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ATX-101 (Deoxycholic Acid Injection) for Reduction of Submental Fat: Results From a 12-Month Open-Label Study

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ABSTRACT

Background: ATX-101 (deoxycholic acid) causes adipocytolysis when injected into subcutaneous fat.
Objective: Evaluate the long-term safety and efficacy of ATX-101 for submental fat (SMF) reduction.
Methods: Adults (N=165) with moderate-to-extreme SMF received ≤6 treatments of open-label ATX-101 (2 mg/cm^2) and were evaluated up to 12 months after last treatment. Efficacy end points included improvements in SMF based on clinician or subject assessment, patient-reported outcomes, downtime (via subject questionnaire), and skin laxity. Safety was evaluated throughout the study.
Results: Twelve weeks after last treatment, most subjects achieved a ≥1-grade improvement in SMF based on clinician (86.8%) or subject (83.8%) evaluation; at 12 months, 90.4% and 80.7% of these responders, respectively, maintained the response. Overall, 84.9% of subjects were satisfied with the appearance of their face/chin. At 12 months, 82.9% of subjects had unchanged, and 10.1% had improved, skin laxity relative to 12 weeks after last treatment. Adverse events were mild to moderate and mainly involved the treatment area. During the 7 days after the first treatment, 13.3% of subjects missed work and 33.9% missed social/leisure activities. Following subsequent treatments, 2.4%–6.0% of subjects missed work and 10.0%–15.7% missed social/leisure activities.
Conclusion: The safety and efficacy of ATX-101 were sustained over 12 months.
ClinicalTrials.gov identifier, NCT01426373

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INTRODUCTION

The submental area impacts facial harmony, balance, and attractiveness.[1-3] In addition, an undesirable submental profile can negatively affect self-perception.[4,5] Accumulation of submental fat (SMF) can occur in individuals not otherwise overweight and is typically resistant to weight reduction measures.[6-8]

Treatment options to improve submental contour have traditionally included surgical procedures.[9] Nonsurgical methods of submental contouring are available, although many tighten skin rather than reduce SMF.[10-13] ATX-101 (deoxycholic acid injection) is an injectable drug approved in the United States (Kybella)[14] and Australia, Canada, Europe, and South Korea (Belkyra)[15] for improvement in the appearance of moderate-to-severe convexity or fullness associated with SMF.

The active ingredient of ATX-101, deoxycholic acid, preferentially targets adipocytes, as the cytolytic activity is diminished in protein-rich tissues such as muscle and skin.[16] When injected into fat, ATX-101 causes adipocytolysis and a local tissue response involving macrophage infiltration to eliminate cellular debris and liberated lipids from the injection site, as well as fibroblast recruitment thought to be responsible for neocollagenesis.[17-19]

The safety and efficacy of ATX-101 have been assessed in 4 large randomized, controlled phase 3 trials.[14,15,20-23] The current trial evaluated the safety and durability of the ATX-101 treatment effect over 12 months. The impact of ATX-101 treatment on work and social/leisure activities was also assessed.

METHODS

Study Design

This open-label, phase 3b trial (ClinicalTrials.gov identifier, NCT01426373) was conducted between August 2011 and June 2013 at 18 sites in the United States in compliance with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

All subjects received open-label ATX-101 (area-adjusted dose: 2 mg/cm^2) by subcutaneous injection into preplatysmal SMF. Consistent with the product label,[14,15] up to 10 mL of ATX-101 could be injected per treatment, and subjects were eligible to receive up to 6 treatments (every 28±5 days). Subjects could receive <6 treatments due to insufficient SMF to safely inject study drug, subject satisfaction with treatment, or safety/tolerability concerns. Subjects were evaluated at Weeks 0, 4, 8, 12, 16, and 20 and at approximately 7 days after each treatment during the open-label period. During the follow-up period, subjects were evaluated at 4 weeks; 12 weeks (primary time point in phase 3 trials); and 6, 9, and 12 months after last treatment. Subjects who did not complete the 12-month visit were considered to have discontinued from the study.

