Clinical trial results:
A phase III, multi-center, randomized, double blind, active and placebo control, single dose trial to demonstrate the efficacy and safety of DWP-450 in adult subjects for treatment of moderate-to-severe glabellar lines

Summary

EudraCT number	2014-001063-12
Trial protocol	SE GB DE
Global end of trial date	27 April 2016

Results information

Result version number	v1 (current)
This version publication date	14 June 2017
First version publication date	14 June 2017

Trial information

Trial identification

Sponsor protocol code	EVB-003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Evolus Inc.
Sponsor organisation address	1027 Garden Street, Santa Barbara, United States, CA 93101
Public contact	Regulatory Affairs, Evolus Inc., +1 805 9794125,
Scientific contact	Rui L. Avelar, Evolus Inc., +1 805-689-8668,

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	27 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2016
Global end of trial reached?	Yes
Global end of trial date	27 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the safety and efficacy of DWP-450 purified botulinum neurotoxin, Type A in treatment of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult subjects at maximum frown.

Protection of trial subjects:

Topical anaesthesia was allowed before the intramuscularly injection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 45
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	France: 126
Country: Number of subjects enrolled	Germany: 226
Country: Number of subjects enrolled	Canada: 119
Worldwide total number of subjects	540
EEA total number of subjects	421

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)	500

From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 497 subjects (later increased to 540 subjects) were to be enrolled at approximately 20 study sites.

Pre-assignment

Screening details:

Subjects were selected from a population of stable healthy adults, at least 18 years of age, who had moderate (GLS score=2) or severe (GLS score =3) glabellar lines at maximum frown, as assessed by the Investigator on the 4-point photonumeric Glabellar Line Scale (GLS, 0=no lines, 1=mild, 2=moderate, 3=severe).

Period 1

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

Blinding implementation details:

To maintain blinding at the time of treatment on Day 0, at each study site, on a per subject basis, an appropriate on-site, protocol-trained designated individual – accessed an online tool, the Interactive Web Response System (IWRS), to obtain the kit number for that subject. The IWRS kit identification system ensured that the study randomization schedule at each site was maintained. Each study vial contained DWP-450, BOTOX or Placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	DWP-450 (botulinum toxin type A)

Arm description:

Subjects were injected intramuscularly into the 5 target sites specified in Methodology with 0.1 mL (4 U) for a total of 0.5 mL (20 U).

Arm type	Experimental
Investigational medicinal product name	Botulinum toxin, Type A
Investigational medicinal product code	DWP-450
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Test product vials, each containing 100 units (U) of vacuum-dried DWP-450 (Botulinum Toxin Type A) were reconstituted gently and without shaking with 2.5 mL of 0.9% sterile, non-preserved saline solution for a final dilution of 4 U/0.1 mL. Using a 30 G needle and 1 cc syringe, subjects were injected intramuscularly into the 5 target sites specified in Methodology with 0.1 mL (4 U) for a total of 0.5 mL (20 U).

Arm title	OnabotulinumtoxinA

Arm description:

Study vials were supplied containing 100 U of Botulinum Toxin Type A.

Arm type	Active comparator
Investigational medicinal product name	Botulinum toxin, Type A
Investigational medicinal product code	DWP-450
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Test product vials, each containing 100 units (U) of vacuum-dried DWP-450 (Botulinum Toxin Type A) were reconstituted gently and without shaking with 2.5 mL of 0.9% sterile, non-preserved saline solution for a final dilution of 4 U/0.1 mL. Using a 30 G needle and 1 cc syringe, subjects were injected intramuscularly into the 5 target sites specified in Methodology with 0.1 mL (4 U) for a total of 0.5 mL (20 U).

Arm title	Placebo (0.9% saline)

Arm description:

Placebo vials contained saline only.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	0.9% saline
Pharmaceutical forms	Powder for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo vials contained 0.9% saline only. Using a 30 G needle and 1 cc syringe, subjects were injected intramuscularly into the 5 target sites specified in Methodology

Number of subjects in period 1	DWP-450 (botulinum toxin type A)	OnabotulinumtoxinA	Placebo (0.9% saline)
Started	245	246	49
Completed	239	244	48
Not completed	6	2	1
Unrelated SAE	-	1	-
Lost to follow-up	6	1	1

Baseline characteristics

Reporting groups	
Reporting group title	DWP-450 (botulinum toxin type A)
Reporting group description:	
Subjects were injected intramuscularly into the 5 target sites specified in Methodology with 0.1 mL (4 U) for a total of 0.5 mL (20 U).	
Reporting group title	OnabotulinumtoxinA
Reporting group description:	
Study vials were supplied containing 100 U of Botulinum Toxin Type A.	
Reporting group title	Placebo (0.9% saline)
Reporting group description:	
Placebo vials contained saline only.	

Reporting group values	DWP-450 (botulinum toxin type A)	OnabotulinumtoxinA	Placebo (0.9% saline)
Number of subjects	245	246	49
Age categorical Units: Subjects			
Patients ≥65 years	17	19	4
Patients <65	228	227	45
Gender categorical Units: Subjects			
Female	220	215	41
Male	25	31	8

Reporting group values	Total		
Number of subjects	540		
Age categorical Units: Subjects			
Patients ≥65 years	40		
Patients <65	500		
Gender categorical Units: Subjects			
Female	476		
Male	64		

Subject analysis sets	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-Treat Population (ITT): all subjects who were randomly assigned to receive treatment	
Subject analysis set title	PP analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who were randomized, received the protocol-required treatment (i.e., for placebo, the total amount administered was 0.5 mL of saline; for DWP-450 or BOTOX, the total amount of dose administered was 20U), and had the primary outcome measure assessed on Day 30, without any major protocol deviation.	

