ORIGINAL ARTICLE

Efficacy, patient-reported outcomes and safety profile of ATX-101 (deoxycholic acid), an injectable drug for the reduction of unwanted submental fat: results from a phase III, randomized, placebo-controlled study

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Abstract

Background Unwanted submental fat (SMF) may result in an unattractive chin profile and dissatisfaction with appearance. An approved and rigorously tested non-surgical method for SMF reduction is lacking.

Objective To evaluate the efficacy and safety of ATX-101 for the pharmacological reduction of unwanted SMF in a phase III randomized, double-blind, placebo-controlled study.

Methods Patients (n = 360) with moderate or severe SMF were randomized to receive ATX-101 1 or 2 mg/cm^2 or placebo injected into their SMF for up to four treatments ~28 days apart, with a 12-week follow-up. Coprimary efficacy endpoints were the proportions of treatment responders, defined as a ≥1-point reduction in SMF on the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS), and those satisfied with their appearance in association with their face and chin after treatment on the Subject Self-Rating Scale (SSRS score ≥4). Secondary efficacy endpoints included a ≥1-point improvement in SMF on the Patient-Reported Submental Fat Rating Scale (PR-SMFRS) and changes in the Patient-Reported Submental Fat Impact Scale (PR-SMFIS). Additional patient-reported outcomes and changes in the Skin Laxity Rating Scale were recorded. Adverse events (AEs) and laboratory test results were monitored.

Results Compared with placebo, a greater proportion of patients treated with ATX-101 1 and 2 mg/cm^2 showed a ≥1-point improvement in CR-SMFRS (58.3% and 62.3%, respectively, vs. 34.5% with placebo; $P < 0.001$) and patient satisfaction (SSRS score ≥4) with the appearance of their face and chin (68.3% and 64.8%, respectively, vs. 29.3%; $P < 0.001$). Patient-reported secondary efficacy endpoints showed significant improvements in SMF severity (PR-SMFRS; $P = 0.009$ for ATX-101 1 mg/cm^2, $P < 0.001$ for ATX-101 2 mg/cm^2 vs. placebo) and emotions and perceived self-image (PR-SMFIS; $P < 0.001$). No overall worsening of skin laxity was observed. AEs were mostly transient, mild to moderate in intensity and localized to the treatment area.

Conclusion ATX-101 was effective and well tolerated, and may be an alternative to surgery for patients desiring improvement of their submental profile.

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Conflicts of interest

BA, KH and UW were investigators in this trial. BH and SL are employees of Bayer HealthCare. PW is a former employee of, and is now an advisor to, KYTHERA Biopharmaceuticals Inc.

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Introduction

Concerns regarding appearance frequently increase with ageing.[1] For some men and women, ageing is associated with loss of social visibility, and some people may consider that an aged appearance will impact negatively on their job prospects.[1] Loss of chin profile definition owing to unwanted submental fat (SMF) distributed both superficially and deep to the platysma muscle (preplatysmal and postplatysmal fat) is one of the signs of ageing of the lower face and neck that may lead to a negative self-image.[1,2] Unwanted SMF may be coincident with other ageing processes such as sagging and lipoatrophy of the lower face.[3–5] Another morphotype related to young as well as older patients, the round face, could result from the combination of SMF deposits on the neck and face, without sagging or facial lipoatrophy.[4,6,7] Unwanted SMF may also have dietary causes or result from a genetic predisposition.[8,9] Regardless of the reasons for unwanted SMF and resulting unsatisfactory submental profile, it can cause low self-esteem, discomfort and anguish.[10] Liposuction and lower face and neck lift, with or without submentoplasty, are effective and commonly used methods for removing unwanted SMF and improving the profile of the neck and chin.[8] However, complications may occur with these procedures, including aesthetic deformity,[11,12] and recovery times of up to 1 year may occur in exceptional cases.[13] In addition, liposuction involves risks of local infection,[14–16] transmission of pathogens[16] and ecchymosis and bruising.[17] Long-term side-effects are also possible, such as contour irregularities caused by skin adherence owing to excessive removal of subcutaneous fat[17,18] and excess skin.[11] Therefore, some patients may not wish to undergo surgery and others may not be appropriate candidates for this type of intervention.[11]

Currently, there is insufficient clinical evidence to support the use of non-surgical energy-based devices for SMF reduction, and even less to consider these as efficient and safe as liposuction.[19,20] Robust evidence for the efficacy and safety of non-specific, unapproved, lipolytic injectables is also limited.[10,21]

ATX-101 is a proprietary formulation of synthetically derived deoxycholic acid (DCA) that has shown efficacy and acceptable tolerability in phase I and II studies for the reduction of unwanted SMF.[22–25] DCA disrupts the membranes of adipocytes through solubilization of the membrane lipids,[26] leading to cell breakdown, and induces a local inflammatory response that clears the adipocyte debris.[21,26,27] In relatively protein-rich tissues, such as muscle and skin, the action of DCA is attenuated by increased protein binding.[26]

The results of a large, European, randomized, double-blind, placebo-controlled, parallel-group phase III clinical study for evaluation of the efficacy and safety of ATX-101 treatment for the reduction of SMF, based on physician- and patient-reported outcomes, are presented here. These results support ATX-101 as the first specific pharmacological, adipocytolytic formulation to be rigorously evaluated as an appropriate alternative to surgery for the reduction of unwanted SMF and improvement of submental profile.

