

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
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# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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## 1 Executive Summary

Deoxycholic acid 1% for injection was superior to placebo in the treatment of submental fat in two studies. Studies 22 and 23 enrolled subjects aged 18 to 65 with scores of 2-3 on the clinician and patient submental fat rating scales (moderate to severe submental convexity on the clinician-reported submental fat rating scale (CR-SMFRS) and moderate to large amount of chin fat on the patient-reported submental fat rating scale (PR-SMFRS).) Subjects were treated in up to 6 treatment sessions at 28-day intervals. Each treatment session involved up to 50 injections (0.2 mL each) spaced on a 1-cm grid. Subjects could stop treatment if they lacked sufficient tissue for injection or were satisfied with the reduction in submental fat. The protocols defined two co-primary endpoints based on improvement on both the CR-SMFRS and the PR-SMFRS. The first co-primary endpoint was defined as at least a 1-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The second co-primary endpoint was defined as at least a 2-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The Agency provided the applicant agreement with regard to the use of the 2-grade improvement endpoint as a primary endpoint. According to the protocol, both primary endpoints were required to demonstrate statistical significance.

The protocols also defined two secondary endpoints: MRI responder (at least 10% reduction in volume from baseline to 12 weeks post-treatment) and change from baseline to 12 weeks post-treatment in patient-reported submental fat impact score (PR-SMFIS) total score, which is an average of scores assessing how unhappy, bothered, self-conscious, embarrassed, older, and overweight the subject feels due to chin fat. MRI response was assessed in a subset of subjects. The primary and secondary endpoints were all statistically significant. Multiplicity for the two secondary endpoints was handled using Holm's method. The efficacy results are presented in Table 1.

**Table 1 – Primary and Secondary Efficacy Endpoints in Studies 22 and 23 (ITT)**

	Study 22		Study 23	
	Deoxy. acid N=256	Placebo N=250	Deoxy. acid N=258	Placebo N=258
2-grades improvement CR-SMFRS / PR-SMFRS <sup>a</sup>	34.3/256 (13.4%)	0.1/250 (<0.1%)	48.0/258 (18.6%)	7.7/258 (3.0%)
	p<0.001		p<0.001	
1-grade improvement CR-SMFRS / PR-SMFRS <sup>a</sup>	179.3/256 (70.0%)	46.6/250 (18.6%)	171.6/258 (66.5%)	57.3/258 (22.2%)
	p<0.001		p<0.001	
≥ 10% reduction in MRI volume <sup>b</sup>	52.0/113 (46.0%)	5.9/111 (5.3%)	45.8/113 (40.5%)	5.8/112 (5.2%)
	p < 0.001		p < 0.001	
Change from baseline in PR-SMFIS [LSmeans (SE)] <sup>b</sup>	-3.61 (0.143)	-1.10 (0.143)	-3.44 (0.158)	-1.46 (0.156)
	p<0.001		p<0.001	

<sup>a</sup> Co-primary endpoints

<sup>b</sup> Multiplicity among the secondary endpoints was handled with Holm's method

Protocol 22 was submitted as a Special Protocol Assessment (SPA). The Agency and sponsor reached agreement on the study design and one of the primary endpoints (at least 2 grades reduction on both the CR-SMFRS and PR-SMFRS). The Agency did not provide agreement regarding the ‘1-grade reduction’ endpoint.

Injection site reactions were common and more than half of deoxycholic acid subjects experienced injection site hematomas, pain, edema, and anesthesia. More than 10% of deoxycholic acid subjects experienced injection site swelling, erythema, induration, paresthesia, pruritus, and nodule. Seven percent of subjects discontinued treatment due to adverse events and 3% discontinued treatment due to withdrawal of consent for further treatments due to discomfort with procedure.