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:
all subjects who were randomized and received treatment

Reporting group values	ITT analysis set	PP analysis set	Safety Analysis Set
Number of subjects	540	527	540
Age categorical Units: Subjects			
Patients ≥65 years	40		40
Patients <65	500		500
Gender categorical Units: Subjects			
Female	476		476
Male	64		64

End points

End points reporting groups

Reporting group title	DWP-450 (botulinum toxin type A)
Reporting group description:	
Subjects were injected intramuscularly into the 5 target sites specified in Methodology with 0.1 mL (4 U) for a total of 0.5 mL (20 U).	
Reporting group title	OnabotulinumtoxinA
Reporting group description:	
Study vials were supplied containing 100 U of Botulinum Toxin Type A.	
Reporting group title	Placebo (0.9% saline)
Reporting group description:	
Placebo vials contained saline only.	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-Treat Population (ITT): all subjects who were randomly assigned to receive treatment	
Subject analysis set title	PP analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who were randomized, received the protocol-required treatment (i.e., for placebo, the total amount administered was 0.5 mL of saline; for DWP-450 or BOTOX, the total amount of dose administered was 20U), and had the primary outcome measure assessed on Day 30, without any major protocol deviation.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
all subjects who were randomized and received treatment	

Primary: GLS Score of 0 or 1 at Maximum Frown on Day 30 by IA

End point title	GLS Score of 0 or 1 at Maximum Frown on Day 30 by IA
End point description:	
The primary efficacy endpoint was defined as the proportion of subjects classified as responders on Day 30. For this endpoint, a responder was a subject with a GLS score of 0 or 1, as assessed by the Investigator at maximum frown on Day 30.	
End point type	Primary
End point timeframe:	
Day 30 after injection	

End point values	DWP-450 (botulinum toxin type A)	OnabotulinumtoxinA	Placebo (0.9% saline)	ITT analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	235	244	48	540
Units: responders				
Responders for the Primary Efficacy Endpoint	205	202	2	415

End point values	PP analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	527			
Units: responders				
Responders for the Primary Efficacy Endpoint	409			

Statistical analyses

Statistical analysis title	Statistical Analysis Plan, Final Version 3.0, June

Statistical analysis description:

Tests of superiority for DWP-450 versus Placebo and for OnabotulinumtoxinA versus Placebo for the primary endpoint were to be performed using the unconditional exact test, by inversion of two one-sided tests using standardized statistics [1]. Non-inferiority of DWP-450 versus OnabotulinumtoxinA for the primary endpoint was to be concluded if the lower bound of the two-sided 95% CI for the difference in the proportions of responders in each group was >-0.10 – i.e., >-10.0%.

Comparison groups	DWP-450 (botulinum toxin type A) v OnabotulinumtoxinA v Placebo (0.9% saline)
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	t-test, 2-sided
Parameter estimate	response rate difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
Variability estimate	Standard error of the mean
Dispersion value	3.25

Notes:

[1] - Method : Fisher's exact test for superiority test, and two sided 95% confidence intervals for the non-inferiority evaluation (Wald asymptotic confidence intervals).
Dispersion value : 3.25% for non-inferiority; for superiority 3.61%.
Confidence interval : -1.9%, 10.8% for non-inferiority; for superiority 70.3%, 89.4%.
Non-inferiority for DWP-450 vs OnabotulinumtoxinA; superiority for DWP-450 vs Placebo.

[2] - P-value "< 0.001" is valid for superiority test [2]. A p-value <0.025 was required for each test to conclude that DWP-450 and OnabotulinumtoxinA were each superior to Placebo.
Confidence interval, lower limit : -10%

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from the time the subject signs the informed consent until exit from the study.

Adverse event reporting additional description:

Safety was assessed by the Investigator at all study visits

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	DWP-450 treatment group
Reporting group description: -	
Reporting group title	BOTOX treatment group
Reporting group description: -	
Reporting group title	Placebo treatment group
Reporting group description: -	

Serious adverse events	DWP-450 treatment group	BOTOX treatment group	Placebo treatment group
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 245 (1.22%)	1 / 246 (0.41%)	1 / 49 (2.04%)
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)			
Breast cancer			
subjects affected / exposed	0 / 245 (0.00%)	0 / 246 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve fibroelastoma			
subjects affected / exposed	0 / 245 (0.00%)	1 / 246 (0.41%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Breast reconstruction			
subjects affected / exposed	0 / 245 (0.00%)	0 / 246 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mastectomy			
subjects affected / exposed	0 / 245 (0.00%)	0 / 246 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 245 (0.41%)	0 / 246 (0.00%)	0 / 49 (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
Eye disorders			
Conjunctival cyst			
subjects affected / exposed	1 / 245 (0.41%)	0 / 246 (0.00%)	0 / 49 (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
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 245 (0.41%)	0 / 246 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 246 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DWP-450 treatment group	BOTOX treatment group	Placebo treatment group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 245 (36.33%)	102 / 246 (41.46%)	15 / 49 (30.61%)
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 245 (13.88%)	25 / 246 (10.16%)	7 / 49 (14.29%)
occurrences (all)	38	26	10
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	21 / 245 (8.57%) 21	28 / 246 (11.38%) 28	2 / 49 (4.08%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported