



Clinical trial results:

An evaluator-blinded multi-center study of combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster as compared to single treatment with either Azzalure/Dysport alone or Restylane/Emervel filler alone

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001202-17 |
| Trial protocol | SE |
| Global end of trial date | 09 March 2017 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 13 February 2020 |
| First version publication date | 13 February 2020 |
| Summary attachment (see zip file) | Effective and safe repeated full-face treatments with abobotulinumtoxinA, hyaluronic acid filler, and skin boosting hyaluronic acid (Heden.2019.Effective and Safe Repeated Full-Face Treatments With AbobotulinumtoxinA, Hyaluronic Acid Filler, and Skin Boosting Hyaluronic Acid.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 05PDF1401 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02297516 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Galderma/Q-Med AB |
| Sponsor organisation address | Seminariegatan 21, Uppsala, Sweden, 75228 |
| Public contact | Medical Affairs Cecilia Skoglund, Galderma/Q-Med AB, +46 18489 1410, cecilia.skoglund@galderma.com |
| Scientific contact | Medical Affairs Cecilia Skoglund, Galderma/Q-Med AB, +46 18489 1410, cecilia.skoglund@galderma.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 | No |

| |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 March 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate if superior global facial aesthetic appearance can be achieved by combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster compared to single treatment with either Azzalure/Dysport or Restylane/Emervel filler alone

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

N/A

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2014 |
| 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: 17 |
| Country: Number of subjects enrolled | France: 32 |
| Country: Number of subjects enrolled | Brazil: 16 |
| Worldwide total number of subjects | 65 |
| EEA total number of subjects | 49 |

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) | 65 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

First subject first visit: 03 Nov 2014

Last subject last visit: 09 Mar 2017

Pre-assignment

Screening details:

There were five screening failures in this study: nasolabial folds not assessed as mild/moderate (n=3); signs/symptoms of eyelid ptosis/compensatory frontalis muscle activity (n=1); and active skin disease, inflammation or related conditions near/on areas to be treated (n=1).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Assessor ^[1] |

Blinding implementation details:

Independent evaluators (assessors) remained blinded to the treatment arm and to the sequence of subject photographs, i.e. they did not know whether a given photograph was taken after the single or combined treatments.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A - Azzalure/Dysport as single treatment |

Arm description:

Subjects in Group a received treatment with ≤ 125 s.U Azzalure/Dysport as single treatment in upper facial lines (at least two of glabellar lines, crow's feet, and/or forehead lines). At month 6 and 12, both groups received combined treatment consisting of ≤ 125 s.U Azzalure/Dysport in upper facial lines, ≤ 2 mL hyaluronic acid filler in nasolabial folds/cheeks and ≤ 1 mL Restylane Skinbooster. An additional Skinbooster treatment was given at Month 7.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Azzalure/Dysport |
| Investigational medicinal product code | |
| Other name | AbobotulinumtoxinA |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Azzalure was used at the European sites and Dysport at the Brazilian site.

Each vial with 125 s.U of Azzalure powder was reconstituted in 0.63 mL of NaCl 0.9% before injection (10 s.U per 0.05 mL of reconstituted solution).

Each vial with 300 s.U of Dysport powder was reconstituted in 1.5 mL of NaCl 0.9% before injection (10 s.U per 0.05 mL of reconstituted solution).

Group A received Azzalure/Dysport injection of at least two of the following upper facial lines: glabellar lines, crow's feet, and/or forehead lines (maximum dose was 125 s.U). Touch-up treatment was allowed after 2 weeks, with a maximum of 125 s.U Azzalure/Dysport based on Investigator expertise and subject expectations.

| | |
|------------------|--|
| Arm title | Group B - hyaluronic acid filler as single treatment |
|------------------|--|

Arm description:

Subjects in Group B received ≤ 1 mL hyaluronic acid filler in nasolabial folds/cheeks as single treatment. At month 6 and 12, both groups received combined treatment consisting of ≤ 125 s.U Azzalure/Dysport in upper facial lines, ≤ 2 mL hyaluronic acid filler in nasolabial folds/cheeks and ≤ 1 mL Restylane Skinbooster. An additional Skinbooster treatment was given at Month 7.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--|
| Investigational medicinal product name | N/A (medical device) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intradermal use |

Dosage and administration details:

A maximum of 1 mL (one syringe) of Restylane or Emervel filler was administered to nasolabial folds and/or cheeks at initial baseline treatment and a maximum of 2 mL was injected at Month 6 and Month 12.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: An open study designed served the study objectives adequately, but to strengthen the results, independent evaluators (assessors) remained blinded to the treatment arm and to the sequence of subject photographs, i.e. they did not know whether a given photograph was taken after the single or combined treatments.

| Number of subjects in period 1 | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment |
|---------------------------------------|---|---|
| Started | 32 | 33 |
| Single treatment | 32 | 33 |
| First combined treatment | 31 | 31 |
| Second combined treatment | 31 | 30 |
| Completed | 31 | 30 |
| Not completed | 1 | 3 |
| Consent withdrawn by subject | - | 1 |
| Medical reason | 1 | - |
| Exclusion criteria | - | 1 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Group A - Azzalure/Dysport as single treatment |
|-----------------------|--|

