Clinical trial results:
A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

Summary

EudraCT number	2021-000240-22
Trial protocol	BE DE
Global end of trial date	14 June 2023

Results information

Result version number	v1 (current)
This version publication date	28 June 2024
First version publication date	28 June 2024

Trial information

Trial identification

Sponsor protocol code	M21-310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04994535
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	14 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate the safety and effects of onabotulinumtoxinA (BOTOX) for the temporary improvement in the appearance of platysma prominence.

Study doctors randomized subjects into 1 of the 2 groups, called treatment arms. There was a 1 in 2 chance that a subject was assigned to placebo. Approximately 400 subjects were to be enrolled in the study across approximately 35 sites in USA, Belgium, Canada, Germany and the UK.

Subjects received a single treatment of intramuscular injection of onabotulinumtoxinA (BOTOX) or placebo on Day 1 during this 4 month long study.

Subjects attended regular monthly visits during the study at the study site.

Protection of trial subjects:

Subjects read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 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	Belgium: 16
Country: Number of subjects enrolled	Canada: 59
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 265
Worldwide total number of subjects	426
EEA total number of subjects	92

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)	417
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

426 subjects were enrolled and randomized into the study (ITT Population); 209 to BOTOX and 217 to placebo. A total of 208 subjects were treated with BOTOX and 216 subjects were treated with placebo (Safety Analysis Set). A total of 381 subjects were included in the modified ITT (mITT) Population; 186 to BOTOX and 195 to placebo.

Pre-assignment

Screening details:

The mITT Population (N=381) included all randomized subjects with a baseline summary score ≥ 19 on the ANLFQ: Impacts questionnaire and was used for the reported efficacy analyses. The Safety Analysis Set (N=424) included all subjects treated with at least 1 dose of study drug and was used for all safety analyses.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo was injected into the platysma muscle on Day 1

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

Dosage and administration details:

Placebo was injected into the platysma muscle on Day 1

Arm title	BOTOX

Arm description:

BOTOX (OnabotulinumtoxinA) was injected into the platysma muscle on Day 1

Arm type	Experimental
Investigational medicinal product name	OnabotulinumtoxinA
Investigational medicinal product code	
Other name	BOTOX
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

BOTOX was injected into the platysma muscle on Day 1

Number of subjects in period 1	Placebo	BOTOX
Started	217	209
Completed	199	194
Not completed	18	15
Other	1	1
Lost to follow-up	7	7
Withdrawal by subject	10	7

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo was injected into the platysma muscle on Day 1	
Reporting group title	BOTOX
Reporting group description:	
BOTOX (OnabotulinumtoxinA) was injected into the platysma muscle on Day 1	

Reporting group values	Placebo	BOTOX	Total
Number of subjects	217	209	426
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)	210	207	417
From 65-84 years	7	2	9
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	46.9	48.0	
standard deviation	± 10.18	± 9.57	-
Gender categorical Units: Subjects			
Female	206	198	404
Male	11	11	22
Race Units: Subjects			
White	202	191	393
Black or African American	5	2	7
Asian	8	11	19
More than one race	2	4	6
American Indian or Alaska Native	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	35	30	65
Not Hispanic or Latino	182	179	361

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo was injected into the platysma muscle on Day 1	
Reporting group title	BOTOX
Reporting group description:	
BOTOX (OnabotulinumtoxinA) was injected into the platysma muscle on Day 1	

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]
End point description:	
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.	
End point type	Primary
End point timeframe:	
Enrollment to Day 120	

Notes:

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

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	208		
Units: subjects	43	34		

Statistical analyses

No statistical analyses for this end point

Primary: Achievement of at Least a 2-grade Improvement From Baseline Based on the Participant's Self-Assessment Using P-APPS at Maximum Contraction at Day 14

End point title	Achievement of at Least a 2-grade Improvement From Baseline Based on the Participant's Self-Assessment Using P-APPS at Maximum Contraction at Day 14
End point description:	
The P-APPS evaluates platysma prominence severity and is a single-item measure that is accompanied by a 5-grade photonumeric scale for subjects to self-assess the severity of their platysma prominence at maximum contraction, ranging from 1 - Minimal to 5 - Extreme.	
End point type	Primary
End point timeframe:	
Day 14	

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Percentage of subjects				
number (confidence interval 95%)	3.9 (1.1 to 6.7)	40.8 (33.5 to 48.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference (%)
Point estimate	36.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.1
upper limit	44.7

Notes:

[2] - P-value derived from Cochran-Mantel-Haenszel (CMH) model stratified by investigator site and baseline C-APPS.

Primary: Achievement of at Least a 2-grade Improvement From Baseline Based on the Investigator's Assessment Using C-APPS at Maximum Contraction at Day 14

End point title	Achievement of at Least a 2-grade Improvement From Baseline Based on the Investigator's Assessment Using C-APPS at Maximum Contraction at Day 14

End point description:

The C-APPS evaluates platysma prominence severity and is a static measurement encompassing the investigator's visual examination of the platysma muscle at maximum contraction, ranging from 1 - Minimal to 5- Extreme.

End point type	Primary

End point timeframe:

Day 14

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Percentage of subjects				
number (confidence interval 95%)	2.2 (0 to 4.3)	41.0 (33.8 to 48.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference (%)
Point estimate	38.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.3
upper limit	46.4

Notes:

[3] - P-value derived from Cochran-Mantel-Haenszel (CMH) model stratified by investigator site and baseline C-APPS.

Secondary: Change From Baseline on the ANLFQ: Impacts Summary Score at Days 30, 60, and 90

End point title	Change From Baseline on the ANLFQ: Impacts Summary Score at Days 30, 60, and 90

End point description:

The ANLFQ: Impacts scale assesses the psychosocial impact of the appearance of the neck and lower face. All items are rated on a 5-point Verbal Descriptor Scale ranging from 1 (Never) to 5 (All of the time), with higher scores indicating greater negative impact from the appearance of the neck and lower face.

End point type	Secondary

End point timeframe:

Day 30, Day 60, Day 90

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Score on a Scale				
least squares mean (standard error)				
Day 30	-3.9 (± 0.54)	-8.8 (± 0.55)		
Day 60	-3.5 (± 0.56)	-8.2 (± 0.56)		
Day 90	-3.5 (± 0.50)	-7.4 (± 0.50)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 [30 Days]
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	Difference (standard error)
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-3.7
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:

[4] - P-value derived from ANCOVA model stratified by investigator site and baseline C-APPS with baseline value as a factor.

Statistical analysis title	Statistical Analysis 2 [60 Days]
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Difference (standard error)
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	-3.6
Variability estimate	Standard error of the mean
Dispersion value	0.59

Notes:

[5] - P-value derived from ANCOVA model stratified by investigator site and baseline C-APPS with baseline value as a factor.

Statistical analysis title	Statistical Analysis 3 [90 Days]
Comparison groups	Placebo v BOTOX

Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference (standard error)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-2.8
Variability estimate	Standard error of the mean
Dispersion value	0.54

Secondary: Percentage of Participants Who Achieved a Rating of Minimal or Mild According to Participant's Self-Assessment Using P-APPS at Maximum Contraction at Days 14

End point title	Percentage of Participants Who Achieved a Rating of Minimal or Mild According to Participant's Self-Assessment Using P-APPS at Maximum Contraction at Days 14

End point description:

The P-APPS evaluates platysma prominence severity and is a single-item measure that is accompanied by a 5-grade photonumeric scale for participants to self-assess the severity of their platysma prominence at maximum contraction, ranging from 1 - Minimal to 5 - Extreme.

End point type	Secondary

End point timeframe:

Day 14

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Percentage of Subjects				
number (confidence interval 95%)	5.2 (1.9 to 8.4)	48.1 (40.7 to 55.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX

Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference (%)
Point estimate	42.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.8
upper limit	51

Notes:

[6] - P-value derived from Cochran-Mantel-Haenszel (CMH) model stratified by investigator site and baseline C-APPS.

Secondary: Percentage of Participants With Responses of "Satisfied" or "Very Satisfied" on the ANLFQ: Satisfaction (Follow-up) Item 5 (Effect of Treatment) at Day 14

End point title	Percentage of Participants With Responses of "Satisfied" or "Very Satisfied" on the ANLFQ: Satisfaction (Follow-up) Item 5 (Effect of Treatment) at Day 14

End point description:

The ANLFQ: Satisfaction scale assesses how satisfied the participants are with the treatment they received for the appearance of their neck and lower face. Item 5 is a verbal descriptor scale ranging from 1 (Very satisfied) to 5 (Very dissatisfied).

End point type	Secondary

End point timeframe:

Day 14

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Percentage of subjects				
number (confidence interval 95%)	11.8 (7.0 to 16.6)	61.2 (54.0 to 68.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference (%)
Point estimate	49.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	40.8
upper limit	58.1

Notes:

[7] - P-value derived from Cochran-Mantel-Haenszel (CMH) model stratified by investigator site and baseline C-APPS.

