Clinical Study Synopsis for Public Disclosure

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2 SYNOPSIS

NAME OF COMPANY: Galderma R&D		***For regulatory use only***
NAME OF FINISHED MEDICINAL PRODUCT: Azzalure®		
NAME OF ACTIVE INGREDIENT: *Clostridium botulinum* type A toxin-haemagglutinin complex		
Title of study:	A multi-centre, randomised, double-blind, placebo-controlled, parallel-group study of CD07743 for the improvement of lateral canthal lines (crow's feet)	

Study centres: 13 centres, 4 in France, 7 in Germany, and 2 in the United Kingdom (UK)

Clinical phase: Phase 3

Study period

- Date of first subject screened: 26 January 2011
- Date of last subject completed (Part A): 31 August 2011
- Safety data collected up to 7 September 2011
- Date of last subject completed (Part B): 02 May 2012

Study objectives

The primary (efficacy) objectives of the study were:

- To determine the efficacy of Azzalure® (30 speywood Units [s.U.]/Lateral Canthal area [LCA]) in the improvement, from baseline to Week 4, of moderate to severe lateral canthal lines "at maximum smile" compared with placebo.
- To determine the duration of effect, by comparing the efficacy of Azzalure® in the improvement of moderate to severe lateral canthal lines "at maximum smile" with placebo at Week 8, 12 and 16.

The key secondary objective of the study was:

- To determine the subjects' level of satisfaction with the appearance of their lateral canthal lines following treatment with Azzalure® compared with placebo at Week 4 and similarly up to Week 16.

Other secondary objectives were:

- To determine the efficacy of Azzalure® in the improvement of lateral canthal lines "at rest" compared with placebo at Week 4, and similarly up to Week 16.
- To determine the safety of Azzalure®:
  - compared to placebo when used for the improvement of moderate to severe lateral canthal lines up to 12 weeks, as assessed by blinded evaluator.
  - following repeated administration when used for improvement of moderate to severe lateral canthal lines for up to 1 year.
  - when used concomitantly for improvement of moderate to severe lateral canthal lines and glabellar lines.
- To evaluate the incidence of antibody response.

The periods over which these primary and secondary efficacy and safety objectives applied are depicted in Figure 1.

Figure 1 Efficacy and safety objectives in Part A and Part B

<table>
<tr><td>1st treatment</td><td colspan="3">No retreatment for lateral canthal lines</td><td colspan="4">Optional repeated treatment in lateral canthal lines ± glabellar lines</td><td>Last follow-up</td></tr>
<tr><td>Visit 2
Baseline</td><td>Visit 3
2 weeks</td><td>Visit 4
4 weeks</td><td>Visit 5
8 weeks</td><td>Visit 6
12 weeks</td><td>Visit 7
16 weeks</td><td>Visit 8
24 weeks</td><td>Visit 9
36 weeks</td><td>Visit 10
48 weeks</td><td>Visit 11
52 weeks or early termination visit</td></tr>
<tr><td colspan="5">Efficacy in lateral canthal lines vs. placebo (Part A)
<----------></td><td colspan="5">[a]</td></tr>
<tr><td colspan="4">Safety in lateral canthal lines vs. placebo (Part A)
<----------></td><td colspan="6">Safety of repeated treatment in lateral canthal lines (Part B)
Safety of treatment used concomitantly for:
lateral canthal lines and glabellar lines (Part B)
<----------></td></tr>
</table>

[a] There were no efficacy objectives for Part B, but descriptive efficacy data on observed cases are presented in the report.

Study design

This was a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study comprising two successive parts for each subject. The same population of subjects was to be used for both Parts A and B.

- Part A: Subjects who satisfied the inclusion/exclusion criteria were randomised in a 3:1 ratio to either Azzalure® or placebo in Part A; this first part evaluated the efficacy, safety and duration of effect of Azzalure® (30 s.U./LCA) and the subjects' level of satisfaction with the improvement of their lateral canthal lines.
- Part B: From Week 12, retreatment was allowed for all subjects and defined the start of Part B, during which all subjects could receive active treatment in lateral canthal lines (30 s.U./LCA, total dose 60 s.U.) and in glabellar lines (50 s.U.), if indicated. Each subject could receive a maximum of four cycles of active treatment, and was to be followed for up to the 12 months duration of the study. This second part of the study evaluated safety, with repeated administrations of Azzalure® for the improvement of lateral canthal lines, and also the safety profile of Azzalure® when used concomitantly for the improvement of moderate to severe lateral canthal lines and glabellar lines.

