

ORIGINAL ARTICLE

Submental fat reduction using sequential treatment approach with cryolipolysis and ATX-101

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Abstract**Background:** Submental fat (SMF) detracts from facial aesthetics and negatively impacts self-image.**Aims:** To evaluate safety, effectiveness, and satisfaction of cryolipolysis and ATX-101 used sequentially to reduce SMF.**Methods:** A prospective, open-label, interventional, single-site study enrolling 22- to 65-year-old participants rated as Grade 4 (extreme) on the Clinician-Rated SMF Rating Scale (CR-SMFRS). Co-primary effectiveness endpoints were proportions of participants with ≥ 1 -grade and ≥ 2 -grade improvement on CR-SMFRS at 12 weeks post final treatment. Additional assessments included ultrasound measurement of fat thickness and Subject Self-Rating Scale (SSRS) scores at 12 weeks post final treatment. Safety was assessed throughout the study.**Results:** Of 16 enrolled participants, 62.5% were female, mean age of 43, and mean body mass index of 31.8 kg/m². 100% of participants achieved ≥ 1 -grade improvement, and 71.4% achieved ≥ 2 -grade CR-SMFRS improvement. Mean (SD) reduction in SMF thickness was 0.2 mm (1.3), and SSRS scores ≥ 4 (slightly to extremely satisfied) were reported by 71.4% of participants. Adverse events (AEs) were mild and resolved by study end. No unanticipated adverse device effects or serious or unexpected AEs occurred.**Conclusion:** Sequential treatment with cryolipolysis and ATX-101 was found safe and effective for reducing extreme SMF, resulting in approximately a 2-grade improvement.**KEYWORDS**

cryolipolysis, deoxycholic acid, submental fat reduction

1 | INTRODUCTION

A common area of facial aesthetic concern is fat accumulation in the preplatysmal submental area (submental fat [SMF]) due to genetics or lifestyle factors, contributing to the loss of chin and jawline definition and an aged or overweight appearance.¹⁻³ The appearance of excess SMF can also contribute to a negative self-perception, which negatively impacts psychosocial behavior.⁴ Although liposuction has been the gold standard for treatment for SMF, it carries the risks

associated with an invasive surgical procedure and may not be a practical option for all patients.⁵ Minimally invasive techniques now available for SMF reduction have become increasingly popular, as they require less recovery time and can be used in a multi-modal approach for customizable treatment plans to suit a broader range of needs.^{6,7}

Cryolipolysis (CoolSculpting[®]) is FDA-cleared for the treatment for visible fat bulges in the submental (under the chin) and submandibular (under the jawline) areas in individuals with a BMI up to 46.2 kg/m².^{8,9} Deoxycholic acid (ATX-101) is a cytolytic drug

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FDA-approved and indicated in the United States for improvement in the appearance of moderate to severe convexity or fullness associated with SMF.^{10,11} The use of cryolipolysis followed by ATX-101 as a multi-step treatment approach provides an easy way to de-bulk the treatment area with minimal downtime and further sculpt the area with fewer treatments than would be needed if ATX-101 was used alone. This study was conducted to examine the safety and effectiveness of 2 cryolipolysis treatments followed by up to 2 ATX-101 treatments when used individually in sequence to reduce extreme SMF.

2 | MATERIALS AND METHODS

2.1 | Participants

This prospective, controlled, open-label, interventional study was conducted at a single center in the United States. Eligible participants were men and women (22–65 years of age) with Grade 4 (Extreme) submental convexity on the Clinician Reported Submental Fat Rating Scale (CR-SMFRS; Figure S1) as assessed by the evaluating investigator (EI); a Subject Self-Rating Scale (SSRS) score of 0, 1, or 2 (scale of 0 = extremely dissatisfied to 6 = extremely satisfied) regarding dissatisfaction with their submental area; a body mass index (BMI) of <40 kg/m² with stable body weight for at least 6 months prior to the first treatment and agreement to maintain weight within 5% of baseline and forgo any treatment or behavior (eg, unshaven facial hair) during the study that may affect the assessments of the submental area.