Subjects

Adults (≥18 years) who had at least moderate SMF (grade 2, 3, or 4 on both the validated Clinician-Reported and Patient-Reported SMF Rating Scale [CR-SMFRS and PR-SMFRS, respectively]) and were dissatisfied with the appearance of their face/chin (score of 0, 1, or 2 on the Subject Self-Rating Scale [SSRS]) were eligible. In addition, body weight had to be stable for ≥6 months. Exclusion criteria included body mass index (BMI) >40 kg/m^2; prior treatment of SMF (liposuction, surgery, lipolytic agents); treatment in the chin/neck within 6 months (botulinum toxin) or 12 months (radiofrequency, lasers, chemical peels, dermal fillers); prior trauma to chin/neck that may affect safety/efficacy evaluations; enlargement of the submental area for any reason other than SMF; history or current symptoms of dysphagia; any medical condition that would compromise the subject's ability to undergo study procedures or interfere with study assessments; or excessive skin laxity (grade 4 on the Submental Skin Laxity Grade [SMSLG] scale) or other anatomical feature (loose skin in the chin/neck, prominent platysmal bands) for which SMF reduction may result in an aesthetically unacceptable outcome.

Assessments

The primary objective was to assess the safety of ATX-101 treatment as evaluated by the incidence and severity of adverse events (AEs) as well as changes in vital signs and clinical laboratory test results. At each visit (before ATX-101 administration), the treatment area was examined by the clinician, and each subject was interviewed in an open-ended manner to inquire about any AEs since the previous visit. In addition to evaluation of spontaneously reported AEs, a checklist of commonly reported AEs was used as a guide for the clinician evaluating the subject. Vital signs were measured at each visit. Clinical laboratory tests (hematology, serum chemistry, urinalysis) were ordered at screening; weeks 4, 8, 12, 16, and 20 during the open-label period; and 4 weeks, 12 weeks, and 12 months after last treatment during the follow-up period.

Efficacy end points included improvements in SMF from baseline as evaluated by the clinician using the CR-SMFRS (wherein clinicians rate SMF on a 5-point scale ranging from absent [0] to extreme [4]) and by the subject using the PR-SMFRS (wherein subjects rate their chin fat on a 5-point scale ranging from none [0] to very large amount [4]). The psychological impact of SMF was assessed by the subject via the validated Patient-Reported SMF Impact Scale (PR-SMFIS), which includes 6 questions, each rated on a scale from 0 (no impact) to 10 (greatest negative impact).[24] Subject satisfaction with the appearance of their face/chin was assessed via the 7-point SSRS, while self-ratings of attractiveness were assessed via the Self-Ratings of Attractiveness questions in which subjects rated their features on a scale of 1 to 9, with higher numbers indicating greater attractiveness. The SMSLG scale (ranging from none [1] to severe [4]) was used by the clinician to evaluate skin laxity. Detailed descriptions of these scales have been previously published.[14,21] SMF thickness was measured using calipers. A questionnaire completed by the subject assessed the effect of ATX-101 treatment on work and social/leisure activities. At select sites, standardized photography was performed at baseline, 12 weeks after last treatment, and 12 months after last treatment.

Statistical Analysis

Safety data are reported for the safety population (subjects who received ≥1 injection of ATX-101). AEs were summarized by severity, association with treatment area, study drug relatedness, and those leading to discontinuation of treatment or death. Efficacy evaluations were based on the treatment effect population (subjects who received ≥1 injection of ATX-101 and who had any post-treatment data for efficacy or skin laxity).

Categories of observed scores and change from baseline were summarized for each visit using frequency counts and percentages. Descriptive statistics were provided for numerical values. Responder analyses were categorized as subjects who achieved a ≥1-grade improvement in SMF from baseline on the CR-SMFRS (CR-1 response), PR-SMFRS (PR-1 response), and both CR-SMFRS and PR-SMFRS (composite CR-1/PR-1 response).

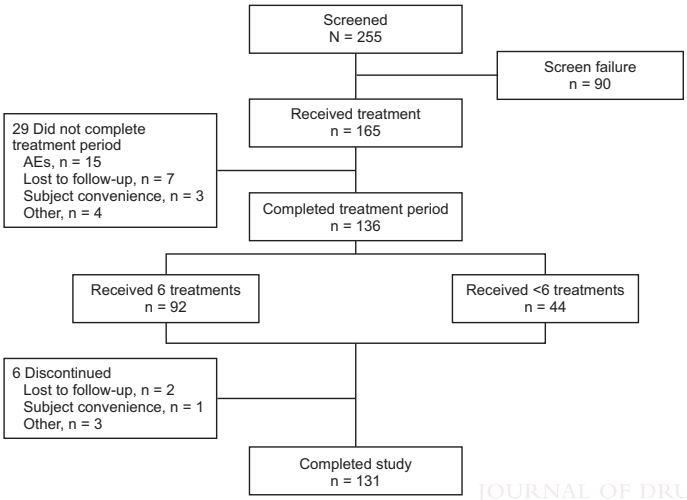
RESULTS

Subject Disposition and Demographics

Of the 255 subjects screened, 165 were enrolled and included in the safety and treatment effect populations (Figure 1). Most subjects (82.4%) completed the open-label period; 79.4% completed the study (including 12 months of follow-up). Of the subjects who discontinued prior to study completion, 6 withdrew due to AEs. Three subjects discontinued due to AEs associated with the treatment area (erythema and edema, anesthesia, or pain) and 3 due to AEs not associated with the treatment area (thyroid cancer, colon cancer, or cardiac death).

Overall, the majority of subjects were female and white with Fitzpatrick skin type II (32.7%) or III (40.0%); mean age was

FIGURE 1. Subject disposition. AE, Adverse event.



46.9 years, and mean BMI was 28.9 kg/m^2 (Table 1). At baseline, 52.1%, 40.0%, and 7.9% of subjects had moderate, severe, and extreme SMF, respectively, based on clinician assessment, whereas 62.0%, 31.3%, and 6.1% had a moderate, large, or very large amount of chin fat based on subject assessment. Mean change from baseline in body weight was 0.4 (6.17) kg at 12 months.

Treatment Characteristics

Overall, 92 subjects received 6 ATX-101 treatments. Of the 73 subjects who received <6 treatments, 29 were due to subject satisfaction with treatment, whereas 15 were due to insufficient SMF to safely inject study drug. Among subjects who received <6 ATX-101 treatments, the mean (SD) number of treatments received was 3.1 (1.5) (median: 3.0; range: 1.0–5.0). The total mean (SD) volume of ATX-101 received per subject was 26.3 (13.7) mL (median: 25.0 mL; range: 4.8–60.0 mL). The mean (SD) volume of ATX-101 injected per treatment was 5.7 (1.9) mL (median: 5.3; range: 2.2–10.0). The mean (SD) number of ATX-101 treatments received was 4.7 (1.8) (median: 6.0; range: 1.0–6.0). Treatment characteristics by SMF severity are listed in Table 2.

TABLE 1.

Demographic and Baseline Characteristics	
Characteristic	**ATX-101 N=165**
Age, mean (SD), y	46.9 (10.9)
Sex, female, n (%)	128 (77.6)
Race, n (%)	2.4
White	129 (78.2)
Black	15 (9.1)
Asian	7 (4.2)
Other	14 (8.5)
Weight, mean (SD), kg	80.4 (15.1)
BMI, mean (SD), kg/m^2	28.9 (4.3)
SMF severity (based on clinician assessment*), n (%)	
Moderate (2)	86 (52.1)
Severe (3)	66 (40.0)
Extreme (4)	13 (7.9)
SMF severity (based on patient assessment†), n (%)	
Moderate (2)	101 (62.0)
Large (3)	51 (31.3)
Very large amount (4)	10 (6.1)
Fitzpatrick skin type, n (%)	
I–III	123 (74.5)
IV–VI	42 (25.5)

BMI, body mass index; SD, standard deviation; SMF, submental fat.
*Evaluated via the validated Clinician-Reported Submental Fat Rating Scale.
†Evaluated via the validated Patient-Reported Submental Fat Rating Scale (n=163).

Treatment Effects

The proportion of CR-1 responders increased over the open-label period, with 86.8% (125/144) achieving the response at 12 weeks after last treatment (Figure 2A). Of the subjects who were CR-1 responders at 12 weeks after last treatment, 90.4% (113/125) maintained this response at 12 months. Nineteen subjects did not achieve a CR-1 response at 12 weeks after last treatment. Three of these 19 subjects did not have assessments performed at 6, 9, or 12 months. Of the remaining 16 subjects, 50.0% achieved a CR-1 response by 6, 9, or 12 months.

TABLE 2.

ATX-101 Treatment Characteristics by SMF Severity				
Treatment Characteristic	**Moderate* SMF (n=86)**	**Severe* SMF (n=66)**	**Extreme* SMF (n=13)**	**All Subjects (N=165)**
Total volume per subject, mean (SD), mL	22.2 (11.5)	29.4 (14.1)	37.9 (15.7)	26.3 (13.7)
Total volume per subject, median (range), mL	23.1 (4.8–50.2)	26.6 (5.0–60.0)	30.0 (15.4–60.0)	25.0 (4.8–60.0)
Total volume per treatment, mean (SD), mL	5.2 (1.5)	6.0 (1.9)	7.3 (2.4)	5.7 (1.9)
Total volume per treatment, median (range), mL	5.1 (2.2–8.6)	6.0 (2.4–10.0)	7.7 (3.9–10.0)	5.3 (2.2–10.0)
No. of treatments, mean (SD)	4.4 (1.9)	5.0 (1.7)	5.3 (1.4)	4.7 (1.8)
No. of treatments, median (range)	5 (1–6)	6 (1–6)	6 (2–6)	6 (1–6)

SD, standard deviation; SMF, submental fat.
*Evaluated via the validated Clinician-Reported Submental Fat Rating Scale (baseline values).

FIGURE 2. Percentages of subjects who achieved a ≥1-grade improvement in SMF on the (A) CR-SMFRS and (B) PR-SMFRS over time. CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; PR-SMFRS, Patient-Reported Submental Fat Rating Scale; SMF, submental fat.

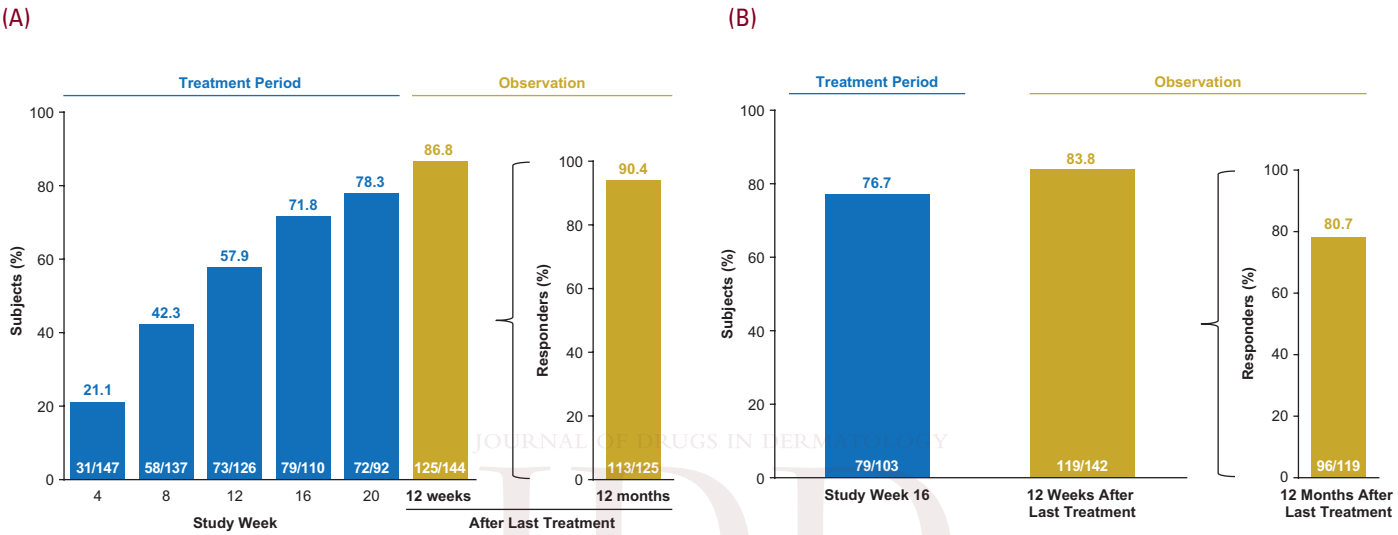


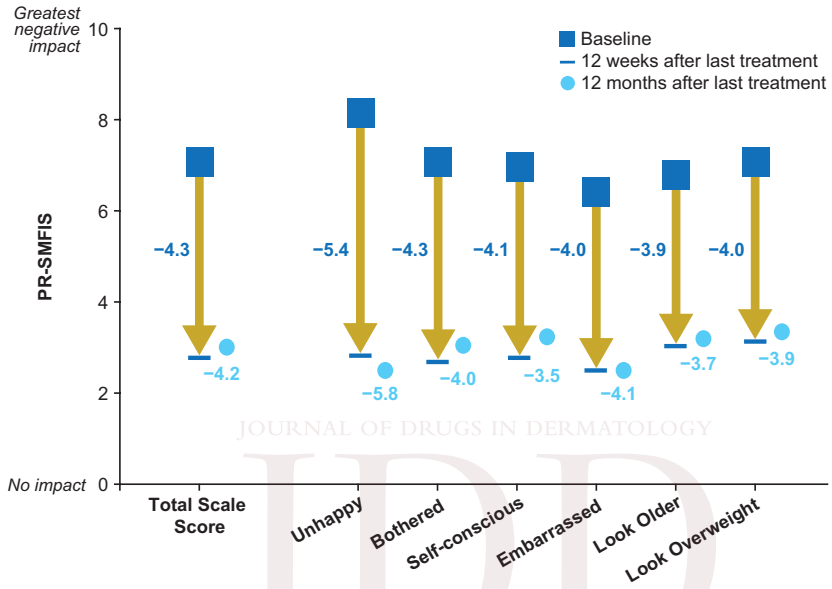
FIGURE 3. Representative photographs of an ATX-101 treatment responder: 45-year-old female subject who underwent 6 ATX-101 treatments (total ATX-101 volume: 25.2 mL) and achieved a 2-grade improvement on the CR-SMFRS and PR-SMFRS at 12 weeks after last treatment. Improvements achieved at 12 weeks after last treatment were maintained at 12 months. BMI, body mass index; CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; PR-SMFRS, Patient-Reported Submental Fat Rating Scale; SMSLG, Submental Skin Laxity Grade; SSRS, Subject Self-Rating Scale.

Baseline	
CR-SMFRS	Moderate (2)
PR-SMFRS	Moderate (2)
SSRS	Dissatisfied (1)
SMSLG	Mild (1)
Weight	54.2 kg
BMI	21.2 kg/m²

12 Weeks After Last Treatment	
CR-SMFRS	Absent (0)
PR-SMFRS	None (0)
SSRS	Extremely satisfied (6)
SMSLG	None (0)
Weight	57.8 kg
BMI	22.6 kg/m²

12 Months After Last Treatment	
CR-SMFRS	Absent (0)
PR-SMFRS	None (0)
SSRS	Extremely satisfied (6)
SMSLG	None (0)
Weight	56.3 kg
BMI	22.0 kg/m²

FIGURE 4. Mean change from baseline in the psychological impact of SMF as measured by the PR-SMFIS total scale score and individual component scores at 12 weeks and 12 months after last treatment. Lower scores indicate improvement or reduced negative impact of these items. PR-SMFIS, Patient-Reported Submental Fat Impact Scale.



At 12 weeks after last treatment, 83.8% (119/142) of subjects achieved a PR-1 response (Figure 2B), of which 80.7% (96/119) maintained this response at 12 months. A composite CR-1/PR-1 response was achieved in 72.5% (103/142) of subjects at 12 weeks after last treatment; 83.5% (86/103) of these subjects maintained this response at 12 months. Representative photographs of an ATX-101 treatment responder are shown in Figure 3.

The mean (SD) PR-SMFIS total scale score of 7.0 (1.8) at baseline indicated substantial psychological impact of SMF. This score decreased by a mean of 4.3 (2.9) at 12 weeks after last treatment, and all 6 individual components of the PR-SMFIS showed similar patterns of improvement (Figure 4). PR-SMFIS scores remained low (indicating reduced psychological impact) at 12 months.

Overall, 87.5% (126/144) of subjects were satisfied with the appearance of their face/chin at 12 weeks after last treatment; 84.9% (107/126) continued to be satisfied at 12 months. Subject self-ratings of attractiveness of their chin/neck area increased from a mean (SD) baseline value of 2.8 (1.7) to 5.4 (1.9) at 12 weeks after last treatment. This effect was maintained at 12 months, with a mean score of 6.6 (1.3).

Caliper assessment of SMF thickness showed mean decreases from baseline of 27.2% and 30.9% at 12 weeks and 12 months

FIGURE 5. Mean percentage change from baseline in SMF thickness based on caliper assessment. SE, standard error; SMF, submental fat.

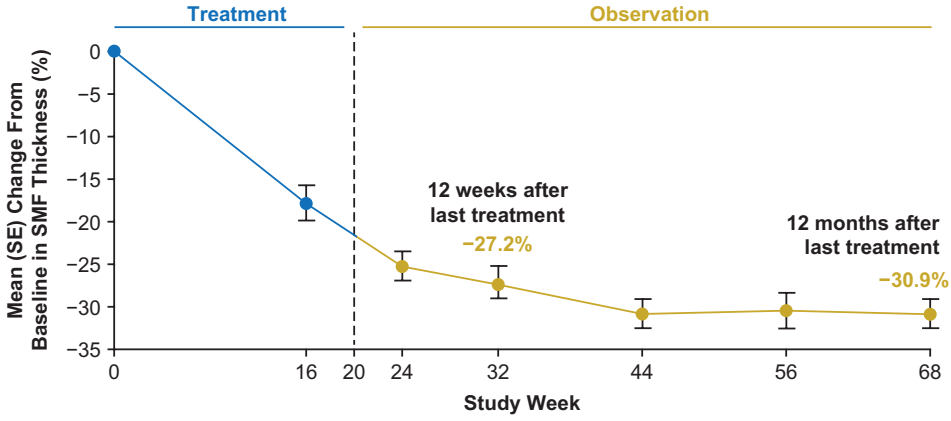
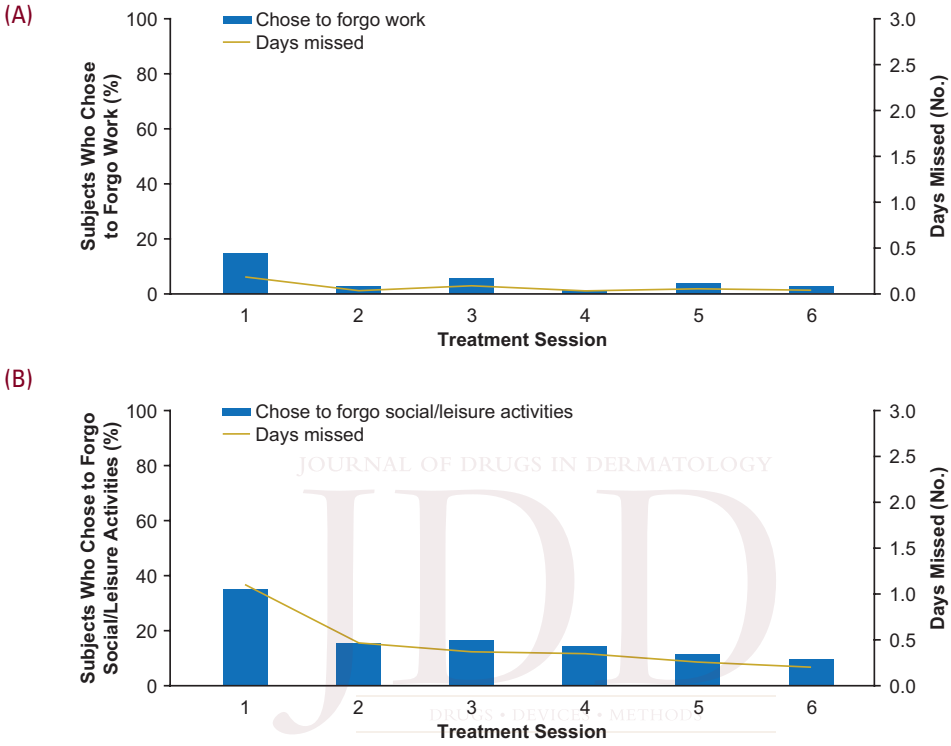