Total number of subjects

A total of 343 subjects were screened and 335 were randomised in a 3:1 ratio to receive Azzalure® (N=252) or placebo (N=83) in a total of 13 centres from 3 countries (7 in Germany, 4 in France and 2 in the UK). Of these 343 subjects, 335 comprised the Safety and Intent-to-Treat (ITT) populations and 325 (97.0%) subjects were included in the Per-protocol (PP) population.

Diagnosis and key inclusion and non-inclusion criteria

- Key inclusion criteria: Male or female subjects, aged 18 – 65 years, with moderate or severe (grade 2 or 3) lateral canthal lines "at maximum smile" and mild to severe (grade 1, 2 or 3) lateral canthal lines "at rest" determined by investigator at Screening and Baseline.
- Key non-inclusion criteria: Prior treatment with botulinum toxin, prior surgery affecting the orbicularis oculi muscle, prior blepharoplasty or brow lift, or any prior cosmetic procedures or scars that would have interfered with the evaluation by the investigator.

Description and usage of test product

Characteristics	Investigational Product
Trade Name or equivalent	Azzalure®
Name of Drug Substance (INN)	Botulinum toxin type A
Internal code *(if applicable)*	CD07743
Pharmaceutical Form	Powder for solution for injections
Concentration	125 s.U. per vial
Packaging (type and size)	Vials of 125 s.U.
Storage Conditions	Stored in a refrigerator (2°C - 8°C). After reconstitution, immediate use was recommended NOT TO BE FROZEN
Dosage	60 to 110 s.U. (10 s.U. per injection site)
Dose regimen	
Route	Intramuscular
Frequency and duration of administration	Maximum of 5 cycles of treatment over the year, if applicable (1 cycle during Part A & 4 cycles during Part B)
Location of treated area	Lateral canthal lines and glabellar lines if indicated
Batch numbers	810E

Reference therapy, dose of administration, batch number(s):

Placebo was presented in identical vials and, during Part A only, was administered in exactly the same manner as the active product. Placebo was not administered in Part B.

Batch numbers: 101001F

Efficacy assessment

Efficacy evaluations: Throughout the study, efficacy assessments for each subject were performed by the investigator and subject, using a relevant 4-point scale.

Primary efficacy criterion:

- The proportion of responders at Week 4 based on severity of lateral canthal lines “at maximum smile”.
- Additionally, in order to assess the durability of the effect, the proportion of responders at each week up to Week 16 was determined.

Secondary efficacy criteria:

- Number and proportion of subjects with each satisfaction grading for the appearance of their lateral canthal lines at all time points.
- Proportion of subjects with a severity of lateral canthal lines "at rest" improved by at least 1 point, as assessed by the investigator.

Maximum smile was achieved by asking the subject to smile as naturally as possible with their eyes open, and with the mouth open or closed.

Safety assessment:

Safety was evaluated by the reporting of adverse events (AEs) at Baseline and each visit.

A blood sample for antibody testing was taken at Baseline and Last Follow-up visit (or Early Termination visit).

Vital signs and/or physical examination were evaluated at Screening, Baseline, all visits from Week 12 (only before each injection if retreatment was indicated) and Last Follow-up visit.

Standardised photographs:

With the subject's agreement at selected sites at Baseline, Week 4 (Visit 4) and each following visit, standardised photographs were taken of the subject's lateral canthal lines "at rest" and "at maximum smile" using identical camera equipment, conditions and settings. Study photographs were not used to assess efficacy, and were used to illustrate the effect of the products for scientific publication or medical communication.

Principal statistical methods

Primary efficacy analysis: the primary efficacy analysis was based on an ITT population, i.e. all subjects randomised and having received treatment. The primary criterion for efficacy was the proportion of responders at Week 4 based on severity of lateral canthal lines "at maximum smile". A positive response (responder) was defined as a grade of 0 or 1 (none or mild), as assessed by the investigator. Responder rates were analysed by the two-sided Mantel-Haenszel (MH) test, using general association (FREQ procedure from SAS).