Methods

Study design

The efficacy and safety of ATX-101 were evaluated in a multicentre, randomized, double-blind, placebo-controlled, parallel-group phase III clinical trial. The aim was to show superiority of ATX-101 over placebo. The study comprised a screening period (Week −8 [Visit 1] to baseline [Visit 2]), followed by a 12-week treatment period with a maximum of four treatment sessions timed approximately 28 days apart (Visits 2–5), and a 4-week (Visit 6) and 12-week (Visit 7) efficacy and safety follow-up. Patients from 29 centres from Belgium, France, Germany, Spain, Italy and the United Kingdom were enrolled. The study followed all local legal and regulatory requirements. Signed informed consent was given by all patients in agreement with the ethical principles established in the Declaration of Helsinki and the International Conference on Harmonisation guideline E6: Good Clinical Practice, before any study-specific procedure was performed.

Inclusion and exclusion criteria

Men and non-pregnant, non-lactating women under medical birth control if of reproductive age were required to be 18–65 years of age to participate. Patients with moderate or severe (grade 2 or 3) SMF according to the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) who were dissatisfied with the appearance of their submental area (Subject Self-Rating Scale [SSRS] rated 0–3) at Visit 2 were considered eligible. Patients were required to have a body mass index (BMI) $\leq$30 kg/m^2 and show no significant abnormality in their clinical and laboratory evaluations. Patients who had one or more of the following were excluded: previous SMF treatment or other recent aesthetic facial treatment; loose skin or previous trauma in the neck or chin area, or prominent platysmal bands that could lead to an aesthetically unacceptable outcome after treatment; any cause of enlargement in the submental area other than localized SMF; any medical condition likely to affect the safety or efficacy assessment or the patient's ability to undergo study procedures or provide informed consent. Patients currently on or considering starting a weight-reduction regimen, or sensitive to any components of the study material or to topical or local anaesthetics were also not eligible.

Randomization

Randomization (1 : 1 : 1) was performed at Visit 2, after baseline evaluations were completed, by allocating a unique randomization number to each patient through an automated computerized voice-response system. ATX-101 1 mg/cm^2, 2 mg/cm^2 and placebo treatment kits were indistinguishable in

appearance, and each treatment kit was identified by a blinded label with one of the randomization numbers attributed by the computerized system.

Interventions

Patients received a maximum of 10 mL of one of two ATX-101 fixed-dose regimens (1 mg/cm^2 or 2 mg/cm^2) or placebo (sodium phosphate and sodium chloride in water for injection) at up to four treatment sessions with an interval of approximately 28 days between each session (Visits 2–5). During each treatment session, 0.2 mL per injection of either ATX-101 (1 mg/cm^2 or 2 mg/cm^2) or placebo was injected subcutaneously directly into the SMF, using a grid to position injection sites 1.0 cm apart and achieve an even distribution. Up to 50 individual injections were administered per treatment session. Anaesthesia with topical lidocaine preparations and ice, and in some cases local lidocaine injections, was provided as required. Vital signs were measured at each visit during treatment and follow-up periods. SMF reduction and occurrence of adverse events (AEs) were assessed at each treatment visit. AEs were also assessed at 7 $\pm$ 3 days after each treatment visit. All AEs and use of concomitant medications were reported. Treatment could be delayed or stopped for efficacy (early therapeutic success) or safety reasons (occurrence of AEs or insufficient fat to safely administer injections), as well as discontinued at the patient's request. All randomized patients were to receive at least one treatment session and attend a 4-week and a 12-week follow-up visit (Visits 6 and 7) after the final treatment session (Fig. 1).

Efficacy outcome measures

The coprimary efficacy outcomes (Table 1) were analysed at Visit 7 (12 weeks after the final treatment) in the intention-to-treat (ITT) population, which comprised all randomized patients who had at least one efficacy assessment (CR-SMFRS or SSRS) at baseline. The two coprimary efficacy endpoints were the proportion of patients classified as responders to treatment with respect to the 5-point CR-SMFRS score (≥1-point improvement from baseline in SMF reduction) and the 7-point SSRS score (patients satisfied with their appearance in association with their chin and face, SSRS ≥4). For both endpoints, an imputation of missing values by using the last observation carried forward method was used. Secondary and other efficacy endpoints included: the proportion of patients with a reduction in SMF of ≥1 point on the Patient-Reported Submental Fat Rating Scale (PR-SMFRS); the effect of treatment on the psychological impact of SMF using the Patient-Reported Submental Fat Impact Scale (PR-SMFIS); patient responses to the Modified Derriford Appearance Scale 24 (modified DAS 24) questionnaire and Subject Global Questions; and the clinician-rated effect of treatment on skin laxity (Skin Laxity Rating Scale [SLRS]). Treatment effects were further documented by acquiring frontal and profile view standardized photographic images at baseline and Visit 7.

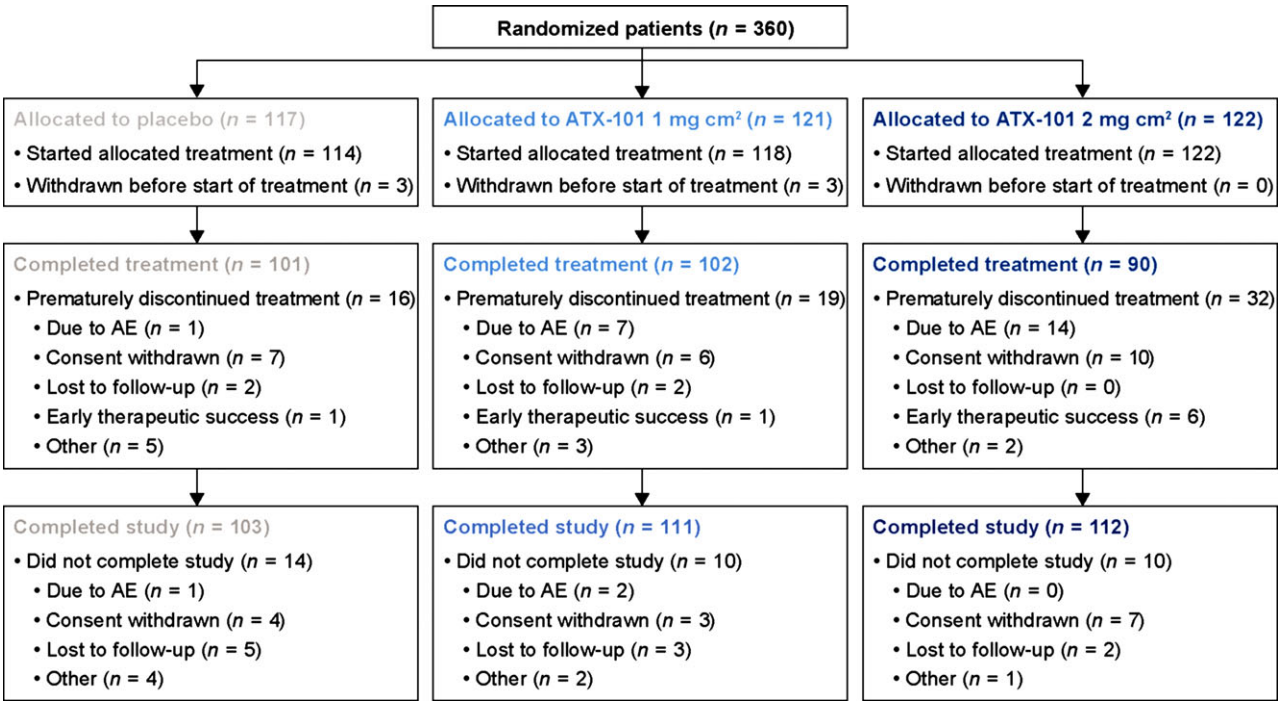


Figure 1 Schematic disposition of randomized patients into different treatment groups. AE, adverse event.

Table 1 Efficacy parameters and scales used in the study

Efficacy outcome	Evaluator	Outcome measure	Method of evaluation	Rating scale (range)
Primary	Physician	SMF severity (submental convexity and amount of SMF)	Clinician-Reported SMF Rating Scale (CR-SMFRS)	0 (absent) to 4 (extreme)
Primary	Patient	Satisfaction with appearance in association with face and chin	Subject Self-Rating Scale (SSRS)	0 (extremely dissatisfied) to 6 (extremely satisfied)
Secondary	Patient	Perceived SMF severity	Patient-Reported SMF Rating Scale (PR-SMFRS)	1 (absent) to 5 (very large amount)
Secondary	Patient	Psychological impact of SMF appearance on feelings and perceived visual self-image	Patient-Reported SMF Impact Scale (PR-SMFIS)	0 (not at all) to 10 (extremely)
Secondary	Patient	Psychological impact of SMF and perceived visual self-image	Modified Derriford Appearance Scale 24 (modified DAS 24)	Improved/no change/worsened
Other	Patient	Satisfaction with the treatment received	Subject Global Questions	'A great deal worse' to 'A great deal better'; 'Extremely dissatisfied' to 'Extremely satisfied'
Other	Physician	Skin laxity	SLRS	1 (no laxity) to 4 (very lax)

SMF, submental fat; SLRS, Skin Laxity Rating Scale.

