for investigator review. The list of acceptable contraception methods was changed, excluding barrier methods and certain progesterone-only options. Barbiturates were added to the list of permitted migraine medications, and prior exposure to migraine prophylactic treatments was detailed. Adverse event reporting rules were revised to allow for quicker reporting in certain locales to comply with German regulations. Language about suicidal ideation for the C-SSRS was clarified. A blinding assessment was added at Week 24, and urine alcohol screenings were centralized. The PGIC assessment at Week 36 was added to the Operations Manual to match the study protocol.

04 April 2023	Version 5.0 The protocol and operations manual were updated to clarify and improve the study processes. Collection time points for EQ-5D-5L and PHQ-9 scores revised to reflect actual collection timing. Enrollment targets were reworded for flexibility. Eligibility was revised to require subjects to be aged 18 to 65 at Visit 1, and applicants must not have allergies to the study drug or its components per UK regulatory feedback. Additional cautions were added for combining aminoglycosides or other agents that affect neuromuscular transmission, also per UK feedback. Ubrogepant is now an allowed migraine-specific treatment during the Open-Label Phase, with restrictions for safety evaluation, and emergency unmasking procedures were clarified. An incorrect pregnancy follow-up statement was removed. The PGI-S score is now used as a baseline covariate for PGIC. At Week 24, weight collection was added for creatinine clearance calculations, and treatment visits should occur every 12 weeks. The PHQ-9 severe depression threshold was updated to include a score of 20; AIM-D was clarified to only one version; and the daily activities domain was corrected to include concentration and clarity assessments. Drug storage requirements were updated; miscellaneous pharmacologic categories are now permitted in all countries; and emergency medical contacts were updated for current personnel.
03 April 2024	Version 6.0 Key updates to the protocol and operations manual included the revision of emergency medical and SAE reporting contacts to reflect current personnel. The secondary endpoint regarding change from baseline in frequency of neck pain days was reclassified as an exploratory endpoint. Additional analyses now focus on moderate or severe neck pain in participants with baseline headache-associated neck pain. The analysis of acute headache medication days was simplified due to insufficient baseline data, and a new statement confirmed all primary and secondary endpoints will also be assessed at monthly intervals for efficacy. The protocol was revised to include further subgroup analyses as per regulatory guidelines, and the multiplicity method schematic for controlling Type I error was updated to reflect endpoint changes. The section addressing study conduct in crisis events was updated to now reference any significant disaster rather than just the COVID-19 pandemic, allowing for remote verification under broader circumstances.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported