



Clinical trial results:

A randomized, evaluator-blinded, comparative study to evaluate the efficacy and safety of different injection volumes of botulinum toxin type A, Azzalure®, in the glabellar lines.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-004646-42 |
| Trial protocol | SE |
| Global end of trial date | 01 December 2014 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 06 February 2020 |
| First version publication date | 06 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 05PF1311 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Q-Med AB |
| Sponsor organisation address | Seminariegatan 21, Uppsala, Sweden, SE-752 28 |
| Public contact | Head of Medical Affairs, Q-Med AB, +46 184749000, info.q-med@galderma.com |
| Scientific contact | Head of Medical Affairs, Q-Med AB, +46 184749000, info.q-med@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 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 September 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the compound muscle action potential (CMAP) using electroneurography
- To assess the severity of glabellar lines, live and from photographs and video, at rest and at maximum frown
- To assess the subject's satisfaction with the treatment by using the Subject Satisfaction Questionnaire
- To evaluate the subjects experience of onset of effect by response to the question "Since being injected, have you noticed any effect on the appearance of your glabellar lines?"
- To evaluate the safety of two different injection volumes of Azzalure® in the glabellar lines by collecting Adverse Events
- To evaluate the subjects pain on injection using the Visual Analogue Scale

Protection of trial subjects:

As required by the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 10 April 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: 62 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 62 |

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) | 62 |

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

Subject disposition

Recruitment

Recruitment details:

The first subject was recruited 10-Apr-2014 and the last subject on 21-May-2014.

Pre-assignment

Screening details:

84 subjects screened. 22 subjects not included due to glabellar lines at rest outside of grade 2-3 (11), previous medical history/physical examination findings/other conditions that made them unsuitable (6), signs and symptoms of eyelid ptosis (3), previous botulinum toxin treatment (1), withdrawn consent (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 | Subject |

Blinding implementation details:

A blinded evaluator assessed primary efficacy endpoints in this study.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A - Azzalure recommended reconstitution volume |

Arm description:

Subjects in this arm received Azzalure treatment according to label:

Dilution volume: 0.63ml NaCl

Dose: 5 injections of 0.05ml/injection point, total dose 50 sU

| | |
|--|-----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Azzalure |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Dilution volume: 0.63ml NaCl

Dose: 5 injections of 0.05ml/injection point, total dose 50 sU (labeled injection volume)

One administration at baseline (blinded), and one optional (unblinded) at the last study visit 6 months after baseline.

| | |
|------------------|--|
| Arm title | Group B - two-fold recommended reconstitution volume |
|------------------|--|

Arm description:

Subjects in this arm received Azzalure treatment with twice-fold the labeled dilution volume:

Dilution volume: 1.25ml NaCl

Dose: 5 injections of 0.1ml/injection point, total dose 50 sU

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

Dosage and administration details:

Dilution volume: 1.25ml NaCl

Dose: 5 injections of 0.1ml/injection point, total dose 50 sU (twice-fold the labeled injection volume)

One administration at baseline (blinded), and one optional (unblinded) at the last study visit 6 months after baseline.

| Number of subjects in period 1 | Group A - Azzalure recommended reconstitution volume | Group B - two-fold recommended reconstitution volume |
|---------------------------------------|---|---|
| Started | 30 | 32 |
| Completed | 30 | 32 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Group A - Azzalure recommended reconstitution volume |
|-----------------------|--|

Reporting group description:

Subjects in this arm received Azzalure treatment according to label:

Dilution volume: 0.63ml NaCl

Dose: 5 injections of 0.05ml/injection point, total dose 50 sU

| | |
|-----------------------|--|
| Reporting group title | Group B - two-fold recommended reconstitution volume |
|-----------------------|--|

Reporting group description:

Subjects in this arm received Azzalure treatment with twice-fold the labeled dilution volume:

Dilution volume: 1.25ml NaCl

Dose: 5 injections of 0.1ml/injection point, total dose 50 sU

| Reporting group values | Group A - Azzalure recommended reconstitution volume | Group B - two-fold recommended reconstitution volume | Total |
|--|--|--|-------|
| Number of subjects | 30 | 32 | 62 |
| 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) | 30 | 32 | 62 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 50.5 | 49 | |
| full range (min-max) | 30 to 63 | 38 to 58 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 30 | 32 | 62 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Group A - Azzalure recommended reconstitution volume |
| Reporting group description: Subjects in this arm received Azzalure treatment according to label: Dilution volume: 0.63ml NaCl Dose: 5 injections of 0.05ml/injection point, total dose 50 sU | |
| Reporting group title | Group B - two-fold recommended reconstitution volume |
| Reporting group description: Subjects in this arm received Azzalure treatment with twice-fold the labeled dilution volume: Dilution volume: 1.25ml NaCl Dose: 5 injections of 0.1ml/injection point, total dose 50 sU | |

Primary: Percentage of subjects with improved wrinkle severity - dynamic

| | |
|---|---|
| End point title | Percentage of subjects with improved wrinkle severity - dynamic |
| End point description: The severity of the subject's glabellar lines at maximum frown (dynamic) was assessed live at all visits. A 5-graded validated Scale for Glabella lines were used. A wrinkle was defined as improved if a one-grade decrease on the scale was achieved. | |
| End point type | Primary |
| End point timeframe: 1, 3, 7, and 14 days, and 1, 3, 4, and 6 months | |

| End point values | Group A - Azzalure recommended reconstitution volume | Group B - two-fold recommended reconstitution volume | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 1 | 50 | 53.1 | | |
| Day 3 | 76.7 | 93.8 | | |
| Day 7 | 93.3 | 93.8 | | |
| Day 14 | 96.7 | 96.9 | | |
| Month 1 | 96.7 | 100 | | |
| Month 3 | 70 | 90.3 | | |
| Month 4 | 58.6 | 67.7 | | |
| Month 6 | 17.2 | 28.1 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Comparison of groups at Month 1 |
| Comparison groups | Group A - Azzalure recommended reconstitution volume v Group B - two-fold recommended reconstitution volume |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

Primary: Percentage of subjects with improved wrinkle severity - at rest

| | |
|---|---|
| End point title | Percentage of subjects with improved wrinkle severity - at rest |
| End point description: The severity of the subject's glabellar lines at rest was assessed live at all visits. A 5-graded validated Scale for Glabella lines was used. A wrinkle was defined as improved if a one-grade decrease on the scale was achieved. | |
| End point type | Primary |
| End point timeframe: 1, 3, 7, and 14 days, and 1, 3, 4, and 6 months | |

| End point values | Group A - Azzalure recommended reconstitution volume | Group B - two- fold recommended reconstitution volume | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 1 | 20 | 28.1 | | |
| Day 3 | 66.7 | 84.4 | | |
| Day 7 | 76.7 | 90.6 | | |
| Day 14 | 83.3 | 96.9 | | |
| Month 1 | 100 | 96.8 | | |
| Month 3 | 86.7 | 93.5 | | |
| Month 4 | 62.1 | 80.6 | | |
| Month 6 | 55.2 | 59.4 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Comparison of groups at Month 1 |
| Comparison groups | Group A - Azzalure recommended reconstitution volume v Group B - two-fold recommended reconstitution volume |

| | |
|---|---------------|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.492 |
| Method | Fisher exact |

Secondary: Compound Muscle Action Potential

| | |
|---|----------------------------------|
| End point title | Compound Muscle Action Potential |
| End point description: Compound Muscle Action Potential (CMAP) was measured separately for each corrugator supercilii muscle in the forehead using electroneurography in subjects (n= 31) at one of the study sites. Surface recording over the corrugator supercilii muscles examined the degree of contraction measured in millivolts. CMAP values are presented as percentage of baseline values (mean of left side and right side values per subject). | |
| End point type | Secondary |
| End point timeframe: Measurements were made at baseline (pre-treatment) and also at Day 1, Day 3, Day 7, Month 1, Month 3, and Month 6. | |

| End point values | Group A - Azzalure recommended reconstitution volume | Group B - two-fold recommended reconstitution volume | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 ^[1] | 16 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 1 | 79.5 | 69.5 | | |
| Day 3 | 54.8 | 44.1 | | |
| Day 7 | 42.2 | 32.6 | | |
| Month 1 | 34.5 | 24.9 | | |
| Month 3 | 40.4 | 35.4 | | |
| Month 6 | 59.7 | 51.6 | | |

