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Reduction of Submental Fat Continues Beyond 28 Days After ATX-101 Treatment: Results From a Post hoc Analysis

Injection of ATX-101 (deoxycholic acid injection) into subcutaneous fat results in adipocytolysis, which induces a predictable, localized inflammatory response to clear cellular debris and liberated lipids from the injection site.[1] In the pivotal Phase 3 trials supporting global registration of Kybella/Belkyra (Kythera Biopharmaceuticals, Inc., Parsippany, NJ, an affiliate of Allergan),[2–4] ATX-101 treatments and evaluations were spaced 28 ± 5 days apart (based on histology data demonstrating resolution of inflammation by Day 28[1]), whereas primary efficacy was evaluated 12 weeks after last treatment. Given the 28-day spacing for treatment and evaluation, assessment of efficacy beyond intervals of 28 days has been limited. Anecdotal evidence suggests that practitioners extend the treatment interval based on observations of increasing efficacy beyond 28 days thus allowing for achievement of maximal improvement with each ATX-101 treatment and complete resolution of induration before retreatment. In a Phase 3b study (NCT02007434) conducted to evaluate various paradigms to manage the adverse events (AEs) common after ATX-101 treatment (pain, bruising, and swelling/edema),[5] subjects received a single ATX-101 treatment and were evaluated at Days 28 and 84. Post hoc analysis of data from this study was conducted to determine whether greater efficacy was observed at Day 84 versus Day 28, lending support for extending the ATX-101 treatment interval to optimize outcomes.

Methods

The study design was previously described[5]; briefly, adults (aged 18–65 years) with a moderate or severe/large amount of submental fat (SMF) (Grade 2 or 3 on the validated Clinician-Reported and Patient-Reported SMF Rating Scales) who were dissatisfied with the appearance of their face/chin were enrolled. Subjects were randomized to a single treatment with either ATX-101 (area-adjusted dose: 2 mg/cm^2) or placebo; both were administered through 0.2-mL subcutaneous injections 1 cm apart into preplatysmal SMF. This post hoc analysis evaluated efficacy among ATX-101–treated subjects (n = 68). Subjects with moderate SMF at baseline based on clinician assessment (n = 49) received 6 mL of ATX-101, whereas subjects with severe SMF (n = 19) received 8 mL.

Efficacy outcomes, evaluated at Days 28 and 84 after ATX-101 treatment, included percentage of subjects who achieved a ≥1-grade improvement in SMF from baseline based on clinician assessment (CR-1 response), subject assessment (PR-1 response), or both clinician and subject assessments (composite CR-1/PR-1 response). Percentage of subjects satisfied with the appearance of their face/chin after ATX-101 treatment (based on response of slightly satisfied, satisfied, or extremely satisfied on the Subject Self-Rating Scale) and mean change in SMF thickness from baseline based on caliper measurement were also assessed.

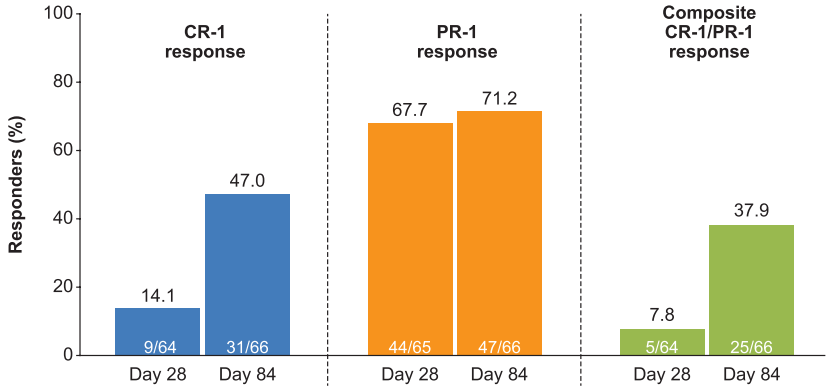

Figure 1. The ATX-101 treatment response builds over time. All measures of efficacy showed an increase in the percentage of responders from Day 28 to Day 84 after ATX-101 treatment. CR-1 response corresponds to achievement of a ≥1-grade improvement in submental fat (SMF) from baseline based on clinician assessment (through the validated 5-point Clinician-Reported SMF Rating Scale); PR-1 response corresponds to achievement of a ≥1-grade improvement in SMF from baseline based on subject assessment (through the validated 5-point Patient-Reported SMF Rating Scale); and composite CR-1/PR-1 response corresponds to achievement of a ≥1-grade improvement in SMF from baseline based on both clinician and subject assessment.

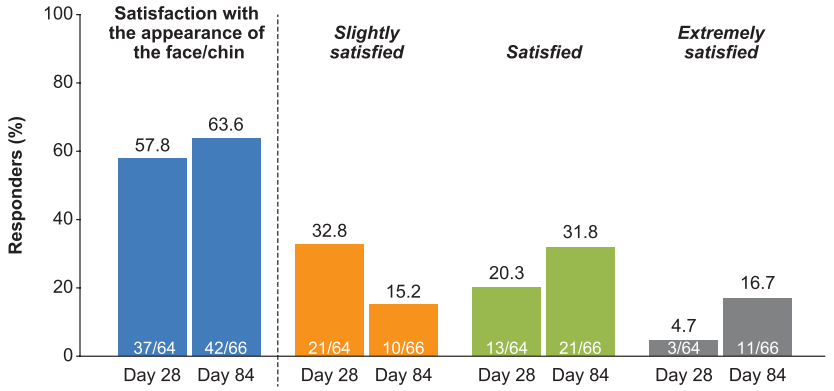

Figure 2. Percentage of subjects satisfied with the appearance of their face/chin after ATX-101 treatment (based on response of slightly satisfied, satisfied, or extremely satisfied on the Subject Self-Rating Scale). The degree of satisfaction increased over time as a greater percentage of subjects was satisfied and extremely satisfied at Day 84 versus Day 28 after ATX-101 treatment.