Safety outcome measures

Safety analyses were performed in the safety population comprising all patients who received at least one treatment. Patients underwent clinical evaluations and examination of the treatment area for AEs at each treatment session before and after administration of the study material and approximately 7 days after each treatment. AEs were characterized by their start and stop date, and relationship with treatment, and were classified by their severity and intensity. Treatment-emergent adverse events (TEAEs) were defined as any undesirable medical occurrence or worsening of an existing condition after the first dose of treatment. Changes from baseline were also determined for clinical laboratory parameters, vital signs, body temperature and body weight.

Statistical methodology

Two previous phase II studies (NCT00618722 and NCT00618618) were used to determine a reduction in the expected CR-SMFRS and SSRS response rates for patients treated with ATX-101 to 80% of the observed rate relative to placebo. A 10% dropout rate (assumed to be non-responders) was anticipated in each treatment group. A conservatively rounded sample size of 120 patients per treatment group to guarantee a power of 90% was determined by using the Pearson chi-square test for two proportions (two-sided test with $\alpha = 0.025$) based on these response rates.

The ITT population was the primary population for the superiority analysis at Visit 7, and missing values were imputed using last observation carried forward. All statistical tests for comparison of treatments were two sided with a type I error rate of 0.05. Treatment comparisons for the two coprimary efficacy endpoints were made using odds ratios (ORs) from binary logistic regression and with a null hypothesis of no difference between each treatment group. The null hypotheses for both coprimary variables had to be rejected at the same significance level. This was accounted for by using the larger of the two *P*-values in the Bonferroni–Holm testing procedure, which serves as adjustment for multiplicity.

A Pearson's chi-square test was applied for comparison of each treatment group with placebo regarding changes from baseline in PR-SMFRS and SLRS scores, and PR-SMFRS improvements of ≥1 point were analysed by binary logistic regression. For PR-SMFIS, descriptive statistics were calculated and the change from baseline was analysed by an overall analysis of variance (ANOVA) and post hoc Fisher's least significant difference tests for continuous variables if ANOVA showed an overall treatment effect. Changes at Visit 7 from baseline for items on the subject-reported modified DAS 24 and Subject Global Questions were analysed using frequency tables and compared between treatment groups using a Pearson's chi-square test if applicable. Descriptive statistics were calculated for demographic and clinical parameters. The number of AEs and patients with each AE were categorized based on association with treatment, study withdrawal, death, severity, intensity, system organ class and preferred term. Statistical summaries were based on TEAEs.

Results

Patient demographics

The study was conducted between January 2011 and February 2012. A total of 360 patients were screened successfully and randomized in a 1 : 1 : 1 ratio to receive treatment with ATX-101 1 mg/cm^2 ($n = 121$) or 2 mg/cm^2 ($n = 122$) or placebo ($n = 117$) (Fig. 1). A total of six patients, three randomized to the

Table 2 Demographic parameters by treatment group and overall safety population

Variable		Placebo (n = 117)	ATX-101 1 mg/cm^2 (n = 121)	ATX-101 2 mg/cm^2 (n = 122)	Overall (N = 360)
Age (years)	Mean (SD)	46.1 (9.50)	45.9 (10.21)	45.9 (9.95)	46.0 (9.87)
Sex	Female (%)	68.4	75.4	72.1	72.0
	Male	31.6	24.6	27.9	28.0
Race	Caucasian (%)	91.2	94.1	93.4	92.9
	Other (%)	8.8	5.9	6.6	7.1
BMI (kg/m^2)	Mean (SD)	26.1 (2.55)	26.3 (2.71)	26.5 (2.67)	26.3 (2.65)

BMI, body mass index; SD, standard deviation.

1 mg/cm^2 ATX-101 group and three to the placebo group, did not receive any treatment, and two other randomized patients who received no treatment and did not comply with the baseline visit were excluded from analyses. The ITT population consisted of 358 patients and the safety population comprised 354 patients. Patient baseline demographic characteristics were similar between groups, indicating an unbiased randomization. Most patients were female (72.0%, n = 255), white (92.9%, n = 329), with a mean overall BMI of 26.3 kg/m^2, a mean age of 46.0 years (Table 2) and with all Fitzpatrick skin types represented.

Of all randomized patients, 90.6% completed the study and 81.4% completed the four planned treatments. Study completion, i.e. at least one treatment session and Visit 7 performed, was similar between all groups (91.7% and 91.8% in the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively, and 88.0% in the placebo group). Treatment discontinuation because of AEs was higher in the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups (5.8% and 11.5%, respectively) compared with placebo (0.9%). The mean ± standard deviation of total injection volume was similar for both ATX-101 treatment groups (16.96 ± 7.87 mL and 15.02 ± 8.24 mL for ATX-101 1 mg/cm^2 and 2 mg/cm^2, respectively) but higher for placebo (19.16 ± 8.03 mL). Early therapeutic success (insufficient SMF for further injections or sufficient patient satisfaction) was associated with ≥1-point improvements in CR-SMFRS, was usually achieved for most patients after the third treatment session and was more frequent with ATX-101 2 mg/cm^2 (4.9%) than with ATX-101 1 mg/cm^2 (0.8%) or placebo (0.9%). Treatment discontinuation because of withdrawal by patient decision was similar across all groups.

