ATX-101 for reduction of submental fat: A phase III randomized controlled trial

Shannon Humphrey, MD,[a,b] Jonathan Sykes, MD,[c] Jonathan Kantor, MD, MSCE, MA,[d,e] Vince Bertucci, MD,[f,g] Patricia Walker, MD, PhD,[h] Daniel R. Lee, MS,[h] Paul F. Lizzul, MD, PhD, MPH, MBA,[h] Todd M. Gross, PhD,[h] and Frederick C. Beddingfield III, MD, PhD[h,i]

Vancouver, British Columbia, and Toronto and Woodbridge, Ontario, Canada; Sacramento, Westlake Village, and Los Angeles, California; St. Augustine, Florida; and Philadelphia, Pennsylvania

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Background: ATX-101, an injectable form of deoxycholic acid, causes adipocytolysis when injected subcutaneously into fat.

Objective: We sought to evaluate the efficacy and safety of ATX-101.

Methods: In this phase III trial (REFINE-2), adults dissatisfied with their moderate or severe submental fat (SMF) were randomized to ATX-101 or placebo. Coprimary end points, evaluated at 12 weeks after last treatment, were composite improvements of 1 or more grades and 2 or more grades in SMF observed on both the validated Clinician- and Patient-Reported SMF Rating Scales. Other end points included magnetic resonance imaging–based assessment of submental volume, assessment of psychological impact of SMF, and additional patient-reported outcomes.

Results: Among those treated with ATX-101 or placebo (n = 258/treatment group), 66.5% versus 22.2%, respectively, achieved a composite improvement of 1 or more grades (Mantel-Haenszel risk ratio 2.98; 95% confidence interval 2.31-3.85) and 18.6% versus 3.0% achieved a composite improvement of 2 or more grades in SMF (Mantel-Haenszel risk ratio 6.27; 95% confidence interval 2.91-13.52; $P < .001$ for both). Those treated with ATX-101 were more likely to achieve submental volume reduction confirmed by magnetic resonance imaging, greater reduction in psychological impact of SMF, and satisfaction with treatment ($P < .001$ for all). Overall, 85.7% of adverse events in the ATX-101 group and 76.9% in the placebo group were localized to the injection site.

From the University of British Columbia[a]; Carruthers & Humphrey, Vancouver[b]; University of California, Davis, Sacramento[c]; Florida Center for Dermatology PA[d]; University of Pennsylvania Perelman School of Medicine[e]; University of Toronto and Women's College Hospital[f]; Bertucci MedSpa, Woodbridge[g]; Kythera Biopharmaceuticals, Inc, Westlake Village[h]; and David Geffen School of Medicine, University of California, Los Angeles.[i]

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Table I, the supplementary table, and the supplementary figures are available at http://www.jaad.org.

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Reprint requests: Shannon Humphrey, MD, Carruthers & Humphrey, 943 W Broadway, Suite 820, Vancouver, British Columbia V5Z 4E1, Canada. E-mail: shannon@carruthers-humphrey.com.

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Limitations: Follow-up was limited to 44 weeks.

Conclusion: ATX-101 is an alternative treatment for SMF reduction. (J Am Acad Dermatol 2016;75:788-97.)

Key words: aesthetics; ATX-101; contouring; deoxycholic acid; efficacy; injectable; minimally invasive; nonsurgical; safety; submental fat.

CAPSULE SUMMARY

- Standard treatment for submental contouring has included aesthetic surgical procedures and liposuction.
- This study used investigator and patient assessment and magnetic resonance imaging to demonstrate the efficacy of ATX-101, an injectable form of deoxycholic acid, for submental fat reduction.
- ATX-101 may be an effective, nonsurgical treatment for submental fat reduction.

Submental fat (SMF) can contribute to an unappealing fullness under the chin, negatively impacting facial appearance and psychological well-being.[1] Aesthetic surgical procedures and liposuction have been the standard treatment for SMF reduction.[2-4] However, ATX-101 (Kybella in the United States and Belkyra in Canada; Kythera Biopharmaceuticals, Inc, Westlake Village, CA [an affiliate of Allergan plc, Dublin, Ireland]), an injectable form of deoxycholic acid, was recently approved for reduction of SMF.[5] When injected subcutaneously into fat, ATX-101 causes adipocytolysis, which stimulates a local tissue response consisting of macrophage infiltration (to remove cellular debris and liberated lipids), fibroblast recruitment, and collagen production (neocollagenesis).[6] The efficacy and safety of ATX-101 have been extensively evaluated.[7-12] In this article, results from the phase III REFINE-2 trial, which supported approval of ATX-101 in the United States and Canada, are reported.

METHODS

Study design

REFINE-2 (NCT01546142) was a randomized, double-blind, placebo-controlled trial conducted at 35 sites in the United States and Canada between March 2012 and August 2013 in accordance with International Conference on Harmonisation Tripartite Guidelines on Good Clinical Practice and applicable Food and Drug Administration regulations. Central and local institutional review boards approved the protocol. All patients provided written informed consent. Financial compensation of patients was at the discretion of each study site.

Patients were randomized 1:1 to receive ATX-101 (dose strength: 2 mg/cm^2) or placebo (phosphate-buffered saline preserved with 0.9% benzyl alcohol) via subcutaneous injections into preplatysmal fat (Supplementary Fig 1). Patients received 10 mL or less (≤100 mg) of study drug per treatment administered in 0.2-mL injections with a 30-gauge, 0.5-in needle attached to a 1-mL syringe at 1.0-cm spacing using a grid. Up to 6 treatments (28 ± 5 days apart) were permitted, but fewer were allowed because of efficacy (insufficient SMF to inject, patient satisfaction with treatment), safety/tolerability concerns, or administrative reasons. Ice or topical/local anesthetics could be applied to the treatment area at the investigator's discretion. Before patient recruitment, investigators attended injection training and were required to view an injection training video.

Patients

Adults aged 18 to 65 years who were dissatisfied with the appearance of their face/chin (rating of 0, 1, or 2 on Subject Self-Rating Scale; details of all scales summarized in Table I) and whose SMF was rated as moderate (grade 2) or severe/large (grade 3) on both the validated Clinician- and Patient-Reported SMF Rating Scales were eligible. Body weight had to be stable for at least 6 months based on investigator judgment. Key exclusion criteria were body mass index higher than 40 kg/m^2; excessive submental skin laxity based on investigator judgment; and prior intervention(s) to treat SMF, including radiofrequency, lasers, chemical peels, or dermal fillers in neck/chin within 12 months, botulinum toxin injections in neck/chin within 6 months, or history of liposuction, surgery, or treatment with lipolytic agents. In addition, for centers selected to conduct magnetic resonance imaging (MRI), any patient with a condition that would render him or her unsuitable for MRI was excluded. Full exclusion criteria are listed in Supplementary Table I.