At time of screening, participants were asked to tense their platysma muscle to isolate supraplatysmal fat. If the aesthetically-trained physicians determined that excessive skin laxity or predominant subplatysmal fat was a cause of the participant's submental fullness and may prevent a desirable outcome after submental lipolysis, the participants were excluded from the study. Participants were also excluded if they had a history of any intervention to treat submental fat (eg, liposuction, surgery, cryolipolysis, or lipolytic agents); any treatment with radiofrequency, micro-focused ultrasound, laser procedures, chemical peels, or dermal fillers within 12 months or botulinum toxin injections in the neck or chin area within 6 months of study start; a history of Raynaud's disease, or any condition with a response to cold exposure that limits blood flow to the skin; a history of dysphagia, facial nerve paresis or paralysis; sensitivity to any components of

ATX-101 or topical or local anesthetics; or consumption of diet pills or weight control supplements within 1 month of study start.

2.2 | Study design

Per protocol, each participant was required to have 2 cryolipolysis treatments (45 min at -11°C each treatment) to the central submental area (under the chin). Treatments were performed 6 weeks apart using a small-volume vacuum cup cryolipolysis applicator (CoolMini™ applicator, ZELTIQ Aesthetics, Inc., an affiliate of Allergan Aesthetics, an AbbVie company).¹² At the 6-week post final cryolipolysis treatment visit, if the CR-SMFRS remained a Grade 2 (Moderate) or Grade 3 (Severe), ATX-101 treatment (deoxycholic acid injection; Kybella [US]/Belkyra [Canada, Australia, Europe, and South Korea]; Kythera Biopharmaceuticals, Inc., an affiliate of Allergan Aesthetics, an AbbVie company) was then used to reduce fat further and enhance the aesthetic appearance of the submental region.¹³ ATX-101 treatment was administered to the entire submental and submandibular area defined by 0.5 cm inferior to the mandible, with gonion as a lateral landmark and hyoid bone as an inferior landmark. Injections were 0.2-mL aliquots spaced 1.0-cm apart (10-mL maximum and 50-injection site maximum) to deliver a dose strength of 2 mg/cm². An optional second ATX-101 treatment was offered 4–7 weeks after the first treatment per the investigator's discretion after evaluating the aesthetic result of the treatments thus far.

Follow-up visits occurred 2 weeks after each treatment and at 12 weeks post final ATX-101 treatment (Figure 1). During all follow-up visits, participants were monitored for adverse events. At the baseline visit, 6 weeks following cryolipolysis, and 12 weeks post final ATX-101 treatment visit, participants were photographed, and ultrasound images were obtained to measure the fat layer in the treated area. This study received Institutional Review Board approval, was conducted in compliance with GCP, and is registered at clinicaltrials.gov (NCT#03510598).

2.3 | Effectiveness assessments

Co-primary endpoints were (1) the proportion of participants who have at least a 1-grade improvement from baseline and (2) the

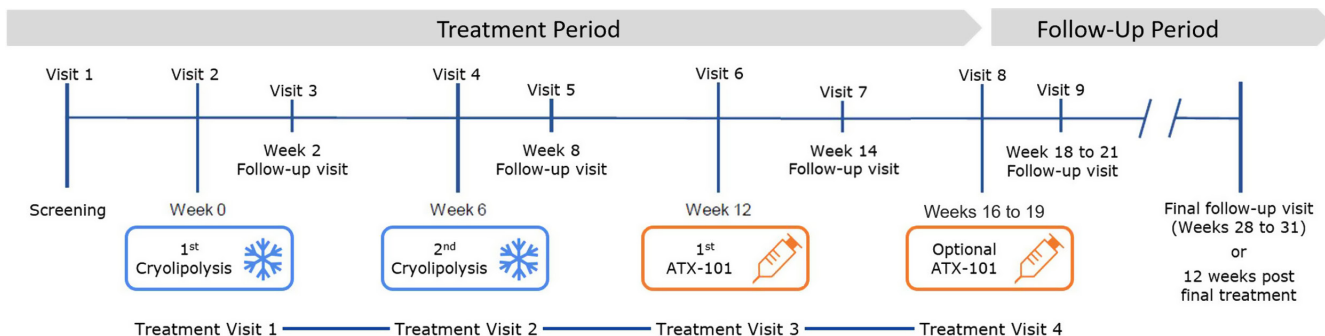


FIGURE 1 Study flow

proportion of participants who have at least a 2-grade improvement from baseline on the CR-SMFRS by the final study visit at 12 weeks post final ATX-101 treatment. The CR-SMFRS score was based on the investigator's clinical evaluation of the participant, which involved palpation of the chin and neck area; anterior, oblique, and profile assessment of the chin and neck; and observation of pronation, supination, and lateral movement of the head.