Primary efficacy outcomes

The proportion of patients in the ATX-101 1 mg/cm^2 (58.3%) and 2 mg/cm^2 (62.3%) groups showing a ≥1-point improvement in CR-SMFRS score at Visit 7 was significantly higher (P < 0.001) than in the placebo group (34.5%) (Fig. 2). The ORs for the improvement in CR-SMFRS were 2.60 (95% CI 1.52–4.43) and 3.13 (95% CI 1.83–5.36) for ATX-101 1 mg/cm^2 and 2 mg/cm^2, respectively, compared with placebo. Overall, satisfaction with appearance in association with the face and chin (SSRS score of ≥4 at Visit 7) was significantly higher (P < 0.001) in patients receiving ATX-101 1 mg/cm^2 and 2 mg/cm^2 (68.3% and 64.8% were responders, respectively) than in patients receiving placebo (29.3%) (Fig. 3). The corresponding ORs were 5.37 (95% CI 3.06–9.44) and 4.62 (95% CI 2.65–8.04) for ATX-101 1 mg/cm^2 and 2 mg/cm^2, respectively, compared with placebo. Both ATX-101 dose groups showed statistically significant efficacy according to the predefined confirmatory testing procedure. SMF reduction and associated improvement in submental profile are demonstrated in photographs of representative patients treated with ATX-101 1 mg/cm^2 and 2 mg/cm^2 (Fig. 4).

Secondary efficacy outcomes

The majority of patients in all treatment groups showed either no change (61.3% and 71.4% for ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively, vs. 80.4% for placebo) or an improvement (29.7% and 21.4%, respectively, vs. 13.7%) in skin laxity (SLRS). A significant improvement in PR-SMFRS score relative to baseline at Visit 7 was reported for 64.9% of patients in the ATX-101 1 mg/cm^2 group (P = 0.009) and 67.3% of patients in the ATX-101 2 mg/cm^2 group (P < 0.001) compared with 44.1% patients receiving placebo (Fig. 5). Patients treated with ATX-101 also reported statistically significant improvements at Visit 7 both for each individual PR-SMFIS question (P < 0.001 for each) and across all questions (P < 0.001): patients receiving either of the ATX-101 dosing regimens felt happier as well as less bothered, less self-conscious, less embarrassed, and that they looked less old and less overweight than those who received placebo (Fig. 6). Treatment with ATX-101 2 mg/cm^2 resulted in a statistically significant increase in improved confidence (P = 0.018), with female patients feeling more feminine and male patients feeling more masculine (P = 0.042), and patients feeling less self-conscious about their chin appearance (P = 0.045), in comparison with patients treated with placebo according to the subject-reported modified DAS 24.

As assessed by Subject Global Questions, a significantly greater proportion of patients (P < 0.001) reported improved chin/neck definition after ATX-101 treatment (24.3% and 25.2%

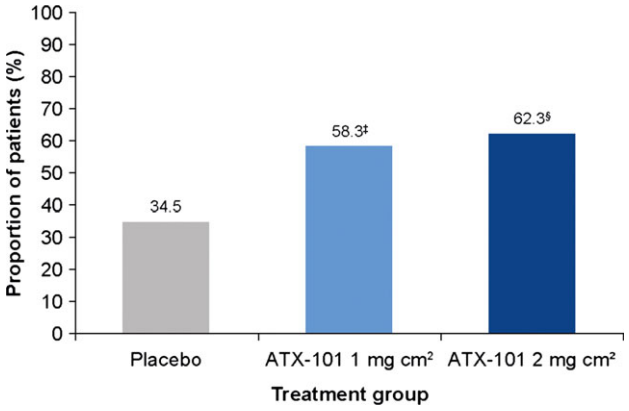


Figure 2 Proportion of responders* to treatment at Visit 7† (12 weeks after the final treatment). Intention-to-treat population. *≥1-point reduction in submental fat on the Clinician-Reported Submental Fat Rating Scale; †last observation carried forward; ‡OR = 2.60 (95% CI 1.52–4.43), binary logistic regression ($P < 0.001$, Bonferroni–Holm testing procedure); §OR = 3.13 (95% CI 1.83–5.36), binary logistic regression ($P < 0.001$, Bonferroni–Holm testing procedure). CI, confidence interval; OR, odds ratio.