Reporting group description:

Subjects in Group a received treatment with ≤ 125 s.U Azzalure/Dysport as single treatment in upper facial lines (at least two of glabellar lines, crow's feet, and/or forehead lines). At month 6 and 12, both groups received combined treatment consisting of ≤ 125 s.U Azzalure/Dysport in upper facial lines, ≤ 2 mL hyaluronic acid filler in nasolabial folds/cheeks and ≤ 1 mL Restylane Skinbooster. An additional Skinbooster treatment was given at Month 7.

| | |
|-----------------------|--|
| Reporting group title | Group B - hyaluronic acid filler as single treatment |
|-----------------------|--|

Reporting group description:

Subjects in Group B received ≤ 1 mL hyaluronic acid filler in nasolabial folds/cheeks as single treatment. At month 6 and 12, both groups received combined treatment consisting of ≤ 125 s.U Azzalure/Dysport in upper facial lines, ≤ 2 mL hyaluronic acid filler in nasolabial folds/cheeks and ≤ 1 mL Restylane Skinbooster. An additional Skinbooster treatment was given at Month 7.

| Reporting group values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | Total |
|---|--|--|-------|
| Number of subjects | 32 | 33 | 65 |
| 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) | 32 | 33 | 65 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 44.5 | 46.0 | |
| full range (min-max) | 35 to 50 | 36 to 50 | - |
| Gender categorical Units: Subjects | | | |
| Female | 31 | 32 | 63 |
| Male | 1 | 1 | 2 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Group A - Azzalure/Dysport as single treatment |
| Reporting group description: Subjects in Group a received treatment with ≤ 125 s.U Azzalure/Dysport as single treatment in upper facial lines (at least two of glabellar lines, crow's feet, and/or forehead lines). At month 6 and 12, both groups received combined treatment consisting of ≤ 125 s.U Azzalure/Dysport in upper facial lines, ≤ 2 mL hyaluronic acid filler in nasolabial folds/cheeks and ≤ 1 mL Restylane Skinbooster. An additional Skinbooster treatment was given at Month 7. | |
| Reporting group title | Group B - hyaluronic acid filler as single treatment |
| Reporting group description: Subjects in Group B received ≤ 1 mL hyaluronic acid filler in nasolabial folds/cheeks as single treatment. At month 6 and 12, both groups received combined treatment consisting of ≤ 125 s.U Azzalure/Dysport in upper facial lines, ≤ 2 mL hyaluronic acid filler in nasolabial folds/cheeks and ≤ 1 mL Restylane Skinbooster. An additional Skinbooster treatment was given at Month 7. | |

Primary: Global facial aesthetic appearance

| | |
|--|------------------------------------|
| End point title | Global facial aesthetic appearance |
| End point description: Percentage of subjects that showed a superior global facial aesthetic appearance after the first combined treatment than after the single treatment as assessed by blinded evaluation of photographs. Primary and secondary endpoints were defined in the CSP version that was approved for use at the French and Brazilian sites, whereas the Swedish amendment of the protocol did not define primary and secondary endpoints. | |
| End point type | Primary |
| End point timeframe: Month 1, Month 7 | |

| End point values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 31 | | |
| Units: Percentage | 67 | 94 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Global facial aesthetic appearance ^[1] |
| Statistical analysis description: Global facial aesthetic appearance was analyzed using a 95% CI for the proportion of subjects for whom the photographs taken 1 month after first combined treatment showed superior global facial aesthetic appearance than the photographs taken after single treatment. This endpoint was considered as a primary endpoint at the Brazilian and French sites; the primary objective was to show that the 95% CI was above 50%. The Swedish amendment of the protocol did not define a primary endpoint. | |
| Comparison groups | Group A - Azzalure/Dysport as single treatment v Group B - hyaluronic acid filler as single treatment |

| | |
|---|---------------------|
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Confidence interval |
| Point estimate | 50 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 50 |

Notes:

[1] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.

Justification: Global facial aesthetic appearance was analyzed using a 95% CI for the proportion of subjects for whom the photographs taken 1 month after first combined treatment showed superior global facial aesthetic appearance than the photographs taken after single treatment. The primary objective was to show that the 95% CI was above 50%, no upper limit was defined.

Other pre-specified: Global facial aesthetic appearance

| | |
|--|------------------------------------|
| End point title | Global facial aesthetic appearance |
| End point description: | |
| Percentage of subjects showing superior global facial aesthetic appearance after single, first combined and second combined treatment. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Month 1, Month 7, Month 13 (one month after each treatment). | |

| End point values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 28 | | |
| Units: percentage | | | | |
| Month 1 | 4 | 4 | | |
| Month 7 | 36 | 36 | | |
| Month 13 | 60 | 61 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Global aesthetic improvement scale - investigator assessment

| | |
|---|--|
| End point title | Global aesthetic improvement scale - investigator assessment |
| End point description: | |
| Percentage of subjects assessed as improved (somewhat improved, much improved, and very much improved) on the Global Aesthetic Improvement Scale (GAIS) by investigators at timepoints Month 1, Month 7 and Month 13, i.e. one month after single treatment, first and second combined treatment. | |
| End point type | Other pre-specified |