To assess the durability of the effect, the proportion of responders at each week up to Week 16 was determined. To control for multiplicity, a sequential step-up analysis was performed at each subsequent time point until Week 16 (in increasing order). If the test versus vehicle was significant at the 0.05 two-sided level at a visit, the statistical test was repeated at the subsequent visit, and so on until Week 16. If a subject was retreated at Week 12 then this was considered as failure in the analysis of Week 16. To assess the coherence of results among centres, the Breslow-Day test was used. A supportive analysis for the primary efficacy endpoint was also performed on the PP population.

Secondary efficacy analyses: The distribution of subjects' level of satisfaction with the appearance of their lateral canthal lines was also analysed using the MH test after ridit transformation. The proportion of subjects with a severity of lateral canthal lines at rest which had improved by at least 1 point, as assessed by investigator was analysed in a similar way to the primary endpoint.

In efficacy analyses of the primary and key secondary endpoints of the blinded comparative phase, subjects that had retreatment at Week 12 were considered as failures at Week 16, by imputing the worst grade of each corresponding scale.

Safety:

Safety analysis was performed on the Safety population. The incidence of AEs was summarised by 12-week periods for subjects still at risk (0 to 12 weeks, 12 to 24 weeks, 24 to 36 weeks and above 36 weeks, based on the AE onset date). Summaries were presented by System Organ Class (SOC) and Preferred term (PT), based on the Medical Dictionary for Regulatory Activities (MedDRA v13.0). Additional summary tables were provided for AEs that were considered serious (SAEs), related to the study drug, of special interest, and leading to discontinuation.

Results:

- **Demographics and baseline characteristics**

Table 1 Demographic data (ITT population)

	Azzalure®	Placebo	Total
Age (years)			
N	252	83	335
Mean ± SD	48.5 ± 8.6	49.3 ± 8.1	48.7 ± 8.5
Median	48.0	50.0	49.0
Range	25-65	31-65	25-65
Q1 – Q3	43-56	44-54	43-55
Gender, n (%)			
Female	234 (92.9)	74 (89.2)	308 (91.9)
Male	18 (7.1)	9 (10.8)	27 (8.1)
Race, n (%)			
Caucasian	249 (98.8)	83 (100.0)	332 (99.1)
Hispanic	1 (0.4)	0	1 (0.3)
Other	2 (0.8)	0	2 (0.6)

Source Data: Section 14, Table 14.1.4. Abbreviations: Q1, lower quartile; Q3, upper quartile

In the ITT population, the overall mean (±SD) age was 48.7 (±8.5) years, with a minimum of 25 years and a maximum age of 65 years. Most subjects were female (308/335, 91.9%) and almost all were Caucasian (332/335, 99.1%). Overall, at Baseline, both treatment groups were comparable with respect to gender, age, race distribution. See Table 1.

Table 2 Baseline characteristics (ITT population)

		Number (%) Subjects	
		Azzalure®	Placebo
		N=252	N=83
Severity of lateral canthal lines at maximum smile	2 – Moderate	94 (37.3)	30 (36.1)
	3 – Severe	158 (62.7)	53 (63.9)
Severity of lateral canthal lines at rest	1 – Mild	73 (29.0)	21 (25.3)
	2 – Moderate	135 (53.6)	47 (56.6)
	3 – Severe	44 (17.5)	15 (18.1)
Subject's level of satisfaction with appearance of their lateral canthal lines	1 – Satisfied	2 (0.8)	0 (0)
	2 – Dissatisfied	175 (69.4)	54 (65.1)
	3 – Very dissatisfied	75 (29.8)	29 (34.9)

Source Data: Section 14, Table 14.2.1.1

All subjects had a baseline score of severity of lateral canthal lines assessed as moderate or severe at maximum smile, as specified by the inclusion criteria. For each type of score, the distributions were similar in both treatment groups.

Almost all subjects were not satisfied with the appearance of their lateral canthal lines at Baseline: 99.2% of subjects in the Azzalure® group and 100% in the placebo group. See Table 2.

- **Efficacy**
  - Primary efficacy criterion:

At Week 4, there was a significant treatment difference in the severity of lateral canthal lines at maximum smile in favour of Azzalure® compared to placebo ($p<0.001$) for the ITT population. The observed responder rates were 47.2% for Azzalure® and 7.2% for placebo. See Table 3.

When responders at Week 4 were compared by age (≤50 years and ≥51 years), in both groups the responder rate was higher in the subjects treated with Azzalure® compared with those treated with placebo: 58.7% vs. 12.5%, respectively (≤50 years) and 30.4% vs. 0%, respectively (≥51 years).

Table 3 Responder rates on the severity of lateral canthal lines at maximum smile assessed by the investigator at Week 4 - ITT population

		Number (%) Subjects			P-value
		Azzalure®	Placebo	Total	
Visit 4 – 4 weeks after Baseline	N	252	83	335	
	Success (responder, 0, 1)	119 (47.2)	6 (7.2)	125 (37.3)	MH test: <0.001 Breslow Day: 0.602
	Failure (non-responder 2, 3)	133 (52.8)	77 (92.8)	210 (62.7)	

Source Data: Section 14, Table 14.2.2.1

Abbreviation: MH, Mantel Haenszel test

Breslow-Day tests for homogeneity of the odds ratios were used to assess the coherence of results among centres.

A responder is defined as a subject with mild or no lateral canthal lines at the specified week after baseline (score of 1 or 0)

Duration of treatment effect

For the ITT population, the difference that was observed at Week 4, was sustained up to Week 12 (p=0.001). Most subjects were retreated at Week 12 and then were imputed as a failure at Week 16: 191 subjects (75.8%) in the Azzalure® group and 73 (87.9%) in the placebo group. Thus, at Week 16, there was no significant difference between the two groups (p=0.249). See Table 4.

Table 4 Responder rates on the severity of lateral canthal lines at maximum smile assessed by the investigator (Part A) - ITT population

		Number (%) Subjects			P-value
		Azzalure®	Placebo	Total	
Visit 2 – Baseline	N	252	83	335	–
	2 – Moderate	94 (37.3)	30 (36.1)	124 (37.0)	–
	3 - Severe	158 (62.7)	53 (63.9)	211 (63.0)	–
Visit 4 – 4 weeks after Baseline	N	252	83	335	
	Success (responder, 0, 1)	119 (47.2)	6 (7.2)	125 (37.3)	MH test: <0.001 Breslow Day: 0.602
	Failure (non-responder 2, 3)	133 (52.8)	77 (92.8)	210 (62.7)	
Visit 5 – 8 weeks after Baseline	N	252	83	335	
	Success (responder, 0, 1)	95 (37.7)	4 (4.8)	99 (29.6)	MH test: <0.001 Breslow Day: 0.629
	Failure (non-responder 2, 3)	157 (62.3)	79 (95.2)	236 (70.4)	
Visit 6 – 12 weeks after Baseline	N	252	83	335	
	Success (responder, 0, 1)	29 (11.5)	0 (0)	29 (8.7)	MH test: 0.001
	Failure (non-responder 2, 3)	223 (88.5)	83 (100.0)	306 (91.3)	
Visit 7 – 16 weeks after Baseline[a]	N	252	83	335	
	Success (responder, 0, 1)	4 (1.6)	0 (0)	4 (1.2)	MH test: 0.249
	Failure (non-responder 2, 3)	248 (98.4)	83 (100.0)	331 (98.8)	

Source Data: Section 14, Table 14.2.2.1

Abbreviation: MH, Mantel Haenszel test

Breslow-Day tests for homogeneity of the odds ratios were used to assess the coherence of results among centres.

A responder is defined as a subject with mild or no lateral canthal lines at the specified week after baseline (score of 1 or 0)

[a] Subjects imputed as failure at Week 16 if retreated at Week 12.

- Secondary efficacy criteria

Regarding the key secondary efficacy criterion, subjects' level of satisfaction with the appearance of their lateral canthal lines following treatment, at Week 4 there was a statistically significant difference between the two treatments ($p<0.001$) in the ITT population, with 65.5% of subjects in the Azzalure® group Satisfied or Very Satisfied compared to only 16.9% in the placebo group. A similar benefit in favour of Azzalure® was seen at Week 4 with the PP population ($p<0.001$). Between-group differences in terms of distribution were sustained until Week 16 ($p=0.010$).

As for the primary criterion, there was a significant difference between the two groups at Week 4 in change in severity of lateral canthal lines at rest ($p<0.001$): 68.3% (172/252) subjects improved by at least 1 point compared to Baseline in the Azzalure® group versus 14.5% (12/83) subjects in the placebo group. This difference was sustained through to Week 12 ($p<0.001$). At Week 16, there was no significant difference between the two groups ($p=0.885$).

Subgroup analyses reflected the results obtained with patients overall. There was a trend towards higher responder rates in subjects aged ≤50 years than in those aged ≥51 years; this difference in favour of the younger age group was also apparent for the distribution and shift of severity of lateral canthal lines at maximum smile.

- **Safety**

The schedule for reporting the incidence of AEs was based on 12-week periods for subjects still at risk (participating to the study for the following quarters: 0 to 12 weeks, 12 to 24 weeks, 24 to 36 weeks and above 36 weeks, based on the AE onset date). Safety data of Part A are presented with the first quarter (0 to 12 Weeks, cut-off date defined at D84) and safety data of Part B are presented throughout the 3 following quarters (12 to 24 weeks, 24 to 36 weeks and above 36 weeks).

The protocol stated that subjects should not be retreated before Week-12 (specified as Day 84 ± 7 days, i.e. not before Day 77 in the protocol). A total of 67 subjects were retreated before Day 84, but only 2 were inadvertently retreated before Day 77 (one subject in the Azzalure® group on Day 60 and one in the placebo group on Day 71). The Part A safety database therefore contains data from these 67 subjects who were retreated before the cut-off.

Extent of exposure

A total of 335 subjects were randomized in Part A to receive the first injection at baseline (active or placebo). Then, 315 of them participated in Part B with 293 subjects followed up to Week 48 and 288 followed for one year. At the beginning of Part B, 307 of the 315 (97.5%) subjects were concomitantly treated with Azzalure® in the lateral canthal and glabellar lines.

The mean number of cycles of treatment for lateral canthal lines was 3.6 cycles in the Azzalure® group and 3.7 cycles in the placebo group (with the first cycle being placebo, and subsequent cycles being with Azzalure®). Overall, subjects received 2.4 cycles of treatment Azzalure® for glabellar lines.

Safety analysis of Part A (Study Days 1-84): first quarter

An overview of treatment-emergent AEs (TEAEs) reported during Part A of the study is presented in Table 5 and treatment-related TEAEs are presented in Table 6.

Table 5 Overview of adverse events reported during Part A (Study Days 1-84) - (safety population)

	Study Days 1-84[a]											
	Azzalure® (N at risk = 252)						Placebo (N at risk = 83)					
	Non-treated area		Treated area		Overall		Non-treated area		Treated area		Overall	
	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects
All TEAEs	12	12 (4.8)	9	8 (3.2)	69	49 (19.4)	4	4 (4.8)	0	0 (0)	23	16 (19.3)
Treatment-related TEAEs	2	2 (0.8)	5	5 (2.0)	14	13 (5.2)	0	0 (0)	0	0 (0)	3	2 (2.4)
All eye disorder TEAEs	2	2 (0.8)	2	2 (0.8)	5	5 (2.0)	0	0 (0)	0	0 (0)	0	0 (0)
Treatment-related eye disorder TEAEs	2	2 (0.8)	1	1 (0.4)	3	3 (1.2)	0	0 (0)	0	0 (0)	0	0 (0)
All SAEs	0	0 (0)	2	1 (0.4)	7	5 (2.0)	0	0 (0)	0	0 (0)	1	1 (1.2)
Treatment-related SAEs	0	0 (0)	0	0 (0)	0	(0)	0	0 (0)	0	0 (0)	0	0 (0)
Severe TEAEs	0	0 (0)	2	1 (0.4)	4	2 (0.8)	0	0 (0)	0	0 (0)	1	1 (1.2)
Treatment-related severe TEAEs	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
TEAEs of special interest	2	2 (0.8)	2	2 (0.8)	11	10 (4.0)	0	0 (0)	0	0 (0)	2	2 (2.4)
Treatment-related TEAEs of special interest	2	2 (0.8)	2	2 (0.8)	11	10 (4.0)	0	0 (0)	0	0 (0)	2	2 (2.4)
TEAEs leading to discontinuation	0	0 (0)	2	1 (0.4)	4	2 (0.8)	0	0 (0)	0	0 (0)	1	1 (1.2)
Treatment-related TEAEs leading to discontinuation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Deaths	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

Source Data: Section 14, Table 14.3.2.1

Abbreviations: SAEs, serious adverse events; TEAEs, treatment-emergent adverse events

TEAEs are defined as events occurring after the first injection.

Numbers in columns cannot be added because a given subject may have reported more than one AE.

N at risk, Number of subjects having at least one visit during the period of time.

'Overall' includes non-treated area, treated area and non-applicable.

[a] Because some subjects were retreated before or on Day 84, this safety summary table also includes TEAEs that occurred after retreatment in some subjects.

Analysis of AEs during Part A (first quarter of the study):

During Part A, the proportion of subjects who experienced TEAEs was similar in the Azzalure® and placebo groups: 69 TEAEs were reported in 49 subjects (19.4%) in the Azzalure® group and 23 TEAEs were reported in 16 subjects (19.3%) in the placebo group. See Table 5.

In the Azzalure® group, the most commonly reported TEAEs were headache, eyelid oedema, injection site haematoma, and nasopharyngitis. In the placebo group, the most commonly reported TEAEs were headache and nasopharyngitis.

- *Related TEAEs reported in Part A:*

The incidence of TEAEs during the first 12 weeks of the study which were considered by the investigator to be related to the study treatment was low overall but slightly higher in the Azzalure® group than the placebo group: 13 subjects (5.2%) vs. 2 subjects (2.4%), respectively. All treatment-related TEAEs resolved without sequelae. The most commonly reported treatment-related TEAEs in the Azzalure® group were headache (2.8%) and eyelid oedema (1.2%). In the placebo group, no preferred term was reported as treatment-related more than once. See Table 6.

Apart from a 2 cases of moderate headache in 2 Azzalure® subjects, all treatment-related TEAEs were mild in intensity. No subject in either group reported a treatment-related TEAE that was severe in intensity or led to discontinuation from the study.

- *TEAEs leading to discontinuation reported in Part A:*

Three subjects experienced TEAEs during Part A that led to discontinuation: 2 treated with Azzalure® and 1 treated with placebo. All the AEs leading to discontinuation were considered serious and unrelated to the study treatment.

- *SAEs reported in Part A:*

Five (2.0%) Azzalure®-treated subjects reported 7 treatment-emergent SAEs, and 1 (1.2%) placebo-treated subject reported 1 SAE, none of which was judged by the investigator to be related to the study treatment. No deaths were reported during Part A.

- *AESIs reported in Part A:*

The incidence of AESIs during Part A was low, but was slightly higher in the Azzalure® group: 10 subjects (4.0%) in the Azzalure® group reported 11 AESIs (7 events of headache, 3 of eyelid oedema and 1 event of injection site haematoma) and 2 subjects (2.4%) in the placebo group reported 2 AESIs (headache and hemicephalgia); all these events were considered to be treatment-related. Typically, the onset of the treatment-related AESIs was within 1-2 days of the injection. The AESI events were all mild in intensity, except for 2 events of headache in Azzalure® subjects, which was moderate in intensity. None led to study discontinuation.

Table 6 Treatment-emergent treatment-related adverse events by system organ class and preferred term in Part A (Study Days 1-84) - (safety population)

	Study Days 1-84[a] – Number (%) Subjects			
SOC	**Azzalure® (N at risk = 252)**			**Placebo (N at risk = 83)**
Preferred Term	**Non-treated area**	**Treated area**	**Overall**	
Total number of treatment-related TEAEs	2	5	14	3
Total number of Subjects with at least 1 treatment-related TEAE	**2 (0.8)**	**5 (2.0)**	**13 (5.2)**	**2 (2.4)**
Eye disorders	**2 (0.8)**	**1 (0.4)**	**3 (1.2)**	**0 (0)**
Eyelid oedema	2 (0.8)	1 (0.4)	3 (1.2)	0 (0)
Gastrointestinal Disorders	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1.2)**
Nausea	0 (0)	0 (0)	0 (0)	1 (1.2)
General disorders and administration site conditions	**0 (0)**	**4 (1.6)**	**4 (1.6)**	**0 (0)**
Injection site haematoma	0 (0)	2 (0.8)	2 (0.8)	0 (0)
Injection site pruritus	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Injection site swelling	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Nervous system disorders	**0 (0)**	**0 (0)**	**7 (2.8)**	**2 (2.4)**
Headache	0 (0)	0 (0)	7 (2.8)	1 (1.2)
Hemicephalalgia	0 (0)	0 (0)	0 (0)	1 (1.2)