The majority of deoxycholic subjects (64% in Study 22 and 54% in Study 23) and placebo subjects (85% in Study 22 and 77% in Study 23) received all 6 injections. Greater numbers of subjects on the deoxycholic acid arm received fewer than 6 treatments than on the placebo arm due to response (insufficient submental fat into which injections may be safely given or subject satisfaction with submental fat reduction) and adverse experiences (adverse events or withdrawal of consent for further treatments due to discomfort with the procedure). See Table 2.

**Table 2 – Reasons for Treatment Discontinuation in Studies 22 and 23**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
Completed 6 treatments	64%	85%	54%	77%
Discontinued treatment due to response <sup>a</sup>	16%	3%	22%	5%
Discontinued treatment due to AE <sup>b</sup>	9%	1%	11%	2%
Discontinued treatment for other reasons <sup>c</sup>	11%	11%	14%	16%

<sup>a</sup> Insufficient SMF into which injections may safely be given or Subject satisfaction with SMF reduction

<sup>b</sup> Adverse event or Withdrawal of consent for further treatments due to discomfort with procedure

<sup>c</sup> Administrative decision, Lost to follow-up, Withdrawal of consent for further treatments due to subject convenience, Other

## 2 Introduction

### 2.1 Overview

#### 2.1.1 Clinical Studies

Deoxycholic acid injection is a new molecular entity intended for the improvement in the appearance of convexity or fullness associated with submental fat. This submission is a 505(b)(1) application. Deoxycholic acid was evaluated in three Phase 2 studies (Studies 3, 7, and 15), two supportive Phase 3 studies conducted in Europe (Studies 16 and 17), and two pivotal placebo-controlled Phase 3 studies conducted in the U.S. and Canada (Studies 22 and 23). The Phase 2 studies and European Phase 3 studies evaluated dose levels of 0.1% up to 2%, various numbers of injections (24 to 50), and injection volumes

(0.2 mL to 0.4 mL) in 4 to 6 treatment sessions four weeks apart. The basic design details and treatment regimens assessed are summarized in Table 3 and Table 4.

**Table 3 – Clinical Studies Overview – Phase 2 Studies**

Study number	Study 3 (N=85)	Study 7 (N=57)	Study 15 (N=129)
Doses	0.5%, 1%, 2%, placebo	0.1%, placebo	0.5%, 1%, placebo
Injection Pattern	up to 24 injections of 0.2 mL each	-up to 48 injections of 0.2 mL each on a 0.7 cm grid -up to 24 injections of 0.2 mL each on a 1 cm grid -up to 24 injections of 0.4 mL each on a 1 cm grid	up to 50 injections of 0.2 mL each on a 1 cm grid
Treatment regimen	up to 4 treatments every 4 weeks	up to 4 treatments every 4 weeks	up to 6 treatments every 4 weeks
Treatment arms and sample size	0.5% : 21 1%: 20 2%: 22 Placebo: 22	-48 inj/0.2 mL/0.7 cm: 0.1% -18; placebo - 3 -24 inj/0.2 mL/1 cm: 0.1% - 12; placebo - 3 -24 inj/0.4 mL/ 1 cm: 0.1% - 18; placebo - 3	0.5%: 41 1%: 43 Placebo: 45
Study location	England, Australia, Canada	England, Australia, Canada	United States
Study dates	Aug. 2007 – Oct. 2008	Apr. 2008 – Dec. 2008	Dec. 2009 – Dec. 2010