FIGURE 6. Percentage of subjects who missed (A) work or (B) social/leisure activities due to ATX-101 treatment and number of days missed.



after last treatment, respectively (Figure 5). At 12 months, skin laxity was unchanged in 82.9% and improved in 10.1% of subjects relative to their assessment at 12 weeks after last treatment.

Safety

As shown in Table 3, most AEs were mild or moderate and related to the treatment area. The majority of treatment area AEs were considered to be related to ATX-101 treatment. The median duration of treatment area AEs ranged from 1.0 day (paresthesia) to 27.5 days (anesthesia). Of all AEs, 32.0% were reported between treatments 1 and 2, and the incidence decreased (17.8% to 9.8%) for all subsequent treatments. The majority of AEs (90.2%) were reported during the open-label treatment period. Seven subjects experienced 8 serious AEs, all of which were unrelated or unlikely to be related to ATX-101 treatment (anxiety attack, arteriosclerosis and stent placement, cardiac death, cervical polyp, colon cancer, diverticulitis, or thyroid cancer). After completing the study, 1 subject died due to sudden myocardial infarction, which was not related to ATX-101 treatment. Headaches were possibly related to ATX-101 treatment in 8 of 15 subjects.

AEs of special interest, including skin ulceration, marginal mandibular nerve (MMN) paresis, and dysphagia occurred in 5 (3.0%), 2 (1.2%), and 1 (0.6%) subject(s), respectively. The skin ulcerations were mild to moderate, resolved within 13 to 31 days, and did not affect study treatment. Both events of MMN paresis (considered definitely related to ATX-101 treatment) resolved within 53 and 115 days. Dysphagia originated and resolved on Day 1 of the study.

No clinically significant changes in hematology, serum chemistry, urinalysis results, or vital signs were observed. No new safety signals were observed during follow-up. Four subjects had ongoing AEs considered related to ATX-101 treatment: headache, swollen lymph node, or scar (n=2).

Downtime

Overall, 13.3% of subjects missed work-related activities after their first ATX-101 treatment, with a mean of 1.1 days missed (Figure 6A). Downtime was less frequent following subsequent treatments, with 2.4% to 6.0% of subjects missing a mean of 0.2 to 0.5 days of work. Social/leisure activities were missed by 33.9% of subjects after their first treatment, with 2.9 missed days (Figure 6B). Subsequent treatments were also followed by less downtime, with 10.0% to 15.7% of subjects forgoing 0.8 to 2.2 days of social/leisure activities.

DISCUSSION

In this open-label study, the data demonstrate that both clinicians and subjects reported decreased SMF at 12 weeks after last treatment, consistent with the observations of the phase

TABLE 3.

Incidence of AEs Reported in ≥2% of Subjects	
AE, n (%)	ATX-101 N=165
Any AE	160 (97.0)
Mild*	48 (29.1)
Moderate†	101 (61.2)
Severe‡	11 (6.7)
Serious AE	7 (4.2)
Injection site AEs	
Other	14 (8.5)
Hematoma	121 (73.3)
Anesthesia	116 (70.3)
Pain	113 (68.5)
Edema	111 (67.3)
Erythema	83 (50.3)
Induration	61 (37.0)
Swelling	49 (29.7)
Pruritus	36 (21.8)
Nodule	32 (19.4)
Paresthesia	31 (18.8)
Discomfort	5 (3.0)
Non-injection site AEs	
Headache	15 (9.1)
Nasopharyngitis	8 (4.8)
Sinusitis	6 (3.6)
Hypertension	4 (2.4)

AE, adverse event.
*Subject was aware of the sign/symptom, but it was easily tolerated.
†Sign/symptom caused discomfort and interfered with the subject's usual activity.
‡Sign/symptom was incapacitating and the subject was unable to engage in usual activity.