Safety outcomes included the incidence of AEs and change from baseline in skin laxity as assessed by the clinician using the Submental Skin Laxity Grade scale.

Results

Most subjects were women (62%) and white (79%).[5] Mean age was 43.4 years, and mean body mass index was 32.1 kg/m^2. At baseline, 49 subjects rated their amount of SMF as moderate, whereas 19 rated their amount of SMF as large, consistent with clinician assessment of SMF severity.

At Day 28, the CR-1 response rate was 14.1%, which increased markedly to 47.0% by Day 84 (Figure 1). The PR-1 response rate was 67.7% at Day 28, which increased slightly to 71.2% by Day 84. The composite CR-1/PR-1 response rate was 7.8% at Day 28 and increased markedly by Day 84 (37.9%). Percentage of subjects satisfied with the appearance of their face/chin based on responder analysis did not notably differ between Days 28 and 84 (Figure 2). To determine whether a higher degree of subject satisfaction was reported over time, satisfaction was analyzed by individual response (slightly satisfied, satisfied, or extremely satisfied). At Day 84 versus Day 28, a greater percentage of subjects reported being satisfied and extremely satisfied (Figure 2). Although SMF thickness increased from baseline at Day 28, it decreased overall by Day 84 (Figure 3).

Most AEs after ATX-101 treatment were related to the injection site and included swelling/edema (100%), pain (100%), induration (99%), bruising/hemorrhage (96%), and discomfort (68%).[5] On both Days 28 and 84, negligible changes in skin laxity were reported.

Discussion

Results from this analysis demonstrate that reduction of SMF continues for at least 2 to 3 months after ATX-101 treatment, providing evidence of a progressive improvement in submental contour beyond the 28-day treatment interval in the pivotal Phase 3 trials, a finding consistent

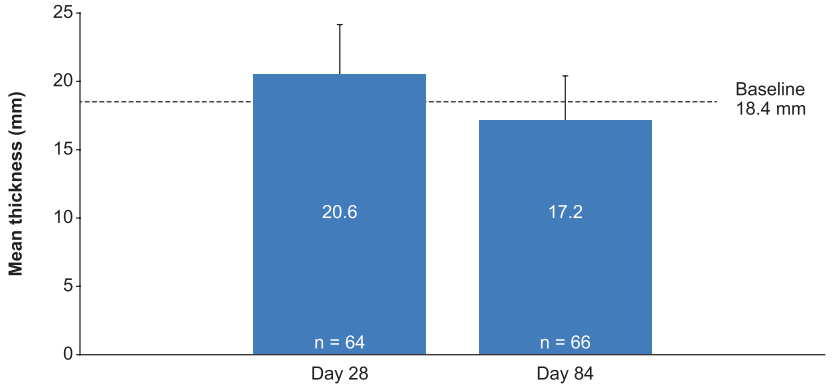

Figure 3. Submental fat (SMF) thickness (based on caliper measurement) decreased over time after ATX-101 treatment. The thickness of SMF was greater than baseline at Day 28 (likely due to residual induration) but was reduced from baseline by Day 84.

with the pivotal program primary efficacy observation time point of 12 weeks after last treatment. Submental fat thickness increased at Day 28, likely due to residual induration within the treatment area; however, it decreased from baseline by Day 84, consistent with the improvement in SMF noted by both the clinician and subjects. In this study, most subjects indicated satisfaction with the appearance of their face/chin after a single ATX-101 treatment. Although the percentage of subjects reporting satisfaction did not markedly differ between Days 28 and 84, the percentage who were satisfied and extremely satisfied increased over time, suggesting that an extended treatment interval may lead to greater patient satisfaction. It is important to note that a 1-grade improvement in SMF (CR-1 or PR-1 response), although clinically meaningful,[1] likely does not correspond to complete resolution of SMF for most patients.

A limitation of this analysis is that subjects received a standardized ATX-101 dose based on baseline SMF severity (given that the primary objective of the Phase 3b study was management of AEs). In clinical practice, the ATX-101 dose is determined by the amount and distribution of SMF and the treatment goal for each patient.

Overall, these findings indicate that efficacy builds over time after ATX-101 treatment. Some subjects may require fewer treatments to achieve their aesthetic goal if an appropriate amount of ATX-101 is used at the initial treatment (6–8 mL for patients with moderate or severe SMF), and the treatment interval is extended. We hypothesize that, after the adipocytolysis and subsequent inflammatory response induced by ATX-101 treatment (shown to largely resolve by Day 28), remodeling of tissues and neocollagenesis within the submental area may occur over several months. Additional studies characterizing the histological/physiological response to ATX-101 treatment beyond 28 days may lend support to this hypothesis.

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