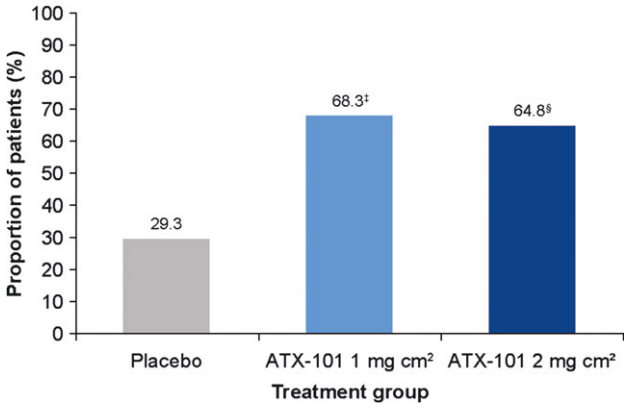


Figure 3 Proportion of patients satisfied with the appearance of their face and chin* at Visit 7† (12 weeks after the final treatment). Intention-to-treat population. *Score ≥4 of a maximum of 6 on the Subject Self-Rating Scale; †last observation carried forward; ‡OR = 5.37 (95% CI 3.06–9.44), binary logistic regression ($P < 0.001$, Bonferroni–Holm testing procedure); §OR = 4.62 (95% CI 2.65–8.04), binary logistic regression ($P < 0.001$, Bonferroni–Holm testing procedure). CI, confidence interval; OR, odds ratio.

for the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively) compared with placebo (4.9%). In addition, a higher percentage of patients receiving ATX-101 1 mg/cm^2 (43.2%, $P = 0.008$) and ATX-101 2 mg/cm^2 (45.0%, $P = 0.049$) reported that they were 'extremely satisfied' with the treatment received during the study than those receiving placebo (35.0%).

Safety outcomes

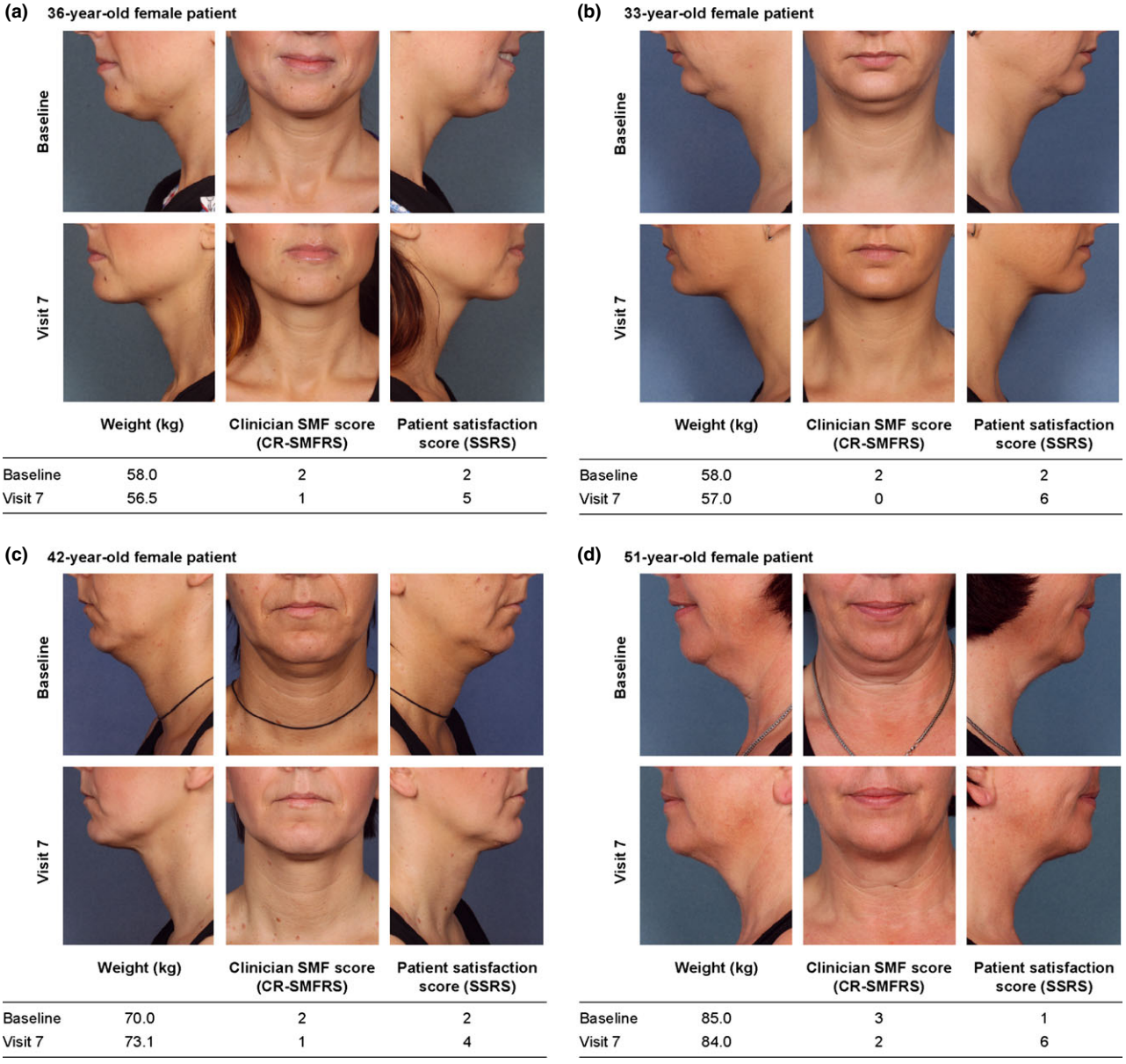
A higher number of patients reported TEAEs in the ATX-101 treatment groups (99.2% for both ATX-101 1 mg/cm^2 and 2 mg/cm^2) than in the placebo group (78.9%), but no difference was seen regarding TEAE incidence between the two ATX-101 doses. Most of these events were related to the treatment area (98.3% and 99.2% of patients in the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively, vs. 69.3% for the placebo group). Some of the most common TEAEs associated with the treatment area were injection-site pain, swelling, numbness, bruising and induration (Fig. 7). These were mostly mild to moderate in intensity, with the exception of pain, which was more frequently moderate to severe but with a short median duration of 1 day for both ATX-101 groups. Injection-site pain was the most frequent study drug-related TEAE to cause withdrawal from ATX-101 treatment.