3 trials that led to approval of ATX-101.[14,15,20-23] High responder rates (>80%) on the validated CR-SMFRS and PR-SMFRS at 12 weeks after last treatment, which were maintained at 12 months, indicate that durable and clinically meaningful improvements in SMF are achieved with ATX-101 treatment. Furthermore, 8 of 19 subjects who were CR-1 nonresponders at 12 weeks after last treatment converted to a responder during follow-up. Skin laxity was unchanged or improved after ATX-101 treatment despite a reduction in SMF (confirmed objectively by caliper assessments); this effect is likely due to neocollagenesis and thickening of fibrous septae following treatment.[18] In most subjects, downtime with regard to work or social/leisure activities was minimal (0.2–2.2 days) following ATX-101 treatment, especially when compared with downtime following liposuction, which has a recovery time of several weeks to months.[25,26] Furthermore, downtime was shown to decrease over subsequent ATX-101 treatments, likely due to less SMF to treat over time.

Notably, about one-third of subjects who completed the open-label period received <6 treatments owing to lack of sufficient SMF to safely inject study drug or subject satisfaction with treatment; this was similar to observations in the phase 3 trials.[14,21] In addition, these results underscore the importance of customizing ATX-101 treatment to each patient, in both the volume administered per treatment (as noted in the larger volume used with increasing SMF severity) and the total number of treatments.

The positive effects of ATX-101 treatment were maintained over 12 months of follow-up in this study. High percentages of subjects who were CR-1 or PR-1 responders at 12 weeks after last treatment maintained the response at 12 months, consistent with follow-up data from phase 2/3 ATX-101 trials.[27] Improvements continued during follow-up as evidenced by a >90% CR-1 response in all subjects at 12 months. Similarly, the reduction in the psychological impact of SMF and increase in satisfaction with the appearance of the face/chin were sustained over follow-up, along with the more objective measure of SMF thickness via caliper measurement, which showed further reductions following the assessment at 12 weeks after last treatment. Subject self-ratings of attractiveness of their chin/neck area also continued to improve during follow-up. Overall, these results suggest efficacy continued after the initial follow-up period. Importantly, none of the effects could be attributed to change in body weight since body weight remained stable throughout the study. Furthermore, maintenance of SMF improvement achieved at 12 weeks after last treatment over 12 months is consistent with the mechanism of action of ATX-101 (adipocytolysis), wherein the effects would be predicted to be durable.

In this study, AEs were mostly mild or moderate and were associated with the treatment area. Most AEs were expected owing to the route of delivery and mechanism of action of ATX-101. The incidence of AEs decreased over subsequent treatments and few led to study discontinuation. The rate of MMN paresis observed in this study is similar to or below the reported incidence for cervical rhytidectomy,[25] although care must be taken to avoid injection of the MMN. Effects on laboratory measures and vital signs were clinically unremarkable. These safety findings were comparable with those of phase 3 ATX-101 trials.[14,15,20-23]

One limitation of this study is its open-label design. However, both the clinician- and patient-reported outcomes were similar to those of randomized, controlled ATX-101 trials.[14,15,20-23]

CONCLUSIONS

ATX-101 treatment was well tolerated and effective in reducing SMF and improving outcomes both in the short term (12 weeks) and long term (12 months). Data from this study are consistent with the established mechanism of action, dosing, and safety of

ATX-101 treatment, as well as the demonstrated clinical results in SMF reduction in multiple randomized, placebo-controlled trials. In summary, the results of these trials demonstrate that ATX-101 is a viable nonsurgical treatment option for submental contouring.

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