End points

Coprimary end points, evaluated at 12 weeks after last treatment, were proportion of patients who achieved improvement of 1 or more grades on both the Clinician- and Patient-Reported SMF

Abbreviations used:

AE:	adverse event
MMN:	marginal mandibular nerve
MRI:	magnetic resonance imaging
PR-SMFIS:	Patient-Reported Submental Fat Impact Scale
SMF:	submental fat

Rating Scales, and proportion of patients who achieved improvement of 2 or more grades on both scales.

The first of 2 secondary end points was proportion of patients who achieved a 10% or more reduction from baseline in MRI-measured submental volume (defined a priori as a responder), which was evaluated in a subset of patients (MRI methodology reported previously[8]). The other secondary end point was change from baseline in psychological impact of SMF using the Total Scale Score from the validated Patient-Reported SMF Impact Scale (PR-SMFIS).

Additional end points included change from baseline in SMF thickness using calipers; change from baseline in PR-SMFIS component scores; proportion of patients who achieved improvement of 1 or more grades or 2 or more grades independently on the Clinician- and Patient-Reported SMF Rating Scales; proportion of patients satisfied with the appearance of their face/chin (based on Subject Self-Rating Scale); proportion of patients satisfied with the fat under their chin, definition between their chin and neck, and with treatment (based on Subject Global Questions 1-3, respectively); and assessment of SMF based on standardized line drawings of submental convexity. All end points were evaluated at 12 and 24 weeks after last treatment with the exception of submental volume (via MRI) and Subject Global Questions, which were only evaluated at 12 weeks after last treatment. For documentation, standardized photography was performed at screening and at 12 and 24 weeks after last treatment.

Safety was evaluated throughout the trial via visual and tactile assessment of the submental area, spontaneous reports of adverse events (AEs), clinical laboratory tests, vital signs, body weight, and physical examinations. Submental skin laxity was graded by the investigator using the Submental Skin Laxity Grade scale.

Statistical analysis

A sample of 250 patients per treatment group provided 92.8% power to detect differences on the 2 coprimary end points (composite ≥1-grade and ≥2-grade responder rate), and 99.9% power for the secondary end point of change from baseline in PR-SMFIS Total Scale Score. A sample of 100 patients per treatment group provided 99.9% power for the secondary end point of MRI-based submental volume responder rate. Power calculations assumed a 10% dropout, 2-tailed tests, $\alpha = 0.05$ for the coprimary end points, and multiplicity-adjusted $\alpha = 0.025$ for the 2 secondary end points, and were based on responder rates observed in an earlier ATX-101 trial (NCT01032889). MRIs were performed at 16 centers (identified before trial start); the first approximately 200 patients randomized at these centers underwent MRI.

Formal hypotheses tests were conducted for the coprimary end points ($\alpha = 0.05$), and for the 2 secondary end points (using a Bonferroni-Holm adjustment for 2 tests), in the intent-to-treat population, with multiple imputation of missing data. A Cochran-Mantel-Haenszel analysis stratified by site was performed for responder end points. Sensitivity analyses assessed the impact of the method of imputation and method of statistical analysis on the primary end point analyses. Continuous variables were analyzed using an analysis of covariance model with treatment as fixed effect and baseline value as covariate. All statistical analyses were performed using SAS, Version 9.2 or higher (SAS Institute, Cary, NC).

RESULTS

Patient disposition and baseline characteristics

Overall, 516 patients were randomized (ATX-101, 258; placebo, 258) (Supplementary Fig 2). Demographic and baseline characteristics are shown in Table II. Across both groups, 86.0% of patients were white, 86.2% were female, mean age was 47.9 years (SD 9.1), and mean body mass index was 29.3 kg/m^2 (4.5). All Fitzpatrick skin types were represented.

Treatment characteristics

The total mean volume (SD) of study drug injected across all treatments was 25.6 (14.6) mL in the ATX-101 group and 32.3 (15.1) mL in the placebo group. Injected volume decreased by 28% and 17% for ATX-101 and placebo patients, respectively, over successive treatments. Overall, 119 of 258 (46.1%) patients treated with ATX-101 received fewer than 6 treatments, with 56 of 119 (47.1%) stopping treatment because of efficacy and 17 of 119 (14.3%) because of AEs (Supplementary Fig 2).

Efficacy

At 12 weeks after last treatment, more patients treated with ATX-101 (66.5%) than placebo (22.2%) achieved a composite improvement of 1 or more

Table II. Demographic and baseline characteristics

	Placebo, n = 258	ATX-101, n = 258
Age, mean (SD), y	47.6 (9.0)	48.2 (9.3)
Female, n (%)	224 (86.8)	221 (85.7)
Race, n (%)		
White	222 (86.0)	222 (86.0)
Black	21 (8.1)	24 (9.3)
Asian	5 (1.9)	4 (1.6)
Other	10 (3.9)	8 (3.1)
Hispanic or Latino, n (%)	39 (15.1)	40 (15.5)
Weight, mean (SD), kg	80.3 (15.0)	81.4 (14.8)
BMI, mean (SD), kg/m^2	29.3 (4.3)	29.2 (4.8)
SMF grade as assessed by CR-SMFRS/PR-SMFRS, n (%)		
Grade 2	131 (50.8)/160 (62.0)	126 (48.8)/162 (62.8)
Grade 3	126 (48.8)/97 (37.6)	131 (50.8)/95 (36.8)
Missing	1 (0.4)/1 (0.4)	1 (0.4)/1 (0.4)
Fitzpatrick skin type, n (%)		
I-III	176 (68.2)	170 (65.9)
IV-VI	82 (31.8)	88 (34.1)

Intent-to-treat population.
BMI, Body mass index; *CR-SMFRS*, Clinician-Reported Submental Fat Rating Scale; *PR-SMFRS*, Patient-Reported Submental Fat Rating Scale; *SMF*, submental fat.

grades in SMF (Mantel-Haenszel risk ratio 2.98; 95% confidence interval [CI] 2.31-3.85; $P < .001$). A greater proportion of those treated with ATX-101 than placebo also achieved the more stringent composite improvement in SMF of 2 or more grades (ATX-101, 18.6%; placebo, 3.0%; Mantel-Haenszel risk ratio 6.27; 95% CI 2.91-13.52; $P < .001$). Furthermore, both primary end points were met in all sensitivity analyses, indicating the results were robust ($P < .001$ for all). Representative photographs of patients with improvement of 1 or more grades (Fig 1, *A* and *B*) and 2 or more grades (Fig 1, *C*) demonstrate clinical outcomes with ATX-101.