As secondary measures of effectiveness, reduction in fat layer thickness was assessed by ultrasound after the second cryolipolysis treatment and again at 12 weeks post final ATX-101 treatment. Participant satisfaction with their face and chin was assessed using the SSRS score (scale of 0 = extremely dissatisfied to 6 = extremely satisfied) after the second cryolipolysis treatment and again at 12 weeks post final ATX-101 treatment. Standardized photography of treatment area was obtained prior to the first cryolipolysis, prior to first ATX-101 treatment, and at 12 weeks final post final ATX-101 treatment. Participant-reported pain scores (scale of 0, no pain, to 10, worst pain imaginable) were obtained at each treatment (during treatment, immediately post-treatment, prior to discharge) and again at all study follow-up visits.

2.4 | Safety assessments

Clinical assessment of the treatment site was made immediately and 2 weeks following each treatment with cryolipolysis or ATX-101, and again at 12 weeks after the final ATX-101 treatment to surveil for cutaneous or sensory effects and were graded on a scale of 0 (None) to 3 (Severe). The anticipated cutaneous/sensory effects consistent with the known safety profile for the CoolMini applicator and ATX-101 include bruising, blanching, erythema, numbness, edema, and tingling.⁸⁻¹¹ In addition, the incidence of reported adverse events (AEs), including serious AEs (SAEs), was monitored throughout the study.

2.5 | Analysis

A two-sided test with $\alpha = 0.05$ cutoff was used to determine level of significant difference. The per-protocol (PP) population was defined as all treated participants followed through the final post-treatment visit who maintained weight within 5% range of weight at initial treatment.

3 | RESULTS

3.1 | Participant baseline characteristics and treatment summary

A total of 16 enrolled participants were mostly female (62.5%) with an average age of 43 years, a weight of 208 lbs, and a BMI of 31.8 kg/m². All were assessed as Grade 4 (Extreme) on the CR-SMFRS, and

all SSRS scores for satisfaction with face and chin were 0 or 1 (extremely dissatisfied or dissatisfied) (Table 1). Of 16 enrolled participants, 15 completed the study, and 14 were included in the PP population. One participant voluntarily withdrew following the first cryolipolysis treatment, and 1 was ultimately excluded from efficacy analysis due to weight change >5%. Fifteen participants received 2 cryolipolysis treatment cycles (45 min at -11°C per cycle) each. The same 15 participants received the first treatment of ATX-101 with a total mean dose of 7.9 mL (range 5.4–10.0 mL) distributed among 39.4 mean injection sites (range 27–50). Subsequently, 14 participants received the optional second ATX-101 treatment with a total mean dose of 8.34 mL (range 6.0–10.0 mL) distributed among 41.7 mean injection sites (range 30–50) (Table 2).

3.2 | Primary effectiveness

Overall, 100% (14/14) of participants had at least a 1-grade improvement in CR-SMFRS, and 71.4% (10/14) had at least a 2-grade improvement in CR-SMFRS at 12 weeks post final ATX-101 treatment (Figure 2).

The overall mean score change from baseline to final study visit was -1.86 grades on the CR-SMFRS with -1.14 mean grade improvement by 6 weeks post final cryolipolysis treatment and an additional -0.71 mean grade improvement by 12 weeks post final ATX-101 treatment (Figure 3).

TABLE 1 Participant baseline characteristics

Characteristic, statistic	Proportion of enrolled participants (N = 16)
Gender, n (%)	
Female	10 (62.5)
Male	6 (37.5)
Mean age, years (range)	43.0 (24.0–58.0)
Mean weight, lbs (range)	208.0 (154.0–327.0)
Mean BMI, kg/m ² (range)	31.8 (25.1–39.0)
Race/ethnicity, n (%)	
Caucasian (not Hispanic)	16 (100)
Fitzpatrick skin phototype	
I–III	10 (62.5)
IV–VI	6 (37.5)
Baseline CR-SMFRS, n (%)	
Grade 4	16 (100)
Baseline SSRS Score, n ^a (%)	
0	9 (64.3)
1	5 (35.7)

Note: Abbreviations: BMI, body mass index; CR-SMFRS, Clinician Reported-Submental Fat Rating Scale; SSRS, Subject Self-Rating Scale (0 = extremely dissatisfied, 1 = dissatisfied, 2 = slightly dissatisfied, 3 = neither satisfied nor dissatisfied, 4 = slightly dissatisfied, 5 = satisfied, and 6 = extremely satisfied).

^aData missing for 2 participants.

TABLE 2 Treatment summary

Cryolipolysis treatment, n (%)	
First treatment	16
Second treatment	15 ^a
ATX-101 treatment	
First, n	15
Mean dose, mL (range)	7.9 mL (5.4–10.0)
Mean # injections (range)	39.4 (27–50)
Second, n	14
Mean dose, mL (range)	8.3 mL (6.0–10.0)
Mean # injections (range)	41.7 (30–50)

^a1 participant excluded after first cryolipolysis treatment due to weight change >5%.

3.3 | Secondary effectiveness

Reduction of SMF thickness was observed by ultrasound measurements but showed no significant difference between baseline and

any other timepoints measured (data not shown). At 6 weeks post final cryolipolysis, the ultrasound measurements showed a mean (SD) fat layer reduction of 0.2 mm (1.0) (range +1.6 mm to –2.3 mm). The subsequent measurement, conducted at 12 weeks post final ATX-101 treatment, showed a mean (SD) reduction of 0.2 mm (1.3) (range +2.4 mm to –2.3 mm).

At 6 weeks post final cryolipolysis, 50% (7/14) of participants reported an SSRS score ≥ 4 (Slightly and Extremely Satisfied), which increased to 71.4% (10/14) at 12 weeks post final ATX-101 treatment (Figure 4).

3.4 | Safety

The average pain score during any treatment session was ≤ 5.3 on a 0 (minimum) to 10 (maximum) scale. With cryolipolysis treatments, average pain scores were 4.1 and 5.3 for the first and second treatments, respectively, and 4.3 and 4.4 for the first and second ATX-101 treatments, respectively.

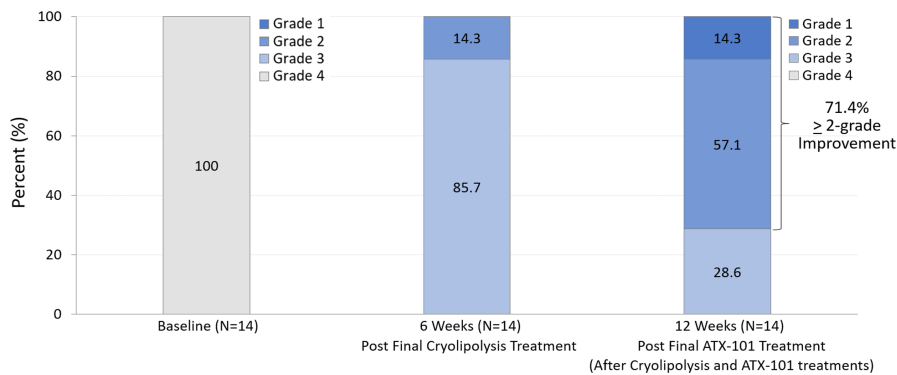


FIGURE 2 Proportions of Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score improvement (by Grade) at 6 weeks after final Cryolipolysis treatment and 12 weeks after ATX-101 treatment. Note: CR-SMFRS scores defined as (0) Absent Submental Convexity: No localized submental fat evident; (1) Mild Submental Convexity: Minimal, localized submental fat; (2) Moderate Submental Convexity: Prominent, localized submental fat; (3) Severe Submental Convexity: Marked, localized submental fat; and (4) Extreme Submental Convexity

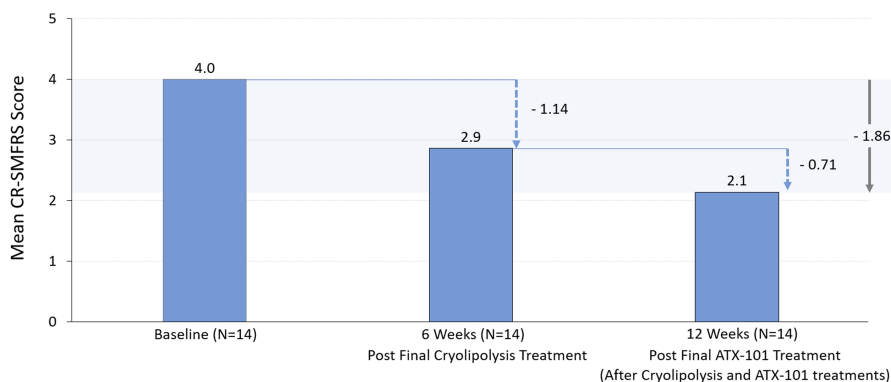


FIGURE 3 Improvement in Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score at 6 weeks after final cryolipolysis treatment and 12 weeks after ATX-101 treatment. Note: CR-SMFRS scores defined as (0) Absent Submental Convexity: No localized submental fat evident; (1) Mild Submental Convexity: Minimal, localized submental fat; (2) Moderate Submental Convexity: Prominent, localized submental fat; (3) Severe Submental Convexity: Marked, localized submental fat; and (4) Extreme Submental Convexity. Mean grade changes between visits may not add up to total (ie, final study visit minus baseline) changes due to rounding

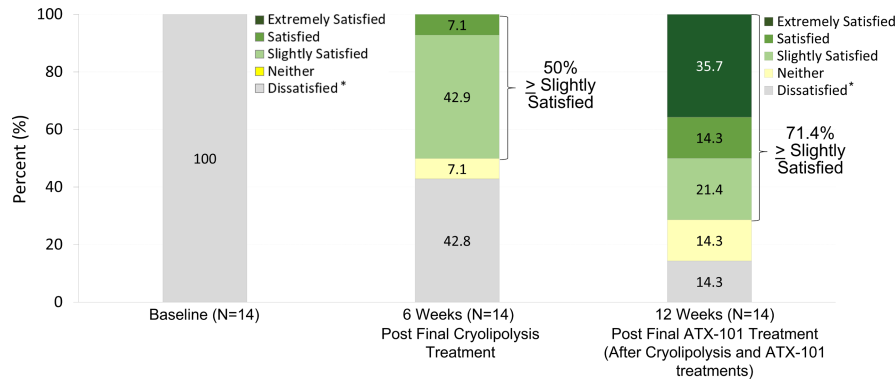


FIGURE 4 Improvement in Subject Self-Rating Scale (SSRS) scores at 6 weeks after final cryolipolysis treatment and at 12 weeks after ATX-101 treatment. Note: SSRS scores: (0) Extremely Dissatisfied; (1) Dissatisfied; (2) Slightly Dissatisfied; (3) Neither Satisfied nor Dissatisfied; (4) Slightly Satisfied; (5) Satisfied; (6) Extremely Satisfied. *Dissatisfied = Extremely Dissatisfied/Dissatisfied/Slightly Dissatisfied

The primary safety endpoint was met, as no unanticipated adverse device effects (UADEs) occurred, and no SAEs related to procedures occurred. The cutaneous effects experienced following cryolipolysis treatments included numbness, edema, erythema, tingling, and bruising; 20 were moderate and 22 were severe (Table 3). The cutaneous effects experienced following ATX-101 treatments included numbness, edema, erythema, tingling, bruising, and blanching; 63 were moderate and 16 were severe (Table 4). All observed cutaneous effects were self-limiting and resolved by the final study visit 12 weeks post final ATX-101 treatment. Three participants experienced AEs that were considered unrelated to device, injection, or procedures which included 1 incident of back pain, 1 occurrence

of urinary tract infection, and 1 occurrence of a foot sprain, which all resolved prior to study end. Overall, no unanticipated device effects, serious AEs, or unexpected treatment-related AEs were reported.

4 | DISCUSSION

Liposuction has traditionally represented the most effective means to reduce extreme SMF. However, as a more invasive procedure, it presents a higher risk of damage to the marginal mandibular nerve, as well as a higher risk of infection and scarring, making it a less desirable or unsuitable option for some patients.⁵

TABLE 3 Summary of cutaneous effects following first and second cryolipolysis treatments

	Post first cryolipolysis treatment			Post second cryolipolysis treatment		
	Immediately (n = 16)	2 weeks (n = 16)	6 weeks (n = 15) ^a	Immediately (n = 15)	2 weeks (n = 15)	6 weeks (n = 15)
Bruising	3	0	0	0	0	0
Minor	3					
Erythema	16	0	0	15	0	0
Minor	16			11		
Moderate	0			4		
Numbness	15	5	1	15	4	1
Minor	2	4	1	1	4	1
Moderate	6	1		5		
Severe	7			9		
Edema	15	0	0	15	0	0
Minor	15			15		
Tingling	5	0	0	11	1	0
Minor	4			2	1	0
Moderate	1			3		
Severe				6		

Note: Clinical assessment for common side effects including bruising, blanching, erythema, numbness, edema, and tingling was made at each time point and scored as 0 = None, 1 = Minor, 2 = Moderate, or 3 = Severe.

^aOne participant withdrew after completing the 2-week post-treatment follow-up visit.

TABLE 4 Summary of cutaneous effects following first and second ATX-101 treatments

	Post first ATX-101 treatment			Post second ATX-101 treatment		
	Immediately (n = 15)	2 weeks (n = 15)	6 weeks (n = 14) ^a	Immediately (n = 14)	2 weeks (n = 14)	12 weeks (n = 15)
Bruising	2	0	0	6	0	0
Minor	2			5		
Moderate				1		
Blanching	0	0	0	1	0	0
Minor				1		
Erythema	15	0	0	14	0	0
Minor	15			14		
Numbness	15	13	9	13	11	0
Minor	2	3	9	2	10	
Moderate	8	10		5		
Severe	5			6	1	
Edema	15	13	4	14	13	0
Minor	4	8	3	7	12	
Moderate	11	5	1	7	1	
Tingling	11	8	1	8	4	0
Minor	2	5	1	4	2	
Moderate	8	2		3	1	
Severe	1	1		1	1	

Note: Clinical assessment for common side effects including bruising, blanching, erythema, numbness, edema, and tingling was made at each time point and scored as 0 = None, 1 = Minor, 2 = Moderate, or 3 = Severe.

^aFor 1 participant, the 6-week post first ATX-101 assessment was performed during the second ATX-101 treatment visit (prior to injection); this participant did not receive a second treatment.

As stand-alone modalities, cryolipolysis and ATX-101 represent effective non-surgical options, which provide uniquely different utilities. While cryolipolysis provides greater impact in de-bulking compartmentalized fat, ATX-101 allows for greater finesse with focally targeted fat reduction tailored to the individual. The need for multiple treatments administered over numerous months may still be required to significantly reduce extreme SMF. This study found that a sequential treatment approach consisting of 2 cryolipolysis treatment cycles (spaced 6 weeks apart) followed by 2 ATX-101 treatments (spaced 4–7 weeks apart) was effective for reducing extreme SMF, as assessed at 12 weeks post final ATX-101 treatment.

By 12 weeks post final ATX-101 treatment, the majority (10/14, 71.4%) of participants achieved a 2-grade CR-SMFRS reduction from their Grade 4 (extreme) baseline score (Figure 2). The overall mean change in the CR-SMFRS score from baseline to final study visit approximated a 2-grade change (Figure 3) with primary improvement (–1.14 grades) occurring by 6 weeks post final cryolipolysis treatment and additional improvement (–0.71 grade) occurring by 12 weeks post final ATX-101 treatment. While the greatest score reduction was associated with the cryolipolysis treatments, the advantage provided by additional treatment with ATX-101 was the ability to refine the lateral jawline area located outside of the zone traditionally treated with cryolipolysis.

