



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 photonic 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) | Onabotulinumt oxinA | 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

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

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|-----------------------|-------------------------|
| 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