MRI analyses, conducted in 225 patients, showed that a greater proportion of patients treated with ATX-101 versus placebo achieved a 10% or more reduction in submental volume (40.2% vs 5.2%, respectively; Mantel-Haenszel risk ratio 7.84; 95% CI 3.30-18.62; $P < .001$) (representative examples in Fig 1, *A* and *B*). The reduction in submental volume was greater with ATX-101 versus placebo treatment ($P < .001$) (Table III). In addition, the percentage reduction in SMF thickness as measured by calipers was greater with ATX-101 versus placebo ($P < .001$) (Table III).

At baseline, patients in both treatment groups reported psychological impact from their SMF (Fig 2). The reduction in PR-SMFIS Total Scale Score was significantly greater for patients receiving ATX-101 than placebo ($P < .001$) (Fig 2). Similar significant differences were observed for the individual PR-SMFIS components ($P < .001$ for all) (Fig 2). In addition, a greater proportion of patients treated with ATX-101 indicated satisfaction with the appearance of their face/chin after treatment versus patients treated with placebo ($P < .001$) (Table III). Additional efficacy results are summarized in Table III.

Safety

Table IV reports the proportion of patients who experienced AEs during the trial. Most AEs were localized to the injection site: 85.7% in the ATX-101 group and 76.9% in the placebo group. Most AEs resolved within 14 days (67.3% in the ATX-101 group and 83.5% in the placebo group) and nearly all resolved by study end (96.8% and 96.6%, respectively). Injection-site AEs reported in 5% or more of patients are listed in Table IV. Fig 3 shows the incidence and severity of injection-site swelling/edema, bruising, and pain over the 6 treatments. Median durations of most injection-site AEs ranged from 3.0 to 15.5 days in the ATX-101 group, except for nodule (20.0 days), induration (26.4 days), and anesthesia (33.0 days). In the placebo group, median durations ranged from 2.0 to 8.7 days. Serious AEs were uncommon and none were related to study drug. One patient in the ATX-101 group died in a motor vehicle accident and 1 patient in the placebo group died from heroin toxicity; neither death was related to study drug. Results of physical examinations, vital signs, and laboratory tests did not suggest a safety signal. Submental skin laxity was unchanged or improved from baseline in 94.1% of those treated with ATX-101 and 94.8% of those treated with placebo.

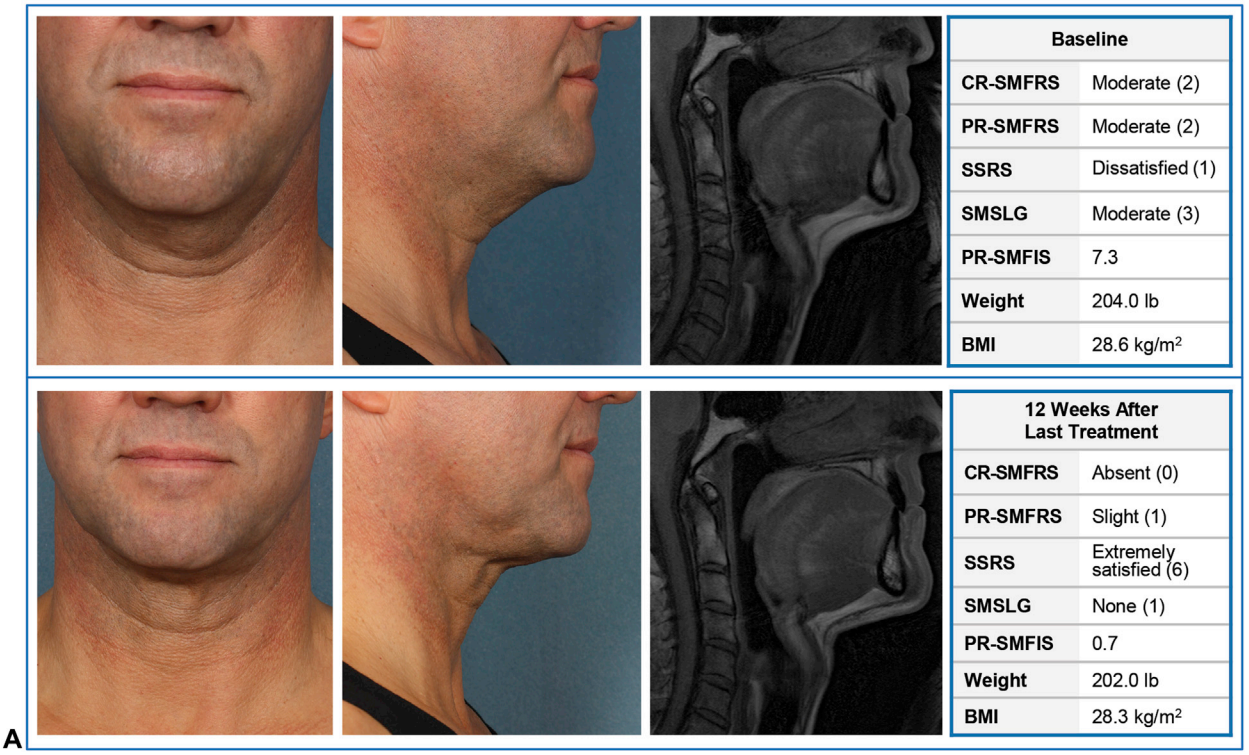

Fig 1. A, Standardized photographs and magnetic resonance imaging (MRI) of a 51-year-old man who underwent 6 treatment sessions with ATX-101 and achieved a composite improvement of 1 or more grades (Clinician-Reported Submental Fat Rating Scale [*CR-SMFRS*]/Patient-Reported Submental Fat Rating Scale [*PR-SMFRS*]) at 12 weeks after last treatment. Percentage reduction in submental volume as assessed by MRI was 14%. **B**, Standardized photographs and MRI of a 56-year-old woman who underwent 5 treatment sessions with ATX-101 and achieved a composite improvement of 1 or more grades (CR-SMFRS/PR-SMFRS) at 12 weeks after last treatment. Percentage reduction in submental volume as assessed by MRI was 2%. **C**, Standardized photographs of a 43-year-old woman who underwent 4 treatment sessions with ATX-101 and achieved a composite improvement of 2 or more grades (CR-SMFRS/PR-SMFRS) at 12 weeks after last treatment. *BMI*, Body mass index; *PR-SMFIS*, Patient-Reported Submental Fat Impact Scale; *SMSLG*, Submental Skin Laxity Grade; *SSRS*, Subject Self-Rating Scale.

Marginal mandibular nerve (MMN) paresis occurred in 11 (4.3%) of those treated with ATX-101 and 2 (0.8%) treated with placebo corresponding to a relative session frequency of 0.9% and 0.1%, respectively. Most events of MMN paresis were mild or moderate and all were temporary and resolved without sequelae. One severe event occurred in a patient treated with ATX-101 (resolved within 85 days); this patient went on to receive additional treatment, was a responder, and was satisfied. Median durations of mild MMN paresis events were 41.0 (range 7.0-60.0) days in the ATX-101 group (n = 8) and 54.0 days in the placebo group (n = 1). Similarly, for moderate MMN paresis events, median durations were 56.5 (range 52.0-61.0) days (n = 2) and 115.0 days (n = 1), respectively. One event of mild superficial skin ulceration occurred in a patient treated with ATX-101 (on the day of the sixth treatment) and resolved within 23 days. Dysphagia associated with the volume of injection or postinjection swelling/pain occurred in 6 (2.3%) of those treated with ATX-101 and 1 treated with placebo (0.4%). Median durations of dysphagia were 2.5 days in the ATX-101 group and 1.0 day in the placebo group and resolved without sequelae.

DISCUSSION

REFINE-2 evaluated the efficacy and safety of ATX-101, a first-in-class injectable drug for SMF reduction. Both coprimary end points were met with a high degree of statistical significance, and all secondary and additional end points significantly favored ATX-101, demonstrating its efficacy for reducing SMF. MRI supported substantial reduction in submental volume after ATX-101 treatment. In

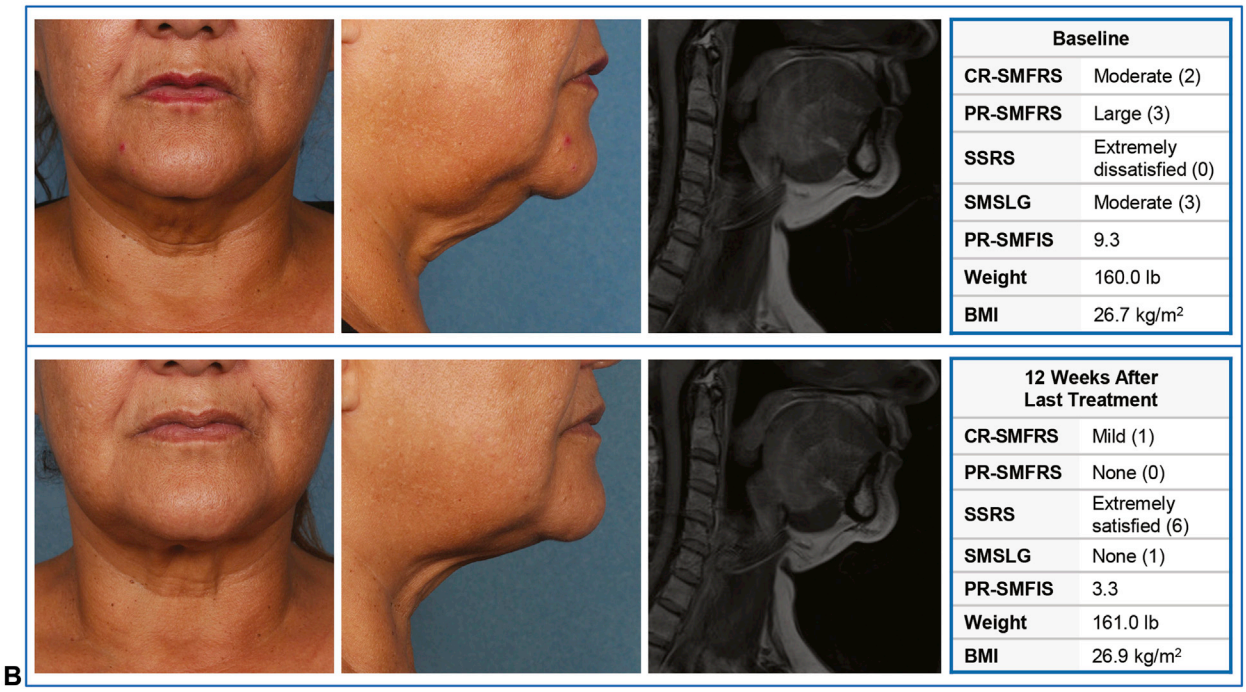

Fig 1. (*continued*).

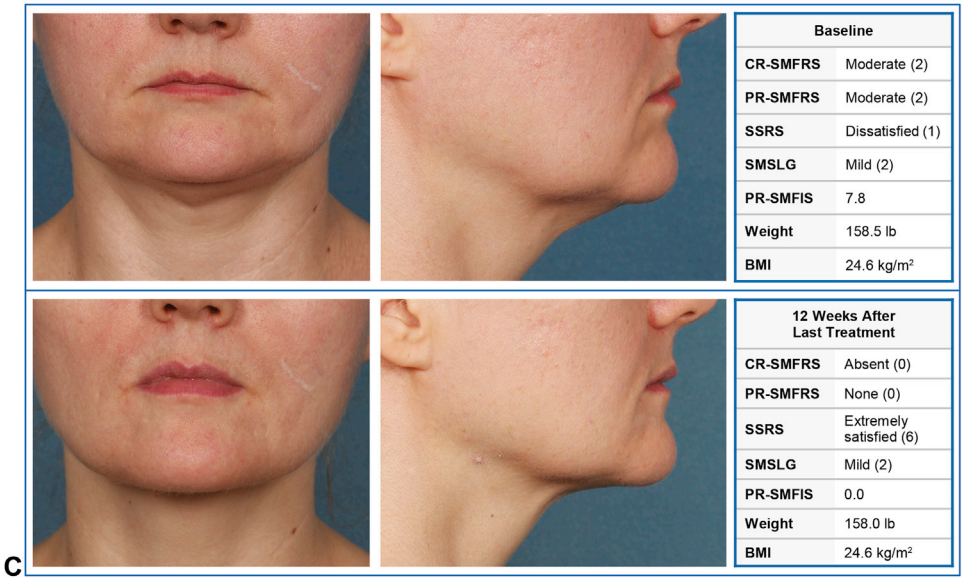

Fig 1. (*continued*).

addition, those treated with ATX-101 experienced a clinically meaningful reduction in psychological impact of their SMF; they were happier, less bothered, less self-conscious, and less embarrassed about their SMF and looked younger and less overweight after ATX-101 treatment. Overall, agreement among investigator-reported, patient-reported, and objective assessments of the submental area strongly suggests that the aesthetic improvement after ATX-101 treatment was clinically meaningful, and the objective tool-based measures showed that there was little SMF reduction in the placebo group relative to the ATX-101 group. Moreover, the results were similar to those of REFINE-1,[8] which used an identical protocol with different investigators, illustrating the consistent effect with ATX-101 treatment.