Although ultrasound measurement showed a mean reduction in SMF thickness at 6 weeks post final cryolipolysis and at 12 weeks post final ATX-101 treatment (0.2 mm), it was not a significant difference from baseline at either time point. This result is in contrast with data from a previous clinical trial where ultrasound measurements showed significant mean (SD) reduction at 12 weeks post final treatment following 2 cryolipolysis treatment cycles (6 weeks apart) of 2 mm (2.0) (range, +2.0 mm to –5.9 mm).⁸ One possible reason that no difference was observed in the present study may be due to the time point of the measurement, which was 6 weeks post final cryolipolysis, and it is possible the full effect of the cryolipolysis treatment of the submental area had not yet been realized. In addition, the 12 weeks post final treatment assessment (after 2 ATX-101 treatments) may not have been enough time for the inflammatory response to resolve prior to ultrasound. Of note, prior ATX-101 studies used MRI to assess fat layer reduction, a different assessment tool. Although objective measurements of change following cryolipolysis and ATX-101 treatments are important, particularly for clinical trials, they do have limitations. Ultrasound techniques do not take into account the overall appearance of the jawline and face, while clinical measurements and participant-reported outcomes may be better able to consider these factors in assessing treatment-related improvements in SMF thickness. Indeed, the majority of participants achieved a 2-grade improvement on the CR-SMFRS.



FIGURE 5 Standardized photographs of a 41-year-old female participant who received 2 cryolipolysis treatments and 2 ATX-101 treatments and achieved a 3-grade improvement in Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score. At baseline (CR-SMFRS =4) (left), at 6 weeks post cryolipolysis (CR-SMFRS =3) (center), and at 12 weeks post final treatment visit (CR-SMFRS =1) (right). Weight change +3.2 lbs. (+2.1%) from baseline

Participant feedback provided in the SSRS (Figure 4) supported the clinical improvement observed with the CR-SMFRS. In contrast to baseline, where 100% were dissatisfied with the appearance of face and chin (9/14 [64.3%] reported “Extreme Dissatisfaction” and 5/14 [35.7%] reported “Dissatisfaction”), by 6 weeks post final cryolipolysis, 50% (7/14) reported “Extremely Satisfied,” “Satisfied,” or “Slightly Satisfied.” Further, at 12 weeks post final ATX-101 treatment, the rate of satisfaction increased to 71.4% (10/14) of participants reporting that they were “Extremely Satisfied,” “Satisfied,” or “Slightly Satisfied” with the appearance of their face and chin.

Pain scores suggested that procedural and post-treatment pain was tolerable, and no participants discontinued due to pain. All cutaneous effects experienced following cryolipolysis and ATX-101 treatments were anticipated effects of treatment, consistent with the known safety profiles, and resolved spontaneously by the final follow-up visit. No unanticipated AEs related to treatment were reported. Representative participant photographs showing a 3-grade improvement are provided in Figure 5.

Patient selection and expectation management are fundamental considerations with SMF reduction.¹⁴ Reduction of SMF could result in suboptimal appearance if the platysma bands or skin imperfections were to be exposed. Prospective patients should be counseled on the number of sessions necessary, side effects, downtime, and cost. Participants with a baseline of Grade 4 (Extreme) SMF were selected for this study to demonstrate a large degree of improvement. The authors recommend limiting patient selection to those with moderate to severe baseline SMF for optimal results. The study was limited by its small population size (15 evaluable participants) and by assessing fat layer reduction measured using ultrasound at 12 weeks following ATX-101 treatment(s). In the authors’ experience with ATX-101, patients continue to improve for up to 6 months following ATX-101 treatment. Furthermore, waiting for at least 8 weeks between retreatments may facilitate greater clearance of the inflammatory response and may provide more acceptable final results.

5 | CONCLUSIONS

These data support the effective use of cryolipolysis for the de-bulking of extreme SMF followed by ATX-101 treatment to

further refine and reduce target areas of residual fat with specificity. Cutaneous effects following treatment with cryolipolysis and ATX-101 were consistent with the known safety profiles, were self-limiting, and resolved by the end of the study. Improvements in SMF thickness and patient satisfaction with face/chin appearance were observed. This multi-modal treatment approach expands the range of options for an individualized treatment plan, particularly for patients desiring reduction in extreme SMF.

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AUTHOR CONTRIBUTIONS

S. Gamio and B. Bowen participated in study design and data analysis. H.R. Jalian and R. Fitzgerald participated in data acquisition. All authors contributed to interpretation of the data and critical revision of the manuscript for intellectual content. All authors approved the final manuscript.

ETHICAL APPROVAL

The Salus institutional review board approved the study protocol and written informed consent was obtained from all participants prior the initiation of study procedures. This study was conducted in compliance with GCP and is registered at clinicaltrials.gov (NCT#03510598).

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research

proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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