Pain mitigation was managed using topical anaesthetic preparations and cooling with ice. Analgesics could also be prescribed at the physician's discretion. To prevent dilution of ATX-101 in the treatment area, local lidocaine injections were generally avoided, and were only administered to 15 and 12 patients in the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively, compared with 14 patients in the placebo group. Among the patients receiving lidocaine injections, ATX-101 treatment still achieved a higher proportion of responders compared with placebo, as seen for the overall population.

ATX-101-related AEs were generally related to the injection procedure and were mostly transient and resolved between treatments (28-day interval). Induration, including fibrosis, for example, had a median duration of 15.0 and 21.0 days in the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively, compared with 39.5 days in the placebo group. Only a very small number of AEs were not resolved at the 3-month follow-up, of which only one was considered a serious TEAE related to study treatment and was classified as injection-site nerve injury. In this case, the patient temporarily experienced an asymmetric smile, possibly due to injury of the branch of the nervus facialis on the right side of the face. This was most probably caused by incorrect injection technique. This patient did not require hospitalization or further treatment and the event subsequently resolved without sequelae. Seven patients reported nine serious TEAEs (one and two patients in the ATX-101 1 mg/cm^2 and 2 mg/cm^2 groups, respectively, and four patients in the placebo group). No deaths occurred. There was no apparent relationship between ATX-101 and AEs that occurred outside the treatment area. In addition, no relevant changes in clinical laboratory tests or vital signs were observed.

Discussion

Treatment with ATX-101 resulted in significant reductions in SMF (CR-SMFRS) and increased patient satisfaction (SSRS) with the appearance of their face and chin. In addition, a range



	Weight (kg)	Clinician SMF score (CR-SMFRS)	Patient satisfaction score (SSRS)
Baseline	58.0	2	2
Visit 7	56.5	1	5

	Weight (kg)	Clinician SMF score (CR-SMFRS)	Patient satisfaction score (SSRS)
Baseline	58.0	2	2
Visit 7	57.0	0	6

	Weight (kg)	Clinician SMF score (CR-SMFRS)	Patient satisfaction score (SSRS)
Baseline	70.0	2	2
Visit 7	73.1	1	4

	Weight (kg)	Clinician SMF score (CR-SMFRS)	Patient satisfaction score (SSRS)
Baseline	85.0	3	1
Visit 7	84.0	2	6

Figure 4 Representative images of the aspect of the SMF of patients before (at baseline) and after treatment (Visit 7) with ATX-101 2 mg/cm^2 (a, b) and 1 mg/cm^2 (c, d). CR-SMFRS, Clinician-Reported SMF Rating Scale; SSRS, Subject Self-Rating Scale; SMF, submental fat.

of secondary efficacy outcomes (PR-SMFRS, PR-SMFIS and other questionnaires) allowed SMF size and definition of the submental area to be reported by the patient, and to determine how SMF and the reduction of SMF may impact patients psychologically and influence their perceived attractiveness. A significant number of patients in both ATX-101 treatment groups reported an improvement in the definition of their chin/neck compared with patients in the placebo group. Overall, reduction in SMF with ATX-101 treatment was not associated with an undesirable increase in skin laxity. A significant level of satisfaction was established in several questionnaires for ATX-101 treatment compared with placebo, with patients expressing improvement in the way they felt about themselves and related to others.

Both ATX-101 regimens showed a similar safety profile, with TEAEs ranging from mild to severe in intensity but being mostly transient and generally associated with the treatment area. Given that the incidence of these events was also high with placebo, many of them may have been related to the injection procedure