The safety profile of ATX-101 is consistent with the injection procedure and its mechanism of action. Most AEs were localized to the injection site,

Table III. Secondary and additional efficacy end points evaluated at 12 weeks after last treatment

Intent-to-treat MRI population	Placebo, n = 112	ATX-101, n = 113
MRI responder,* n (%)	6 (5.2)	45 (40.2)
Submental volume, LSM (SE) percentage change from baseline	1.1 (0.9)	−8.6 (0.9)
Intent-to-treat population	**Placebo, n = 258**	**ATX-101, n = 258**
CR-SMFRS ≥1-grade improvement, n (%)	89 (34.5)	201 (77.9)
PR-SMFRS ≥1-grade improvement, n (%)	97 (37.8)	202 (78.4)
CR-SMFRS ≥2-grade improvement, n (%)	26 (9.9)	100 (38.7)
PR-SMFRS ≥2-grade improvement, n (%)	20 (7.9)	80 (30.8)
Caliper measurements of SMF thickness, LS mean (SE) percentage change from baseline	−8.4 (1.3)	−17.8 (1.3)
SSRS responder,† n (%)	83 (36.2)	163 (75.1)
SGQ responder,‡ n (%)		
1 (Fat under chin)	56 (24.7)	152 (70.7)
2 (Definition between chin and neck)	49 (21.6)	145 (67.4)
3 (Satisfied with treatment)	77 (33.9)	162 (75.3)
Patient line drawing assessment, LSM (SE) change from baseline	−0.4 (0.1)	−1.2 (0.1)

$P < .001$ for all comparisons between ATX-101 and placebo.
CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; *LSM*, least squares mean; *MRI*, magnetic resonance imaging; *PR-SMFRS*, Patient-Reported Submental Fat Rating Scale; *SGQ*, Subject Global Question; *SMF*, submental fat; *SSRS*, Subject Self-Rating Scale.
*Defined a priori as achieving ≥10% reduction from baseline in submental volume via MRI.
†Response was slightly satisfied, satisfied, or extremely satisfied.
‡Response was 1 of the 2 highest positive categories (ie, moderately better or a great deal better; moderately satisfied or extremely satisfied).

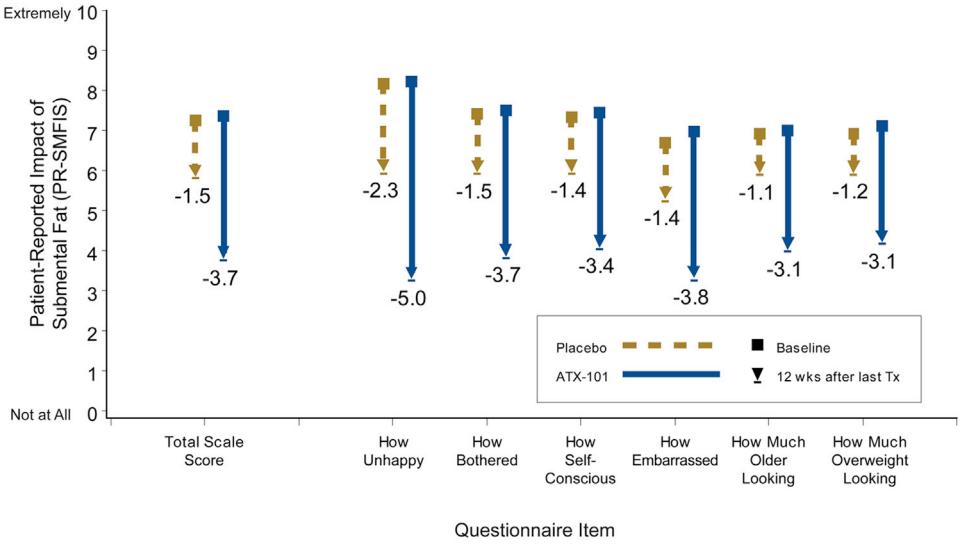

Fig 2. Mean change from baseline in the Total Scale Score and individual component scores of the Patient-Reported Submental Fat Impact Scale (*PR-SMFIS*) at 12 weeks after last treatment. $P < .001$ for all comparisons between ATX-101 and placebo. *Tx*, Treatment.

mild/moderate, transient, did not prevent continued treatment, and decreased in incidence over subsequent treatments. Implementation of additional comfort measures (eg, injected lidocaine, nonsteroidal anti-inflammatory drugs) may reduce the incidence and severity of common treatment area reactions, such as swelling, bruising, and pain. Although instances of MMN paresis were primarily mild and always temporary, these observations emphasize the importance of physician training and education regarding anatomy of the submental area before ATX-101 administration. The anatomical course of the MMN is variable and runs both inferior and superior to the mandibular border.[13] Posterior to

Table IV. Summary of adverse events (safety population)

AE, n (%)	Placebo, n = 256	ATX-101, n = 258
AEs	236 (92.2)	252 (97.7)
Mild*	141 (55.1)	100 (38.8)
Moderate†	92 (35.9)	120 (46.5)
Severe‡	3 (1.2)	32 (12.4)
Serious§	10 (3.9)*	7 (2.7)†
Injection-site AEs reported in ≥5% of patients in either treatment group		
Pain	100 (39.1)	190 (73.6)
Hematoma (bruising)	186 (72.7)	188 (72.9)
Edema	93 (36.3)	175 (67.8)
Anesthesia (numbness)	18 (7.0)	169 (65.5)
Erythema	65 (25.4)	91 (35.3)
Swelling	40 (15.6)	75 (29.1)
Induration	9 (3.5)	73 (28.3)
Pruritus	21 (8.2)	42 (16.3)
Paresthesia	11 (4.3)	38 (14.7)
Nodule	11 (4.3)	37 (14.3)
Skin tightness	5 (2.0)	19 (7.4)
Noninjection-site AEs reported in ≥5% of patients in either treatment group		
Headache	8 (3.1)	23 (8.9)
Upper respiratory tract infection	18 (7.0)	15 (5.8)
Nasopharyngitis	13 (5.1)	12 (4.7)

AE, Adverse event.
*Patient is aware of a sign or symptom but it is easily tolerated.
†Discomfort or interference with usual activity.
‡Incapacitating with inability to engage in usual activity.
§An event that may constitute a significant medical hazard or side effect regardless of relationship to the study drug, including but not limited to it: is fatal, is life-threatening, requires hospitalization or prolongs hospitalization, results in persistent or significant disability/incapacity, and is a congenital anomaly/birth defect. Serious AEs in the placebo group were: acute congestive heart failure (n = 1), pancreatitis (n = 1), vaginal repair (n = 1), transient ischemic attack (n = 1), breast cancer (n = 1), heroin toxicity (n = 1), diverticulitis (n = 1), influenza (n = 1), spinal cord infection (n = 1), hip surgery (n = 1). Serious AEs in the ATX-101 group were: ovarian cancer/uterine cancer (n = 1), uterine prolapse/cystocele/rectocele/uterine leiomyoma (n = 1), gastroesophageal reflux disease (n = 1), intervertebral disc operation (n = 1), motor vehicle accident (n = 1), recurrent breast cancer (n = 1), urinary tract infection (n = 1).

the antegonial notch, the MMN courses inferior to the mandible. Anterior to this bony landmark (at the anterior portion of the masseter muscle), the MMN courses superficially over the mandible to innervate the lip depressors.[14] To prevent MMN injury, it is recommended to avoid injecting ATX-101 above a line drawn 1.0 to 1.5 cm below the inferior mandibular border.[5] One instance of skin ulceration occurred, underscoring the importance of injecting ATX-101 midway into the SMF to avoid the dermis.

Submental skin laxity was unchanged or improved in the large majority of patients in REFINE-2, which is remarkable because MRI and caliper assessments showed significant reductions in submental volume and SMF thickness in those treated with ATX-101. All things being equal, one might expect a worsening of skin laxity after SMF reduction without concomitant skin retraction. Evidence of neocollagenesis and thickening of fibrous septae have been observed after ATX-101 treatment[6] and may contribute to skin retraction despite submental volume reduction observed across phase III ATX-101 trials.[7,8,10]

In REFINE-2, follow-up was limited to 44 weeks (24 weeks after last treatment), which limits conclusions regarding the long-term durability of ATX-101 treatment. However, a durable response is expected once the aesthetic goal is achieved because ATX-101 destroys adipocytes and creates fibrosis.[6] Follow-up of patients from phase II/III trials has demonstrated that improvements in submental contour achieved with ATX-101 are maintained over time in most patients (current data supporting maintenance of effect for up to 4 years).[15] Based on results from the REFINE trials, ATX-101 was approved in the United States and Canada for adults with moderate to severe SMF. Studies to evaluate ATX-101 in additional populations, such as patients with mild or extreme SMF and patients older than 65 years, are underway. In addition, CONTOUR (Condition of Submental Fullness and Treatment Outcomes Registry) is evaluating the management of submental fullness in clinical practice and will provide real-world data on ATX-101.

In summary, the results from REFINE-2 are clinically meaningful, statistically significant, and consistent with efficacy and safety outcomes observed in other phase III ATX-101 trials.[7,8,10] The current findings further support ATX-101 as a minimally invasive alternative to aesthetic surgical procedures and liposuction for SMF reduction.

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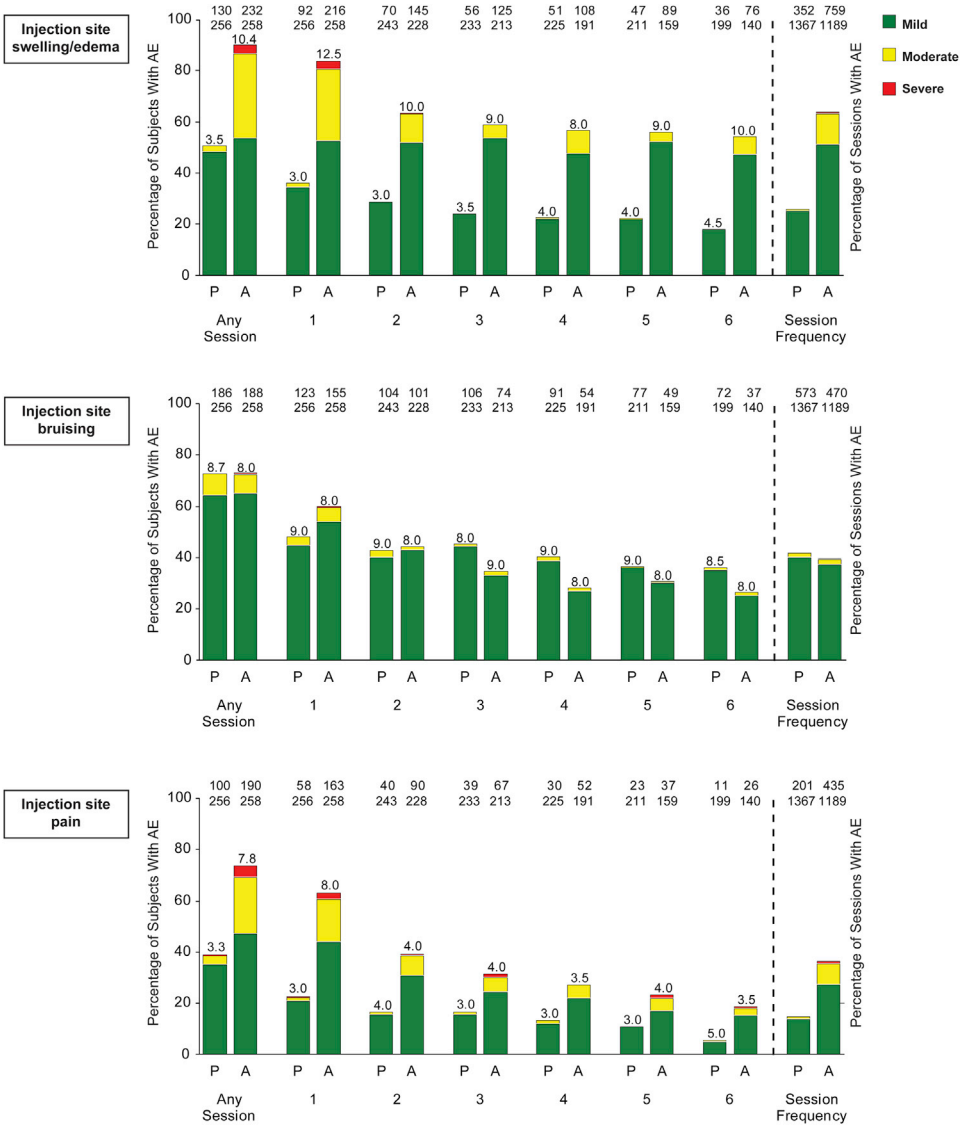

Fig 3. Incidence, severity, and duration of injection-site adverse events (*AE*) (swelling/edema, bruising, and pain) for individual treatment sessions. At the top of the graph, the number of patients reporting the AE is listed in the first row; the total number of patients is listed in the second row. The number listed at the top of each bar is the median duration of the AE in a particular session. For session frequency, the data for the percentage of sessions for which the AE was reported are shown. *A*, ATX-101; *P*, placebo.

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Table I. Scales used in the REFINE-2 trial

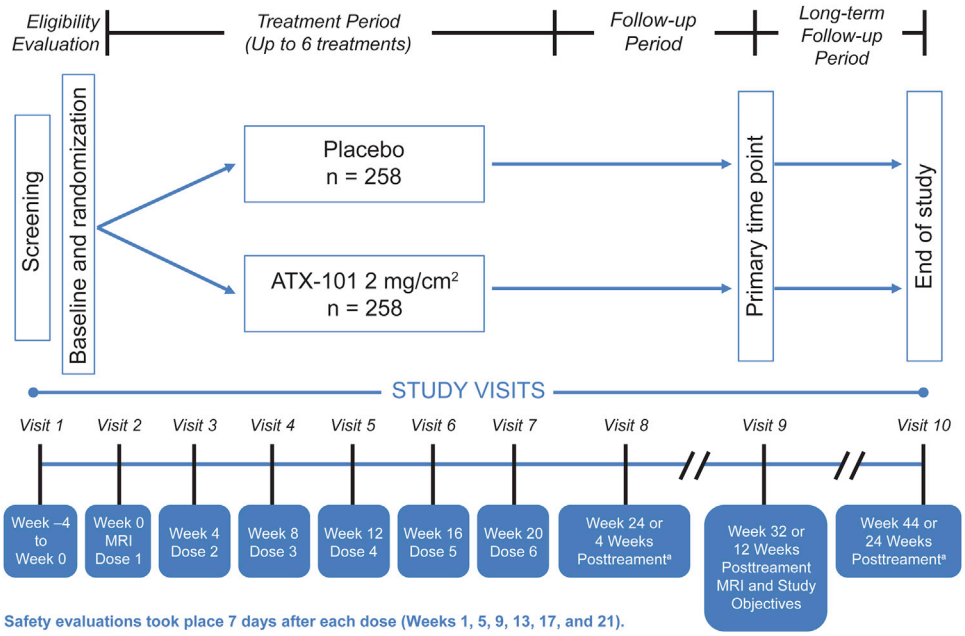
Scale	Description
CR-SMFRS*	• Submental convexity evaluated by the clinician on a 5-point ordinal scale with: ○ 0 = absent ○ 1 = mild ○ 2 = moderate ○ 3 = severe ○ 4 = extreme • Photonumeric guide included to assist clinicians in applying the ratings (Supplementary Fig 3)
PR-SMFRS*	• SMF evaluated by the patient on a 5-point ordinal scale with: ○ 0 = no chin fat at all ○ 1 = a slight amount of chin fat ○ 2 = a moderate amount of chin fat ○ 3 = a large amount of chin fat ○ 4 = a very large amount of chin fat
PR-SMFIS*	• Psychological impact of SMF on self-perception of 6 emotional and visual characteristics related to the appearance of submental fullness assessed with the following items: ○ How happy are you with the appearance of your chin fat? ○ How bothered are you by the appearance of your chin fat? ○ How self-conscious are you about the appearance of your chin fat? ○ How embarrassed are you about the appearance of your chin fat? ○ How much older do you look because of your chin fat? ○ How much overweight do you look because of your chin fat? • Each item rated on an 11-point numeric scale (0-10) ○ Scores for the 6 items were combined to generate a PR-SMFIS Total Scale Score ○ Lower scores indicate improvement or reduced negative impact of these items
SSRS	• Overall satisfaction with the appearance of the face and chin evaluated by the patient on a 7-point scale with: ○ 0 = extremely dissatisfied ○ 1 = dissatisfied ○ 2 = slightly dissatisfied ○ 3 = neither satisfied nor dissatisfied ○ 4 = slightly satisfied ○ 5 = satisfied ○ 6 = extremely satisfied • A responder was a patient whose response was 4, 5, or 6
SGQ	• Fat under chin (SGQ no. 1) and definition between chin and neck (SGQ no. 2) compared with how they were before treatment, and satisfaction with treatment (SGQ no. 3) evaluated by the patient • Response options for SGQ nos. 1 and 2: ○ A great deal worse ○ Moderately worse ○ A little worse ○ About the same ○ A little better ○ Moderately better ○ A great deal better • Response options for SGQ no. 3: ○ Extremely dissatisfied ○ Moderately dissatisfied ○ A little dissatisfied ○ Neither dissatisfied or satisfied ○ A little satisfied ○ Moderately satisfied ○ Extremely satisfied • A responder was a patient whose response was 1 of the 2 highest positive categories

Continued

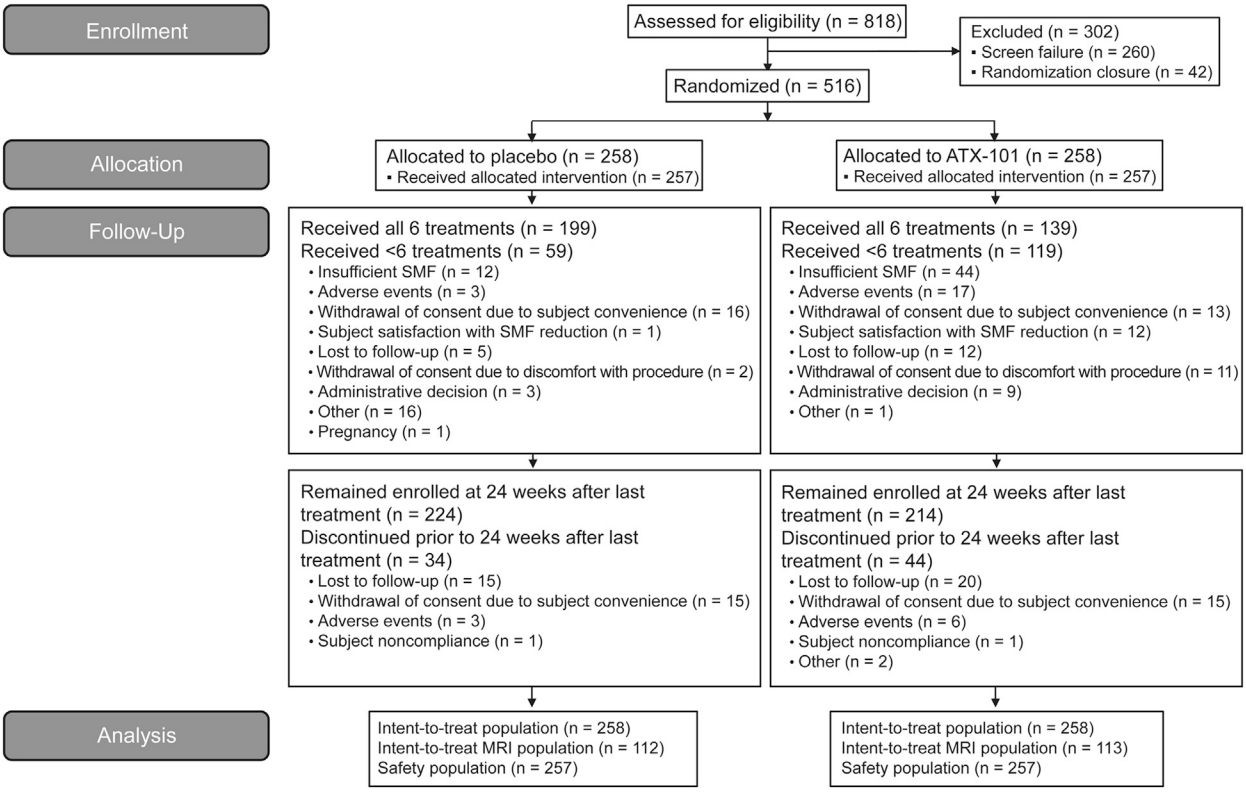
Table I. Cont'd

Scale	Description
SMSLG	• Skin laxity assessed by the clinician as an integration of 3 features: skin wrinkling, adherence to underlying neck structures (bone and muscle), and redundancy (horizontal and vertical folds) on a 4-point scale with: ○ 1 = none ○ 2 = mild ○ 3 = moderate ○ 4 = severe • Each grade (none, mild, moderate, and severe) defines the maximal allowed limit for skin wrinkling, adherence to underlying structures, and redundancy. The feature with the highest grade determines the SMSLG • Photonumeric guide included to assist clinicians in applying the ratings (Supplementary Fig 4)
Standardized line drawings of submental convexity	• From 10 line drawings that included 2 examples representing each of the 5 CR-SMFRS scores, provided to the patient in a shuffled order, patients were asked to select the drawing that best represented their profile • Assessments scored from 0 to 4, where 0 = lowest SMF score and 4 = highest SMF score, such that a lower score was better

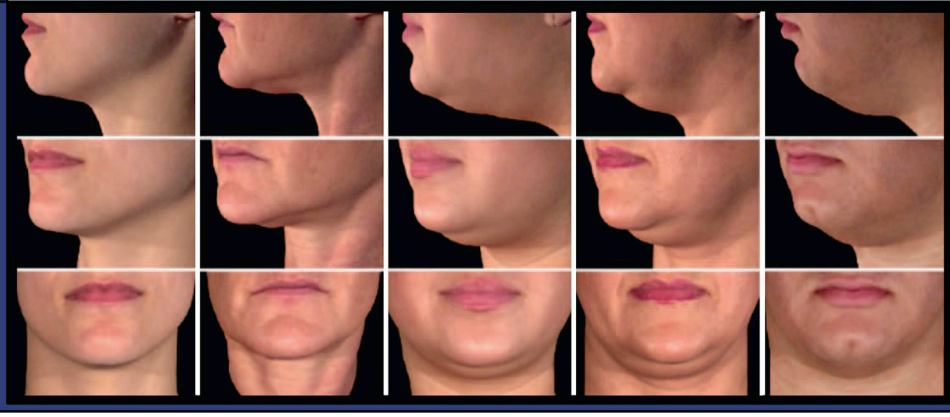
CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; *PR-SMFIS*, Patient-Reported Submental Fat Impact Scale; *PR-SMFRS*, Patient-Reported Submental Fat Rating Scale; *SGQ*, Subject Global Question; *SMF*, submental fat; *SMSLG*, Submental Skin Laxity Grade; *SSRS*, Subject Self-Rating Scale.
*Validated scale.



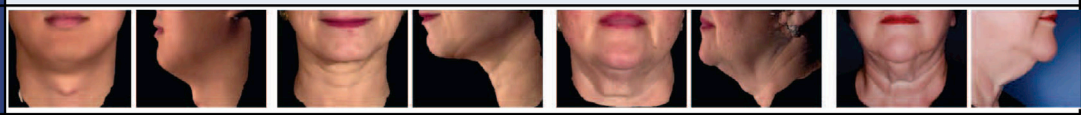
Supplementary Fig 1. Study design. [a]Posttreatment, relative to the patient's last treatment session, irrespective of when that occurred. Analyses were made after the last patient completed visit 9 (week 32; 12 weeks after last treatment). *MRI*, Magnetic resonance imaging.



Supplementary Fig 2. Patient disposition. The intent-to-treat population included all randomized patients and was used to evaluate efficacy. Magnetic resonance imaging (*MRI*) assessments were conducted on a subgroup of the intent-to-treat population. The safety population included all randomized patients who received 1 or more injections of study drug and was used to evaluate safety. *SMF*, Submental fat.

Scale	0	1	2	3	4
Submental Convexity	Absent	Mild	Moderate	Severe	Extreme
Description	No localized submental fat evident	Minimal localized submental fat	Prominent localized submental fat	Marked localized submental fat	Extreme submental convexity
Representative Photographs					

Supplementary Fig 3. Photonumeric guide for assessment of submental fat (SMF) using the Clinician-Reported Submental Fat Rating Scale. Adapted from McDiarmid J, Ruiz JB, Lee D, et al. Results from a pooled analysis of two European, randomized, placebo-controlled, phase 3 studies of ATX-101 for the pharmacologic reduction of excess submental fat. *Aesthetic Plast Surg*. 2014;38:849-60.[9]

Scale	1	2	3	4
Skin Laxity	None	Mild	Moderate	Severe
Description	None or minimal superficial wrinkles	Mild superficial wrinkles	Moderate superficial wrinkles	Superficial wrinkling present, may be marked
Representative Photographs				

Supplementary Fig 4. Photonumeric guide for assessment of skin laxity using the Submental Skin Laxity Grade scale. Reproduced with permission from Jones DH, Carruthers J, Joseph JH, et al. REFINE-1, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial with ATX-101, an injectable drug for submental fat reduction. *Dermatol Surg*. 2016;42:38-49.[8]

Supplementary Table I. Full list of exclusion criteria

- History of any intervention to treat SMF (eg, liposuction, surgery, lipolytic agents)
- History of trauma associated with the chin/neck area
- A grade of 4 on the Submental Skin Laxity Grade or other anatomical feature (eg, predominant postplatysmal fat, loose skin in the neck/chin area, prominent platysmal bands), as assessed within 28 d before randomization, for which reduction in SMF may, in the judgment of the investigator, result in an aesthetically unacceptable outcome
- Evidence of any cause of enlargement in the submental area (eg, thyroid enlargement, cervical adenopathy) other than localized SMF
- BMI >40 kg/m^2
- History or current symptoms of dysphagia
- A result on coagulation tests (prothrombin time, partial thromboplastin time) obtained within 28 d before randomization indicating the presence of any clinically significant bleeding disorder
- Any medical condition (eg, respiratory, cardiovascular, hepatic, neurologic disease, thyroid dysfunction) that would interfere with assessment of safety or efficacy or compromise the patient's ability to undergo study procedures or give informed consent
- Treatment with radiofrequency, laser procedures, chemical peels, or dermal fillers in the neck/chin area within 12 mo before randomization
- Treatment with botulinum toxin injections in the neck/chin area within 6 mo before randomization
- History of sensitivity to any components of the study drug
- History of sensitivity to topical or local anesthetics (eg, lidocaine, benzocaine, procaine)
- Previous randomization in this study or previous participation in a Kythera Biopharmaceuticals, Inc—sponsored ATX-101 study
- Treatment with an investigational device or agent within 30 d before randomization

BMI, Body mass index; *SMF*, submental fat.