

Improvements in Submental Contour Up to 3 Years After ATX-101: Efficacy and Safety Follow-Up of the Phase 3 REFINE Trials

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Abstract

Background: ATX-101 (deoxycholic acid) significantly reduced submental fat (SMF) severity in two 24-week Phase 3 studies (REFINE-1 and REFINE-2).

Objectives: The aim of this study was to evaluate the durability of effect and long-term safety of ATX-101.

Methods: REFINE study patients who maintained ≥ 1 -grade improvement on the Clinician-Reported SMF Rating Scale (CR-1 responders) 12 weeks after their last REFINE treatment were eligible for enrollment in this multicenter, double-blind, nontreatment, long-term, follow-up study (NCT02163902). The primary endpoint was CR-1 response at Years 1, 2, and 3. Patient-reported satisfaction, psychological impact, and adverse events were monitored.

Results: In total, 224 patients (ATX-101, $n = 113$; placebo, $n = 111$) were enrolled. Maintenance of CR-1 response was significantly better in the ATX-101 group than in the placebo group at Year 1 (86.4% vs 56.8%; $P < 0.001$), Year 2 (90.6% vs 73.8%; $P = 0.014$), and Year 3 (82.4% vs 65.0%; $P = 0.03$). Most (74%) ATX-101-treated patients satisfied at 12 weeks remained satisfied at Year 3. Significant reductions from baseline in psychological impact scores were sustained through Year 3 ($P < 0.001$). No new treatment-related adverse events were reported.

Conclusions: Improvements in submental contour achieved with ATX-101 are maintained for 3 years in most patients. No new safety signals emerged.

Level of Evidence: 2

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Excessive submental fat (SMF) and loss of submental definition can negatively affect an individual's overall facial

appearance and emotional well-being.^{1,2} SMF can be resistant to diet and exercise, and, historically, the only

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treatment options for SMF reduction were invasive surgical procedures and/or liposuction.³

ATX-101 (deoxycholic acid injection, sold as Kybella in the United States and as Belkyra in Canada, Australia, and Europe [Allergan Sales, LLC, an AbbVie Company, Madison, NJ])^{4,5} is a nonsurgical treatment that was approved by the US FDA in 2015 to treat the appearance of moderate to severe convexity or fullness associated with SMF.⁵ The efficacy and safety of ATX-101 was demonstrated in 4 multicenter, double-blind, placebo-controlled, Phase 3 trials, including 2 conducted in Europe^{6,7} and 2 conducted in the United States and Canada (REFINE-1⁸ and REFINE-2⁹).

There is a paucity of data on the duration of treatment effect and long-term safety profile of ATX-101. The REFINE studies followed patients for 24 weeks after the last treatment.^{8,9} The current nontreatment study followed patients from the REFINE trials for up to 3 years after the last treatment in REFINE to evaluate the maintenance of treatment effect and long-term safety of ATX-101 vs placebo.

METHODS

Study Design

This multicenter, double-blind, nontreatment study (NCT02163902) in patients who maintained ≥ 1 -grade improvement on the Clinician-Reported SMF Rating Scale (CR-SMFRS; CR-1 responders) 12 weeks after their last treatment in 1 of the 2 Phase 3 antecedent studies (REFINE-1 [NCT01542034] and REFINE-2 [NCT01546142]) was conducted between December 2013 and January 2016 at 13 sites in the United States and 2 sites in Canada. The IRB at each site (Chesapeake, United States; Veritas, Canada) reviewed and approved the protocol and informed consent form (approval #MOD00080448). All patients provided informed consent prior to participation and the study was conducted in compliance with the International Council for Harmonisation Good Clinical Practice guidelines. The study authors disclosed their potential conflicts of interest to all study participants.

In both antecedent studies, enrolled adults had either moderate or severe SMF (graded by clinicians according to the validated CR-SMFRS), had a moderate or large amount of SMF (graded by patients according to the validated Patient-Reported SMF Rating Scale [PR-SMFRS]), and were extremely to slightly dissatisfied with the appearance of their face/chin (on the Subject Self-Rating Scale [SSRS], which assesses overall satisfaction with the appearance of the face and chin evaluated by patients on a 7-point scale where 0 = extremely dissatisfied and 6 = extremely satisfied). Enrolled patients had no prior intervention for SMF (eg, liposuction, surgery, or lipolytic agents). Patients received treatment with ATX-101 (area-adjusted dose, 2 mg/cm²)

or placebo for ≤ 6 treatment sessions (every 28 ± 5 days). Detailed methods of the REFINE studies have been published.⁸⁻¹⁰ After completing the antecedent study, patients could have enrolled in this follow-up study at any time for ≤ 36 months (± 90 days) after the last treatment, although entry at 12 months after last REFINE treatment was preferred. Safety and maintenance of treatment effect was evaluated at 3 visits that occurred 1 year (± 45 days), 2 years (± 45 days), and 3 years (± 90 days) after the last REFINE treatment.

Patients

Eligibility criteria for the REFINE trials have been published.⁸⁻¹⁰ To enroll in this long-term follow-up study, patients must have completed visits at 12 and 24 weeks after their last REFINE treatment. Patients were excluded if they had undergone any other treatment or developed any condition since enrollment in the antecedent study that may have affected safety or efficacy assessments.

Assessments

The primary efficacy endpoint was maintenance of ≥ 1 -grade improvement in CR-SMFRS score (CR-1 response) at Years 1, 2, and 3. Secondary efficacy endpoints evaluated the 1-, 2-, and 3-year maintenance of response achieved at 12 weeks after the last treatment in REFINE and included: CR-2 response (≥ 2 -grade improvement in CR-SMFRS score), PR-1 and PR-2 responses (≥ 1 - and ≥ 2 -grade improvements in PR-SMFRS score), and composite CR-1/PR-1 or CR-2/PR-2 response (≥ 1 - or ≥ 2 -grade improvements in both CR-SMFRS and PR-SMFRS scores). Additional efficacy endpoints were patient-reported satisfaction with appearance of face/chin on the SSRS, psychological impact of SMF on the Patient-Reported Submental Fat Impact Scale (PR-SMFIS) total scale score (TSS), and submental skin laxity assessed by investigators according to the Submental Skin Laxity Grade scale at Years 1, 2, and 3. The SSRS was provided to patients and self-completed on paper during the study visit without input from staff or clinicians. The PR-SMFIS TSS includes assessments of emotional/visual characteristics (eg, happiness, bother, self-consciousness, embarrassment, looking older, looking overweight) relative to the appearance of chin fat.¹⁰ Lower scores indicate improvement or reduced negative impact.

Safety assessments included the incidence, severity, and duration of newly reported or continuing adverse events (AEs). All AEs that were ongoing at the conclusion of the antecedent studies, regardless of relatedness to treatment, were followed until resolved or medically stable. Treatment-emergent AEs (TEAEs) were defined as AEs that started or worsened in severity after first exposure to the study drug in the antecedent studies.

Statistical Analysis

Based on clinical, rather than statistical, considerations, a sample size of ~200 patients (100 ATX-101, 100 placebo) was considered sufficient to evaluate the long-term effects of treatment. The safety population comprised all patients enrolled in the long-term follow-up study. For the primary and secondary efficacy endpoints, the proportion of patients who maintained CR-1, PR-1, or composite CR-1/PR-1 response status at each visit was compared between treatments with a Cochran-Mantel-Haenszel (CMH) test stratified by antecedent study. The proportion of patients who were SSRS responders (response of 4 = slightly satisfied, 5 = satisfied, or 6 = extremely satisfied) at each visit was compared between treatments with a CMH test stratified by antecedent study. Change from pretreatment baseline in mean PR-SMFIS TSS was analyzed with an analysis of covariance model with effects of treatment and baseline value.

RESULTS

Demographics and Baseline Characteristics

Of 257 patients from the REFINE studies screened for the long-term follow-up study, 224 patients (ATX-101, $n = 113$; placebo, $n = 111$) were enrolled. The most common reason not to enroll was lack of patient interest or availability ($n = 24$); 200 patients (89.3%; ATX-101, $n = 102$; placebo, $n = 98$) completed the study. Table 1 summarizes patient demographics and pretreatment baseline characteristics. Overall, most patients were female (85.3%, $n = 191$; males 14.7%, $n = 33$) and white (87.9%), with a mean age of 50.6 years (range, 23-67 years) and mean BMI of 29.1 kg/m² (range, 19.5-42.8 kg/m²).

At 12 weeks after their last treatment in the REFINE studies, 62.8% of patients in the ATX-101 group and 12.6% in the placebo group had absent or mild SMF ratings on the CR-SMFRS. Ninety-five patients (84.0%) in the ATX-101 group and 46 patients (41.4%) in the placebo group were CR-1 responders at 12 weeks after their last treatment. Ninety-eight patients (86.7%) and 58 patients (52.3%), respectively, were PR-1 responders at 12 weeks after their last treatment.

Maintenance of Efficacy

Clinician-rated SMF severity

Maintenance of CR-1 response in patients who were CR-1 responders at 12 weeks after their last treatment in REFINE was achieved at significantly higher rates in the

Table 1. Demographics and Baseline Characteristics

	Placebo	ATX-101
	$n = 111$	$n = 113$
Age (years)	50.1 [9.0]	51.0 [8.2]
Range (years)	24-67	23-67
Sex, female	95 (85.6)	96 (85.0)
Race		
White	101 (91.0)	96 (85.0)
Black	7 (6.3)	12 (10.6)
Asian	1 (0.9)	4 (3.5)
Other	2 (1.8)	1 (0.9)
Weight (kg)	79.9 [13.6]	80.6 [13.3]
Range (kg)	52.7-108.7	53.5-116.2
BMI (kg/m ²)	28.8 [4.0]	29.3 [4.5]
Range (kg/m ²)	21.3-42.8	19.5-40.4

Unless otherwise indicated, values are mean [standard deviation] or n (%).

ATX-101 group vs placebo at Years 1, 2, and 3 (Figure 1). Among patients who had a ≥ 2 -grade improvement in SMF (CR-2 response) at 12 weeks after their last treatment in REFINE, the CR-2 response was maintained by 75.0% of patients in the ATX-101 group and 18.2% in the placebo group at Year 1, by 72.5% and 33.3% at Year 2, and by 65.8% and 33.3% at Year 3 (Figure 2). There was no consistent difference in the mean number of treatments received and efficacy duration when analyzing ATX-101 responders vs nonresponders by year (data not shown).

Patient-rated SMF severity

For patients who achieved ≥ 1 -grade improvement from baseline in SMF (PR-1 response) at 12 weeks in REFINE, the rate of maintenance of response was higher in the ATX-101 group vs placebo at Years 1, 2, and 3 (Figure 1). Of 54 patients (47.8%) in the ATX-101 group and 11 patients (9.9%) in the placebo group who achieved ≥ 2 -grade improvement (PR-2 response) at 12 weeks in REFINE ($P < 0.001$), the PR-2 response was maintained by 59.0% (22/39) and 63.6% (7/11) at Year 1, 57.5% (23/40) and 60.0% (6/10) at Year 2, and 59.5% (22/37) and 70.0% (7/10) at Year 3, respectively.

Composite clinician- and patient-rated SMF severity

Among patients who achieved a composite CR-1/PR-1 response at 12 weeks after their last treatment in REFINE, significantly higher proportions of patients maintained a

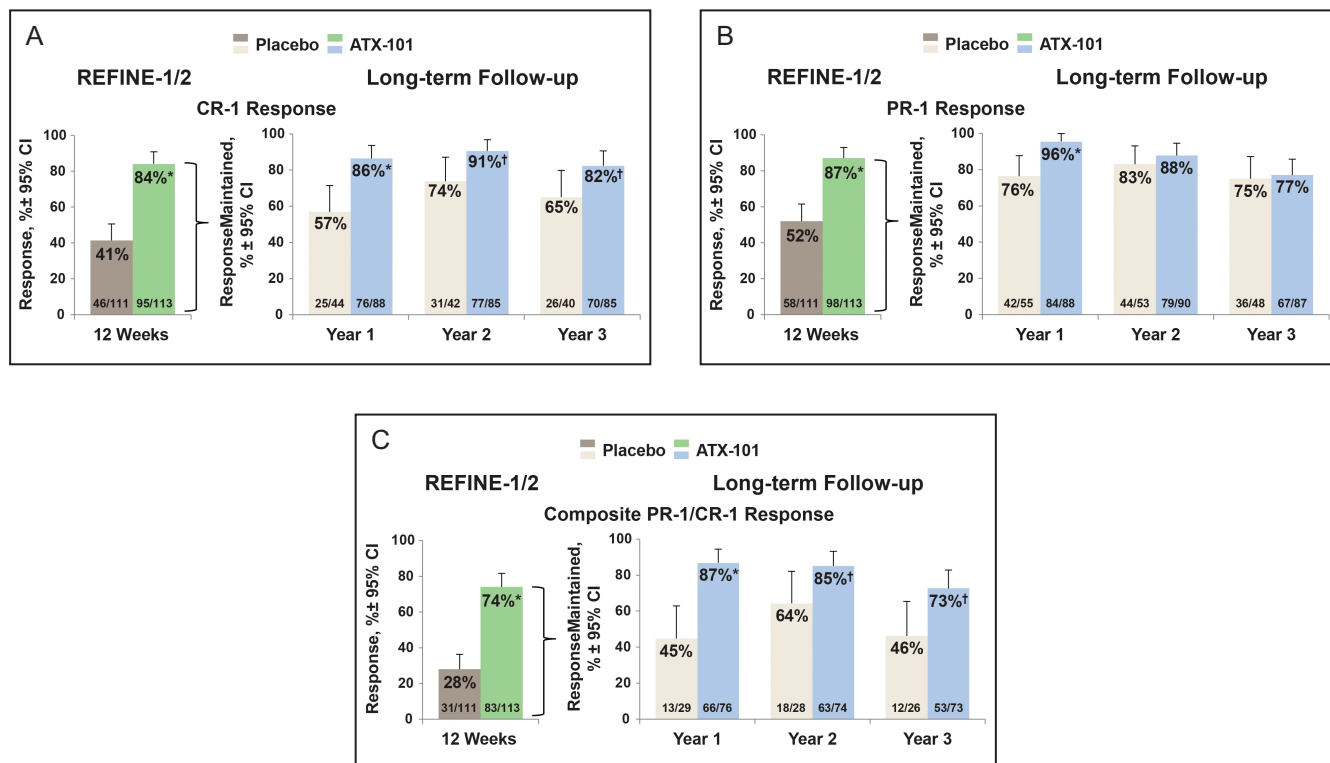


Figure 1. Three-year durability of REFINE study response. Percentage of patients who had achieved a ≥ 1 -grade improvement in SMF from baseline at 12 weeks after their last REFINE treatment and the percentage of responders who maintained the response for up to 3 years (long term) are shown: (A) clinician assessment via the CR-SMFRS (CR-1 response) at 12 weeks and long term; (B) patient assessment via the 5-point PR-SMFRS (PR-1 response) at 12 weeks and long term; and (C) composite CR-1/PR-1 response at 12 weeks and long term. * $P < 0.001$ for ATX-101 vs placebo; † $P < 0.05$ for ATX-101 vs placebo. CR-SMFRS, Clinician-Reported Submental Fat Rating Scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme¹⁰); PR-SMFRS, Patient-Reported Submental Fat Rating Scale (0 = no chin fat, 1 = slight amount, 2 = moderate amount, 3 = large amount, 4 = very large amount¹⁰); SMF, submental fat.

composite response in the ATX-101 group vs the placebo group at Years 1, 2, and 3 (Figure 1). Composite 2-grade responses were achieved by 18 patients (15.9%) in the ATX-101 group and by 3 patients (2.7%) in the placebo group at 12 weeks after their last treatment in REFINE ($P < 0.001$) and were maintained by 41.2% (7/17), 43.8% (7/16), and 50.0% (7/14) of responders in the ATX-101 group at Years 1, 2, and 3, respectively, by none of the responders in the placebo group at Years 1 and 2, and by 1 patient (1/2; 50%) in the placebo group at Year 3.

Patient satisfaction

For patients who were slightly to extremely satisfied with the appearance of their face/chin (SSRS responders) at 12 weeks after their last treatment in REFINE, maintenance of the SSRS response was significantly higher in the ATX-101 group vs placebo at Years 1 and 2, and was numerically higher at Year 3 (Figure 3).

Psychological impact of SMF

Mean PR-SMFIS scores were consistently lower in the ATX-101 group vs placebo at all time points through Year 3, reflecting the reduced psychological impact of SMF after ATX-101 treatment (Figure 4). The mean change from baseline in PR-SMFIS scores was significantly greater with ATX-101 vs placebo at all time points up to Year 3.

Skin laxity

Submental skin laxity was unchanged or improved from baseline in most patients in both treatment groups at Year 1 (81% [ATX-101] vs 75% [placebo]), Year 2 (78% vs 76%), and Year 3 (75% vs 74%). Of note, a trend was observed for nonresponders to be more likely to have weight increases than the responder group, although the patient numbers were too small to draw any firm conclusions.

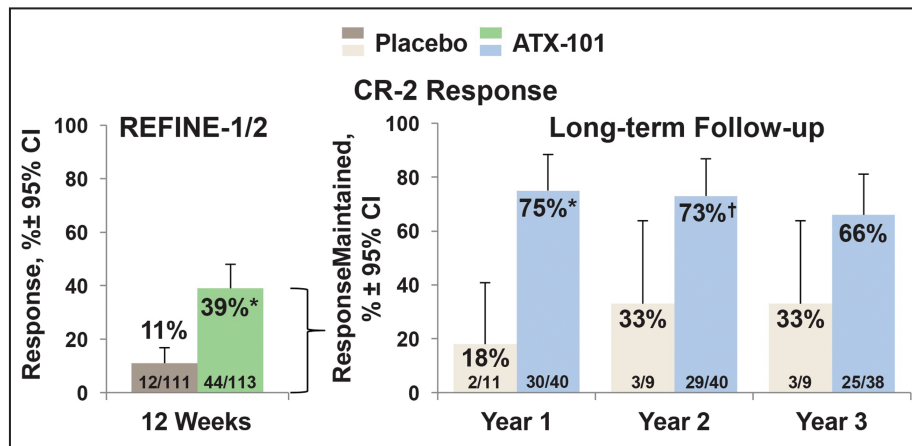


Figure 2. Three-year durability of REFINE study ≥ 2 -grade CR-SMFRS response. Responses for the percentage of patients who had achieved a ≥ 2 -grade improvement in SMF from baseline according to the CR-SMFRS (CR-2 response) are shown at 12 weeks and up to 3 years (long-term follow-up) after their last REFINE treatment. * $P < 0.001$ for ATX-101 vs placebo; † $P < 0.05$ for ATX-101 vs placebo. CR-SMFRS, Clinician-Reported SMF Rating Scale; SMF, submental fat.

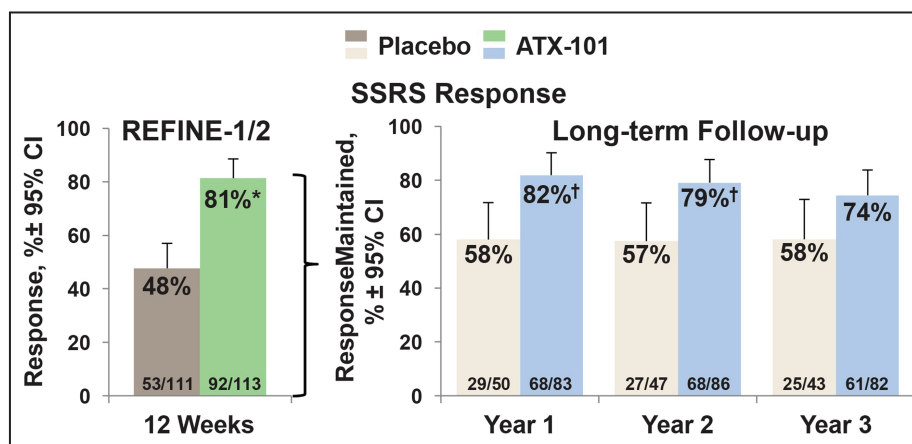


Figure 3. Three-year durability of REFINE study patient satisfaction response. Patient-reported satisfaction with appearance of face and chin on the SSRS. SSRS responders reported a score of 4 (slightly satisfied), 5 (satisfied), or 6 (extremely satisfied). Percentage of patients who were SSRS responders at 12 weeks after their last REFINE treatment, and percentage of SSRS responders at 12 weeks who maintained response for up to 3 years during the long-term follow-up are shown. * $P < 0.001$ for ATX-101 vs placebo; † $P < 0.05$ for ATX-101 vs placebo. SSRS, Subject Self-Rating Scale (0 = extremely dissatisfied, 1 = dissatisfied, 2 = slightly dissatisfied, 3 = neither satisfied nor dissatisfied, 4 = slightly satisfied, 5 = satisfied, 6 = extremely satisfied¹⁰).

Safety

All 224 patients enrolled in the long-term follow-up study were included in safety analyses. Newly reported or continuing TEAEs occurred in 33.6% (38/113) and 18.9% (21/111) of patients in the ATX-101 and placebo groups, respectively. Most TEAEs were mild (70.6% [36/51] of events in the ATX-101 group and 71.0% [22/31] in the placebo group) or moderate (25.5% [13/51] and 25.8% [8/31], respectively). There were 2 severe unrelated TEAEs in the ATX-101 group and 1 in the placebo group. Serious unrelated

TEAEs occurred in 3.5% (4/113) of ATX-101-treated patients and in none of the placebo-treated patients. There were no deaths or discontinuations due to AEs.

Fifteen TEAEs were first reported in the 3-year evaluation period since last treatment in REFINE: 11 in the ATX-101 group (diverticulitis, $n = 2$; and back pain, breast reconstruction, drug hypersensitivity, hemorrhoids, influenza, lipoma, small cell lung cancer, uterine prolapse, and vitamin D deficiency in 1 patient each) and 4 in the placebo group (anaphylactic shock, abnormal hormone level, osteoarthritis, and urinary tract

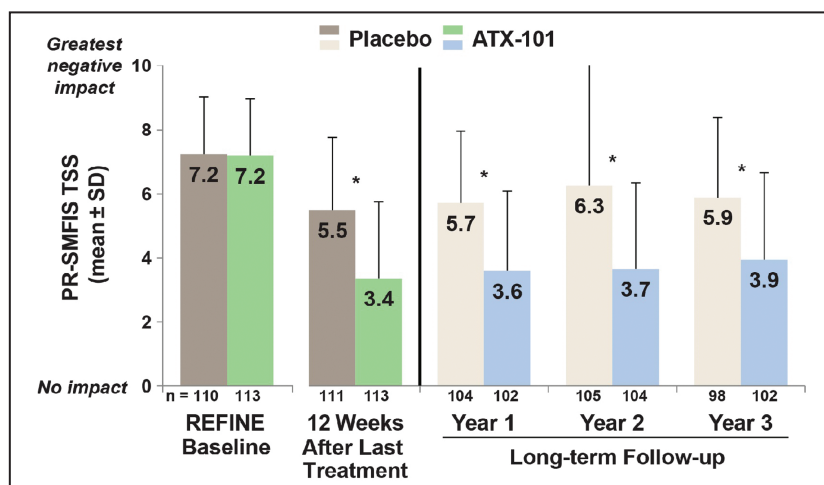


Figure 4. Three-year durability of REFINE study psychological impact of SMF response. Patient assessment of the psychological impact of SMF according to the PR-SMFIS at baseline, at 12 weeks after last treatment, and for up to 3 years of long-term follow-up are shown. * $P < 0.001$ for change from baseline with ATX-101 vs placebo. PR-SMFIS, Patient-Reported Submental Fat Impact Scale; SMF, submental fat; TSS, total scale score.

infection in 1 patient each). None of these events were treatment related.

Four treatment-related TEAEs reported in the antecedent studies continued in the long-term follow-up study, all in 1 patient each (hypothyroidism, low T3, increased white blood cell count, and proteinuria). Mild TEAEs associated with the treatment area occurred in 2 patients (1.8%) in the ATX-101 group (injection site lymphadenopathy [$n = 1$] and application site discoloration [$n = 1$]) and 1 patient (0.9%) in the placebo group (injection site discoloration and hirsutism in the same patient). All of these events were first reported during the REFINE studies and were considered unrelated to treatment.

DISCUSSION

This study evaluated the durability of effect and the safety profile of ATX-101 for 3 years after the last ATX-101 treatment in the REFINE studies. The improvements in submental contour achieved with ATX-101 at 12 weeks after the last treatment in the REFINE studies were maintained for up to 3 years in the majority of patients, based on separate and composite SMF ratings by the clinician and the patient. Patient satisfaction with the appearance of the face/chin remained high in the ATX-101 group for up to 3 years. Approximately three-quarters of patients who reported being satisfied at 12 weeks after last treatment were still satisfied with their appearance at Year 3. Significant reductions in the psychological impact of SMF were maintained for up to 3 years, with mean decreases from baseline in PR-SMFIS total score remaining

significantly greater with ATX-101 than placebo up to Year 3.

The observed durability of treatment response in the ATX-101 group is consistent with the mechanism of action of ATX-101. Phase 1 clinical histology and preclinical data showed that injection of ATX-101 into subcutaneous fat physically disrupts the cell membrane of adipocytes, causing adipocytolysis.¹¹⁻¹⁵ Adipocytolysis occurs within the first day after treatment and is followed by neutrophilic inflammation at Days 1 to 3 and subsequent clearing of cellular debris and free lipids by macrophages.¹² Inflammation is largely resolved within 1 month after treatment, when fibroblasts and thickening of fibrous septa can be observed, suggesting that neocollagenesis occurs in the treated area.^{11,12}

Although there was a substantial placebo effect observed in maintenance of patient ratings of SMF severity, it was less apparent in the results of the other patient-reported outcomes, including satisfaction (SSRS response) and psychological impact scores (PR-SMFIS TSS). These outcome measures may be a better representation of the patient voice than PR-SMFRS. Additionally, it is noteworthy that the patient numbers were uniformly lower in the placebo responder ($n = 40-55$) vs ATX-101 responder ($n = 85-90$) subgroups during the 3-year follow-up period. Thus, comparing the percentages may be misleading without also considering the numbers of contributing patients.

No new safety signals were observed during the long-term follow-up study. Most ATX-101-related AEs reported in the REFINE studies were inflammatory (eg, edema/swelling, pain, erythema, and hematoma) and

related (eg, anesthesia and paresthesia) events associated with the injection site^{10,16} that are not unexpected based on the adipocytolytic mechanism of deoxycholic acid.^{10,17} Most AEs resolved within 1 month of the REFINE treatment session, with the incidence, severity, and duration of AEs declining after each subsequent session.^{10,16} No treatment-related TEAEs had onset during the 3-year long-term follow-up study. All TEAEs associated with the treatment area were first reported before the end of the antecedent studies (within 6 months of last treatment) and all were considered unrelated to treatment.

Possible limitations of this study include aspects of the study design that may affect generalizability of results. Although all patients who completed the 12- and 24-week follow-up visits in the antecedent studies were eligible for the long-term follow-up study, patients who were satisfied with their SMF improvement in the antecedent trials may have been more likely to enroll. This could have occurred not only for patients in the ATX-101 group, but also for patients in the placebo group who believed that they were receiving an active drug and reported some improvement. The numbers of patients enrolled in each group in REFINE were nearly equivalent, although the number of actual responders was much lower for placebo patients than for ATX-101 patients. Attrition often affects long-term follow-up studies, yet ~90% of enrolled patients overall and within each treatment group completed this study. Nevertheless, patients who felt their results worsened or who were dissatisfied with their experiences during the long-term follow-up period may have been more likely to discontinue the study before completing the full 3 years of follow-up. In addition, the results for 2-grade improvements in SMF severity are limited by the small number of patients who had these responses at 12 weeks in the antecedent studies. Lastly, another limitation is the absence of objective evaluations in the form of magnetic resonance imaging or 3-dimensional photographic assessments during this long-term follow-up study.

CONCLUSIONS

This long-term follow-up study demonstrates that improvements in submental contour achieved with ATX-101 are maintained for up to 3 years in the majority of patients. Patient satisfaction and the psychological impact of SMF also remained improved for up to 3 years after treatment. No new safety signals were observed. Overall, the durable treatment response and long-term safety profile are consistent with the adipocytolytic mechanism of action of ATX-101.

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Disclosures

Drs Humphrey, Cohen, L. Green, and J. Green are investigators for Allergan Aesthetics (Dublin, Ireland), an AbbVie Company. Dr Bhatia has served as a consultant to Allergan Aesthetics, an AbbVie Company. Dr Bowen is an employee of AbbVie (North Chicago, IL) and may own stock/stock options in the company.

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