Secondary: Percentage of Participants With Responses of 'Not at All Bothered' or 'A Little Bothered' on the BAS-PP Scale Item 2 (Jawline) at Day 14

End point title	Percentage of Participants With Responses of 'Not at All Bothered' or 'A Little Bothered' on the BAS-PP Scale Item 2 (Jawline) at Day 14

End point description:

The BAS-PP Scale is a 2-item measure that asks participants to rate how bothered they are by the appearance of their vertical neck bands (Item 1) and jawline (Item 2) where items are rated from 1 (Not at all bothered) to 5 (Extremely bothered).

End point type	Secondary

End point timeframe:

Day 14

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Percentage of Subjects				
number (confidence interval 95%)	20.6 (14.7 to 26.4)	49.4 (42.1 to 56.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference (%)
Point estimate	28.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.4
upper limit	38.2

Notes:

[8] - P-value derived from Cochran-Mantel-Haenszel (CMH) model stratified by investigator site and baseline C-APPS.

Secondary: Percentage of Participants With Responses of 'Not at All Bothered' or 'A Little Bothered' on the BAS-PP Scale Item 1 (Vertical Neck Bands) at Day 14

End point title	Percentage of Participants With Responses of 'Not at All Bothered' or 'A Little Bothered' on the BAS-PP Scale Item 1 (Vertical Neck Bands) at Day 14

End point description:

The BAS-PP Scale is a 2-item measure that asks participants to rate how bothered they are by the appearance of their vertical neck bands (Item 1) and jawline (Item 2) where items are rated from 1 (Not at all bothered) to 5 (Extremely bothered).

End point type	Secondary

End point timeframe:

Day 14

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Percentage of Subjects				
number (confidence interval 95%)	11.9 (7.2 to 16.6)	47.8 (40.5 to 55.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference (%)
Point estimate	35.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.2
upper limit	44.6

Notes:

[9] - P-value derived from Cochran-Mantel-Haenszel (CMH) model stratified by investigator site and baseline C-APPS.

Secondary: Change From Baseline on the ANLFQ: Impacts Summary Score at Day 14

End point title	Change From Baseline on the ANLFQ: Impacts Summary Score at Day 14

End point description:

The ANLFQ: Impacts scale assesses the psychosocial impact of the appearance of the neck and lower face. All items are rated on a 5-point Verbal Descriptor Scale ranging from 1 (Never) to 5 (All of the time), with higher scores indicating greater negative impact from the appearance of the neck and lower face.

End point type	Secondary

End point timeframe:
Day 14

End point values	Placebo	BOTOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	186		
Units: Score on a Scale				
least squares mean (standard error)	-3.0 (± 0.50)	-7.7 (± 0.51)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BOTOX
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	ANCOVA
Parameter estimate	Difference (standard error)
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	-3.7
Variability estimate	Standard error of the mean
Dispersion value	0.54

Notes:

[10] - P-value derived from ANCOVA model stratified by investigator site and baseline C-APPS with baseline value as a factor.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and adverse event tables include events reported from enrollment to end of study. The median time participants were followed was 120 days for both the BOTOX and Placebo treatment groups.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	BOTOX

Reporting group description: -

Serious adverse events	Placebo	BOTOX	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 216 (0.46%)	0 / 208 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
ADNEXA UTERI CYST			
subjects affected / exposed	1 / 216 (0.46%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	BOTOX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 216 (2.78%)	7 / 208 (3.37%)	
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 216 (2.78%)	7 / 208 (3.37%)	
occurrences (all)	6	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2021	Protocol Version 2.0 (Amendment 1) In addition to administrative and clerical edits made to align with current protocol standards/templates, the following edits were included: • Updates to timing of C-APPS and P-APPS evaluations • A gated enrollment strategy was added • COVID-19-related acceptable protocol modifications were deleted for PROs
02 August 2022	Protocol Version 3.0 (Amendment 2) In addition to the correction of minor clerical errors for consistency throughout the protocol, the following changes were included: • Updated Sponsor contact information • Updated supporting information and eligibility criteria related to COVID-19 • Clarified that prohibited medication/treatment listed are prohibitive due to the potential confounding impact to efficacy assessment and not due to any potential safety risk to the subject • Clarified the investigational medicinal product and updated units • Added statement that partner pregnancy information will not be collected • Updated the number of imputation datasets • Updated definition of end-of-study
22 November 2022	Protocol Version 4.0 (Amendment 3) In addition to the correction of minor clerical errors for consistency throughout the protocol, the following changes were included: • Updates and clarifications to endpoints for the US • Reordered endpoints • Updated responder definitions for additional analyses of C-APPS/P-APPS • Updated eligibility criterion 26 • Updates and clarifications to statistical analysis procedures • Updates to safety data overview • Updated confidentiality section per AbbVie standard for studies conducted in EMA

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported