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

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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.

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Kythera Biopharmaceuticals, Inc is an affiliate of Allergan plc, Dublin, Ireland.

The REFINE-2 trial was sponsored by Kythera Biopharmaceuticals, Inc, an affiliate of Allergan plc, Dublin, Ireland. Writing and editorial assistance was provided to the authors by Karen Stauffer, PhD, CMPP, an employee of Evidence Scientific Solutions, Philadelphia, PA, which contracted with Kythera Biopharmaceuticals, Inc to provide professional medical writing assistance and project management support in the development of this manuscript; work by Dr Stauffer was funded by Allergan plc, Dublin, Ireland.

Drs Humphrey and Sykes (receiving funding) and Drs Kantor and Bertucci (receiving institutional funding) served as investigators for Kythera Biopharmaceuticals, Inc. Drs Humphrey, Sykes, and Bertucci served as speakers, consultants, and advisory board members (receiving honoraria) for Kythera Biopharmaceuticals, Inc. Dr Walker was a salaried employee of Kythera Biopharmaceuticals, Inc during the execution of this trial. Mr Lee was a salaried employee and stockholder of Kythera Biopharmaceuticals, Inc during the execution of this trial. Dr Lizzul was Senior Medical Director; Dr Gross was Vice President of Clinical Development, Biostatistics, and Data Management; and Dr Beddingfield was Chief Medical Officer at Kythera Biopharmaceuticals, Inc, where they were salaried employees, stockholders, and holders of stock options during the execution of this trial. Drs Lizzul and Beddingfield are current employees of Sienna Biopharmaceuticals, Inc, Westlake Village, California. All authors met International Committee of Medical Journal Editors authorship criteria. Neither honoraria nor payments were made for authorship.

These data were presented previously at the Anti-Aging Medicine European Congress in Paris, France, October 11-12, 2013, and the Annual Meeting of the American Academy of Dermatology in Denver, Colorado, March 21-24, 2014.

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

Accepted for publication April 11, 2016.

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Published online July 15, 2016.

0190-9622

http://dx.doi.org/10.1016/j.jaad.2016.04.028

Limitations: Follow-up was limited to 44 weeks.

Conclusion: ATX-101 is an alternative treatment for SMF reduction. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.04.028.)

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

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.

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.

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