Notes:

[1] - At Month 6, 14 subjects in this group were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject experience of onset of effect

| | |
|--|---------------------------------------|
| End point title | Subject experience of onset of effect |
| End point description: The subjects were asked at Day 1 and onwards (until their response was Yes) if they had noticed any effects on the appearance of their glabellar lines since the injections. Reported results are percentage of subjects answering Yes on corresponding Day. | |
| End point type | Secondary |

End point timeframe:

1, 3, 7, and 14 days.

| End point values | Group A - Azzalure recommended reconstitution volume | Group B - two- fold recommended reconstitution volume | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 1 | 30 | 28.1 | | |
| Day 3 | 46.7 | 65.6 | | |
| Day 7 | 23.3 | 6.3 | | |
| Day 14 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects satisfied with aesthetic outcome

| | |
|-----------------|---|
| End point title | Percentage of subjects satisfied with aesthetic outcome |
|-----------------|---|

End point description:

The subjects were asked at the Month 1, Month 3 and Month 6 visits: 'How satisfied are you with the aesthetic outcome of the injected area?', and chose between Very satisfied/Satisfied/Neutral/Dissatisfied/Very dissatisfied. Results are presented as percentage of subjects answering 'Very satisfied' or 'Satisfied', at the pre-specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 1, Month 3, Month 6

| End point values | Group A - Azzalure recommended reconstitution volume | Group B - two- fold recommended reconstitution volume | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 ^[2] | 32 ^[3] | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Month 1 | 93 | 88 | | |
| Month 3 | 90 | 87 | | |
| Month 6 | 86 | 78 | | |

Notes:

[2] - 29 subjects at Month 6

[3] - 31 subjects at Month 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of pain on Visual Analogue Scale

| | |
|-----------------|---|
| End point title | Assessment of pain on Visual Analogue Scale |
|-----------------|---|

End point description:

Injection pain was assessed both immediately and 10 minutes after injection. The pain was assessed by a 100-mm visual analog scale (VAS) where 0 mm was defined as "no pain" and 100 mm as "the worst pain imaginable."

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Immediately (0 minutes) and 10 minutes after injection.

| End point values | Group A - Azzalure recommended reconstitution volume | Group B - two- fold recommended reconstitution volume | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0 minutes | 7.0 (± 5.9) | 6.9 (± 7.8) | | |
| 10 minutes | 3.3 (± 6.0) | 4.3 (± 5.3) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

7 months, 1 week (first enrolment - last completed)

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Group A - Azzalure recommended reconstitution volume |
|-----------------------|--|

Reporting group description:

Subjects in this arm received Azzalure treatment according to label:

Dilution volume: 0.63ml NaCl

Dose: 5 injections of 0.05ml/injection point, total dose 50 sU

| | |
|-----------------------|--|
| Reporting group title | Group B - two-fold recommended reconstitution volume |
|-----------------------|--|

Reporting group description:

Subjects in this arm received Azzalure treatment with twice-fold the labeled dilution volume:

Dilution volume: 1.25ml NaCl

Dose: 5 injections of 0.1ml/injection point, total dose 50 sU

| Serious adverse events | Group A - Azzalure recommended reconstitution volume | Group B - two-fold recommended reconstitution volume | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 32 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Group A - Azzalure recommended reconstitution volume | Group B - two-fold recommended reconstitution volume | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 30 (26.67%) | 7 / 32 (21.88%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 4 / 32 (12.50%) | |
| occurrences (all) | 2 | 4 | |
| Tension headache | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 32 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 32 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 0 / 30 (0.00%) 0 | 1 / 32 (3.13%) 1 2 / 32 (6.25%) 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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27399956>