Source Data: Section 14, Table 14.3.2.6

Abbreviations: SOC, System Organ Class; TEAE, treatment-emergent adverse event

Treatment-emergent adverse events are defined as events occurring the day or after the first injection

A subject was counted once per preferred term even if more than one occurrence of the event was experienced

A subject was counted once per SOC even if more than one event was experienced within the SOC

N at risk, Number of subjects having at least one visit during the period of time

Overall includes non-treated area, treated area and not applicable.

Eyelid oedema was not always considered to be in the treated area, as in some cases it was localised away from the injection site.

[a] Because some subjects were retreated before 85 days, this safety summary table also includes TEAEs that occurred after retreatment in some subjects.

Safety analysis of Part B (Study Days 85 to end of study):

An overview of treatment-emergent AEs (TEAEs) reported during Part B of the study is presented in Table 7 by quarter, i.e. second quarter of the study (Study Days 85-168), third quarter of the study (Study Days 169-252) and final quarter of the study (Study Days >252).

Table 7 Overview of adverse events reported during Part B– safety population

	Study Days 85-168 (2nd quarter of the study) TOTAL (N at risk=326)						Study Days 169-252 (3rd quarter of the study) TOTAL (N at risk=315)						Study Days >252 days (4th quarter of the study) TOTAL (N at risk=310)					
	Non-treated area		Treated area		Overall		Non-treated area		Treated area		Overall		Non-treated area		Treated area		Overall	
	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects
All TEAEs	13	13 (4.0)	5	5 (1.5)	58	44 (13.5)	8	6 (1.9)			38	30 (9.5)	2	2 (0.6)	9	6 (1.9)	52	38 (12.3)
Treatment-related AEs	5	5 (1.5)	5	5 (1.5)	16	12 (3.7)	2	1 (0.3)			4	3 (1.0)	0	0	8	5 (1.6)	12	7 (2.3)
All eye disorder TEAEs	4	4 (1.2)	0	0	6	6 (1.8)	2	1 (0.3)			2	1 (0.3)	0	0	3	2 (0.6)	6	5 (1.6)
Treatment-related eye disorder TEAEs	4	4 (1.2)	0	0	6	6 (1.8)	2	1 (0.3)			2	1 (0.3)	0	0	3	2 (0.6)	4	3 (1.0)
All SAEs	0	0	0	0	6	6 (1.8)	1	1 (0.3)			2	2 (0.6)	0	0	0	0	3	3 (1.0)
Treatment-related SAEs	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	3	3 (0.9)	1	1 (0.3)			2	2 (0.6)	0	0	0	0	3	3 (1.0)
Treatment-related severe TEAEs	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0
TEAEs of special interest	5	5 (1.5)	2	2 (0.6)	13	11 (3.4)	2	1 (0.3)			4	3 (1.0)	0	0	1	1 (0.3)	5	4 (1.3)
Treatment-related AEs of special interest	5	5 (1.5)	2	2 (0.6)	13	11 (3.4)	2	1 (0.3)			4	3 (1.0)	0	0	1	1 (0.3)	5	4 (1.3)
TEAEs leading to discontinuation	0	0	0	0	2	2 (0.6)	0	0			0	0	0	0	0	0	0	0
Treatment-related AEs leading to discontinuation	0	0	0	0	1	1 (0.3)	0	0			0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0

Source Data: Section 14, Table 14.3.2.1,

Abbreviations: SAEs, serious adverse events; TEAEs, treatment-emergent adverse events, TEAEs are defined as events occurring after the first injection.

Numbers in columns cannot be added because a given subject may have reported more than one AE.

N at risk, Number of subjects having at least one visit during the period of time.

'Overall' includes non-treated area, treated area and non-applicable.

