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 photonumeric grading scale was used, where each severity grade was illustrated by as 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 photonumeric grading scale was used, where each severity grade was illustrated by as 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