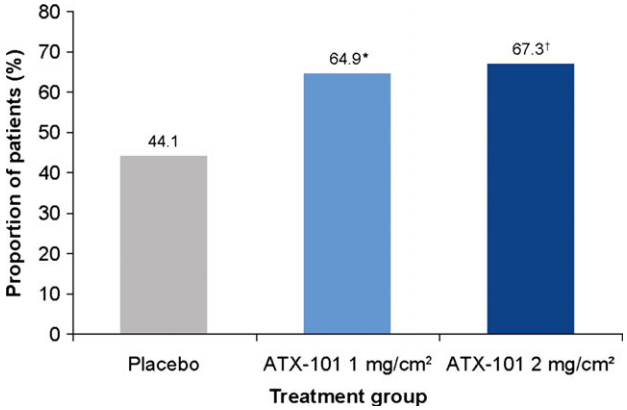


Figure 5 Proportion of patients with an improvement in Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score from baseline to Visit 7 (12 weeks after the final treatment). Intention-to-treat population. *$P = 0.009$; †$P < 0.001$ relative to placebo (Pearson's chi-square test).

itself. Injection-site pain, bruising, swelling, erythema, numbness and induration were the most frequently experienced AEs. Appropriate, practiced technique is fundamental to adequate ATX-101 delivery into the SMF and to achieve efficient reduction with limited side-effects. The local inflammatory response that is induced by adipocytolysis, and is responsible for the clearance of cellular debris and removal of breakdown products,[21,26,27] may also contribute to the observed TEAEs. The transient nature of these TEAEs was predictable based on phase I studies, which showed that ATX-101 does not accumulate at the injection site and is absorbed rapidly and removed through protein binding.[26]

A considerable placebo effect was observed during this study for outcomes such as CR-SMFRS, SSRS and PR-SMFRS scores and Subject Global Questions. The placebo effect is an extensively documented phenomenon, particularly in the aesthetic field,[28] where outcomes based on subjective reports are frequently used. However, ATX-101 treatment achieved

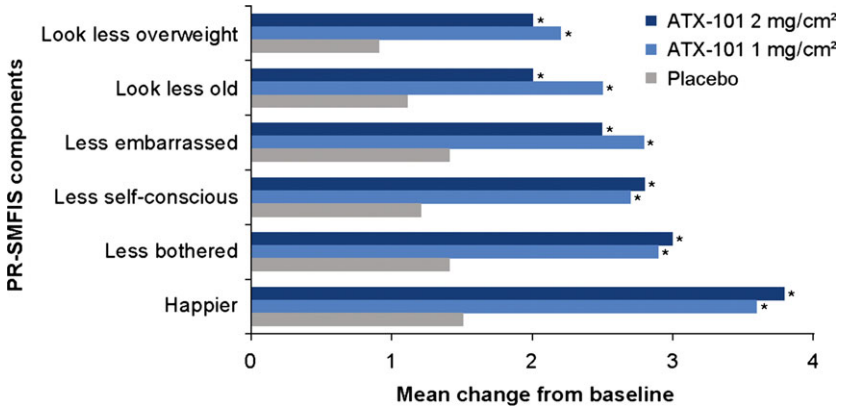


Figure 6 Change in patient evaluations of the psychological impact of their submental fat (Patient-Reported Submental Fat Impact Scale [PR-SMFIS] component scores) from baseline to Visit 7 (12 weeks after the final treatment). Intention-to-treat population. *$P < 0.001$ relative to placebo (analysis of variance and post hoc Fisher's least significant difference tests).

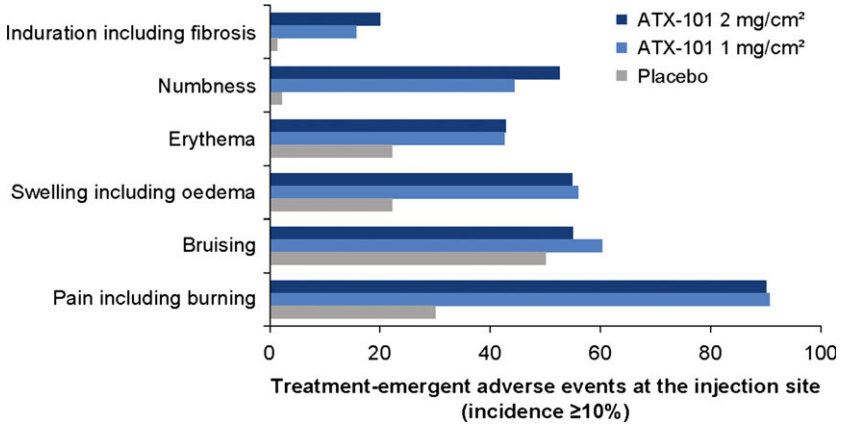


Figure 7 Treatment-emergent adverse events at the injection site (incidence ≥10%). Percentages are based on the number of patients in the safety population.

significantly better outcomes than placebo across the range of efficacy measures evaluated, with a consistent improvement recorded in the active treatment groups.

Overall, ATX-101 treatment resulted in a statistically significant reduction in the submental convexity and amount of SMF, a significantly improved visual appearance of the submental area and, consequently, of the general appearance of the face. ATX-101 treatment had a positive impact on psychological quality of life/well-being, resulting in significant patient satisfaction with treatment and appearance in association with their face and chin. Therefore, ATX-101 represents an effective and well-tolerated, minimally invasive injectable means of reducing unwanted SMF in patients who are either unsuitable or unwilling to undergo extensive surgery.

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