Analysis of AEs during Part B (2nd, 3rd and 4th quarters of the study):

The proportion of subjects who experienced TEAEs was similar across the three quarters of the Part B as follows:

- 58 TEAEs in 44 (13.5%) subjects during the second quarter of the study,
- 38 TEAEs in 30 (9.5%) subjects in the third quarter of the study and
- 52 TEAEs in 38 subjects (13.2%) during the final quarter of the study.

The proportion of subjects who experienced TEAEs in Part B was lower than that seen during Part A in both the Azzalure (19.4%) and placebo groups (19.3%).

During the second quarter of the study, the most commonly reported TEAEs were headache (in 6 subjects, 1.8%) and nasopharyngitis (3 subjects, 0.9%). During the third quarter of the study, the most commonly reported TEAE was nasopharyngitis (6 subjects, 1.9%), and during the final quarter of the study, the most commonly reported TEAEs were headache (6 subjects, 1.9%), influenza (5 subjects, 1.6%) and bronchitis (4 subjects, 1.3%).

During Part B, severe TEAEs were reported in 8 subjects in total. None of the severe TEAEs were considered to be related to treatment.

- *Related TEAEs reported in Part B:*

The overall incidence of TEAEs considered by the investigator to be related to the study treatment was low. Treatment-related events were reported in 12 subjects (3.7%) during the second quarter of the study (most frequently headache in 3 subjects, 0.9%), 3 (1.0%) subjects during the third quarter of the study (no preferred term reported more than once) and 7 subjects (2.3%), during the final quarter of the study (most frequently headache and injection site hematoma both reported in 3 subjects, 1.0%).

Typically, the onset of the treatment-related TEAEs was within 1-2 days of the injection. All treatment-related events were mild or moderate in intensity and all resolved.

Of the treatment-related TEAEs reported, some were associated with canthal lines treatment, some with glabellar lines treatment and others with both, with no clear trend for a difference in the occurrence of treatment-related TEAEs between the areas.

- *TEAEs leading to discontinuation reported in Part B:*

One TEAE led to discontinuation from the study during Part B; a treatment-related AESI of mild eyelid edema.

- *SAEs reported in Part B:*

SAEs were reported in 11 subjects in total (11 events), none of which were treatment-related. One SAE during Part B led to discontinuation from the study (breast cancer). There were no deaths during Part B.

- *AESIs reported in Part B:*

The proportion of subjects experiencing AESIs during Part B was lower than in the Azzalure® group during Part A (when they were reported by 4.0% of subjects), with AESIs reported in 3.4% of subjects during the second quarter of the study, 1.0% during the third quarter and 1.3% during the final quarter. All the AESIs were mild in severity, except for moderate events of headache (3 events), eyelid ptosis and muscular weakness. All the AESIs were considered to be treatment-related.

- *Incidence of antibody response:*

No subjects tested were positive for binding antibodies against BoNT/A at baseline and after receiving multiple treatments with Azzalure® over one year.

Conclusion

From these data, it can be concluded that Azzalure® at a total dose of 60 s.U. (30 s.U./LCA) is effective in the treatment of subjects with lateral canthal lines which are moderate or severe "at maximum smile", and mild, moderate or severe "at rest". At this dose, Azzalure® was statistically significantly more effective than placebo up to 12 weeks after treatment.

Treatment with Azzalure® provided high subject satisfaction. The subjects' assessment of satisfaction with the change in appearance of their lateral canthal lines from Baseline up to Week 16 was statistically significantly greater after treatment with Azzalure® compared to placebo.

The incidence of TEAEs considered by the investigator to be related to Azzalure® treatment was low: 5.2% during Part A (compared to 2.4% with placebo), and 3.7%, 1.0% and 2.3% during Part B in the second, third and final quarters of the study respectively when canthal and glabellar lines were treated concomitantly. The safety data showed that the overall safety profile seen with canthal lines treatment was maintained when canthal and glabellar lines were treated concomitantly. The safety profile in lateral canthal lines alone, and the safety profile in canthal and glabellar lines treated concomitantly is consistent with the known safety profile of Azzalure® when used in glabellar lines. There was no clear trend for a difference in the occurrence or type of treatment-related TEAEs between the canthal and glabellar lines. Treatment with Azzalure® is safe and associated with a low incidence of known side effects when used up to the total dose of 110 s.U.

No subjects tested were positive for binding antibodies against BoNT/A at baseline and after receiving multiple treatments with Azzalure® over one year.