End point timeframe:

Month 1, Month 7, Month 13

| End point values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 33 | | |
| Units: Percentage | | | | |
| Month 1 | 100 | 91 | | |
| Month 7 | 100 | 100 | | |
| Month 13 | 100 | 100 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subject satisfaction with facial appearance

End point title Subject satisfaction with facial appearance

End point description:

The subjects were asked to answer the question "How satisfied are you today with the appearance of your face?" with "Very/somewhat satisfied", "neither/nor", or "Very/somewhat dissatisfied". Satisfied criteria was fulfilled for those subjects that answered "Very/somewhat satisfied".

End point type Other pre-specified

End point timeframe:

Baseline, Month 1, Month 7, Month 13

| End point values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 33 | | |
| Units: Percentage | | | | |
| Month 1 | 87 | 64 | | |
| Month 7 | 100 | 94 | | |
| Month 13 | 97 | 100 | | |
| Baseline | 31 | 36 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Wrinkle severity glabellar lines at rest - investigator assessment

| | |
|-----------------|--|
| End point title | Wrinkle severity glabellar lines at rest - investigator assessment |
|-----------------|--|

End point description:

The wrinkle severity of Azzalure/Dysport treated glabellar lines at rest was evaluated by the investigator at all visits. A validated 5-grade photonic grading scale was used, where each severity grade was illustrated by a set of photographs.

0 = no glabella lines

1 = mild glabella lines

2 = moderate glabella lines

3 = severe glabella lines

4 = very severe glabella lines

Improvement was defined as going from a higher score to a lower score.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Months 7, 13

| End point values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 31 | | |
| Units: Percentage | | | | |
| Month 7 | 71 | 74 | | |
| Month 13 | 73 | 66 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Wrinkle severity glabellar lines at maximum frown - investigator assessment

| | |
|-----------------|---|
| End point title | Wrinkle severity glabellar lines at maximum frown - investigator assessment |
|-----------------|---|

End point description:

The wrinkle severity of Azzalure/Dysport treated glabellar lines at maximum frown was evaluated by the investigator at all visits. A validated 5-grade photonic grading scale was used, where each severity grade was illustrated by a set of photographs.

0 = no glabella lines

1 = mild glabella lines

2 = moderate glabella lines

3 = severe glabella lines

4 = very severe glabella lines

Improvement was defined as going from a higher score to a lower score.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Months 7, 13

| End point values | Group A - Azzalure/Dysport as single treatment | Group B - hyaluronic acid filler as single treatment | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 31 | | |
| Units: Percentage | | | | |
| Month 7 | 100 | 100 | | |
| Month 13 | 100 | 100 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 years, 4 months, 6 days (first enrolment - last completed).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Group A after single treatment with Azzalure/Dysport |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--------------------------------|
| Reporting group title | After single treatment Group B |
|-----------------------|--------------------------------|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | After first combination treatment - all subjects |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|---|
| Reporting group title | After second combination treatment - all subjects |
|-----------------------|---|

Reporting group description: -

| Serious adverse events | Group A after single treatment with Azzalure/Dysport | After single treatment Group B | After first combination treatment - all subjects |
|---|---|--------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 33 (3.03%) | 0 / 62 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | Additional description: The subject had cholecystitis of severe intensity, and was hospitalized from 09 Apr 2015 to 15 Apr 2015. The cholecystitis was treated pharmacologically and the subject also had an endoscopic retrograde cholangio-pancreatography. | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 33 (3.03%) | 0 / 62 (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 |

| Serious adverse events | After second combination treatment - all subjects | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|---|--|--|
| Cholecystitis | Additional description: The subject had cholecystitis of severe intensity, and was hospitalized from 09 Apr 2015 to 15 Apr 2015. The cholecystitis was treated pharmacologically and the subject also had an endoscopic retrograde cholangio-pancreatography. | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Group A after single treatment with Azzalure/Dysport | After single treatment Group B | After first combination treatment - all subjects |
|---|--|--------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 32 (15.63%) | 3 / 33 (9.09%) | 22 / 62 (35.48%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 1 / 33 (3.03%) | 4 / 62 (6.45%) |
| occurrences (all) | 3 | 1 | 4 |
| General disorders and administration site conditions | | | |
| Implant site bruising | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 3 / 33 (9.09%) | 15 / 62 (24.19%) |
| occurrences (all) | 0 | 3 | 15 |
| Implant site swelling | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 33 (0.00%) | 3 / 62 (4.84%) |
| occurrences (all) | 0 | 0 | 3 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 33 (0.00%) | 0 / 62 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| Non-serious adverse events | After second combination treatment - all subjects | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 61 (24.59%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|------------------|--|--|
| General disorders and administration site conditions | | | |
| Implant site bruising | | | |
| subjects affected / exposed | 14 / 61 (22.95%) | | |
| occurrences (all) | 14 | | |
| Implant site swelling | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |

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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31334927>