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