**Table 4 – Clinical Studies Overview – Supportive Phase 3 Studies**

Study number	Study 16 (N=363)	Study 17 (N=360)
Doses	0.5%, 1%, placebo	0.5%, 1%, placebo
Injection Pattern	up to 50 injections of 0.2 mL each on a 1 cm grid	up to 50 injections of 0.2 mL each on a 1 cm grid
Treatment regimen	up to 4 treatments every 4 weeks	up to 4 treatments every 4 weeks
Treatment arms and sample size	0.5% : 120 1%: 121 Placebo: 122	0.5%: 121 1%: 122 Placebo: 117
Primary endpoints	-At least 1 grade reduction on the CR-SMFRS <sup>1</sup> -Score of 4 or higher on the SSRS <sup>2</sup>	-At least 1 grade reduction on the CR-SMFRS <sup>1</sup> -Score of 4 or higher on the SSRS <sup>2</sup>
Study location	Belgium, France, Germany, Spain, UK	Belgium, France, Germany, Spain, Italy, UK
Study dates	Dec. 2010 – Jan. 2012	Jan. 2011 – Feb. 2012

<sup>1</sup>Clinician-Reported Submental Fat Rating Scale

<sup>2</sup>Subject Self Rating Scale

The US Phase 3 studies evaluated deoxycholic acid 1% versus placebo with a dosing regimen of up to 50 injections of 0.2 mL each on a 1 cm grid. Subjects received up to 6 treatment sessions every four weeks. Study 22 randomized 256 subjects to deoxycholic acid and 250 subjects to placebo. Study 23 randomized 258 subjects to deoxycholic acid and 258 subjects to placebo. Both studies enrolled subjects age 18 to 65 with scores of 2 or 3 on the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) and the Patient-Reported Submental Fat Rating Scale (PR-SMFRS) and a history of stable body weight. Both the CR-SMFRS and PR-SMFRS are 5-point scales. The primary efficacy endpoints were ‘at least 1 grade reduction on both the CR-SMFRS and PR-SMFRS’ and ‘at least 2 grades reduction on both the CR-SMFRS and PR-SMFRS’ 12 weeks after the last treatment. Both studies were conducted in the US and Canada. An overview of the US Phase 3 studies is presented in Table 5. This review will focus on the two US Phase 3 studies.

**Table 5 – Clinical Studies Overview – Pivotal Phase 3 Studies**

Study number	Study 22 (N=506)	Study 23 (N=516)
Doses	1%, placebo	1%, placebo
Injection Pattern	up to 50 injections of 0.2 mL each on a 1 cm grid	up to 50 injections of 0.2 mL each on a 1 cm grid
Treatment regimen	up to 6 treatments every 4 weeks	up to 6 treatments every 4 weeks
Treatment arms and sample size	1%: 256 Placebo: 250	1%: 258 Placebo: 258
Inclusion Criteria	Adults age 18 to 65 with scores of 2 or 3 on both the CR-SMFRS <sup>1</sup> and PR-SMFRS <sup>2</sup> and a history of stable body weight.	Adults age 18 to 65 with scores of 2 or 3 on both the CR-SMFRS <sup>1</sup> and PR-SMFRS <sup>2</sup> and a history of stable body weight.
Primary endpoints	-At least 1 grade reduction on both the CR-SMFRS <sup>1</sup> and PR-SMFRS <sup>2</sup> - At least 2 grades reduction on both the CR-SMFRS <sup>1</sup> and PR-SMFRS <sup>2</sup>	-At least 1 grade reduction on both the CR-SMFRS <sup>1</sup> and PR-SMFRS <sup>2</sup> - At least 2 grades reduction on both the CR-SMFRS <sup>1</sup> and PR-SMFRS <sup>2</sup>
Study location	US, Canada	US, Canada
Study dates	Feb. 2012 – Aug. 2013	Mar. 2012 – Aug. 2013

<sup>1</sup>Clinician-Reported Submental Fat Rating Scale (Range: 0 to 4)

<sup>2</sup> Patient-Reported Submental Fat Rating Scale (Range: 0 to 4)

### 2.1.2 Regulatory History

The IND for deoxycholic acid was opened in 2007 with a dose-escalation pharmacokinetics study. The following meetings were held with the sponsor:

- Guidance meeting (8/19/2009)
- End of Phase 2 meeting (4/20/2011)

- Pre-NDA meeting (11/13/2013)

Protocol 22 was submitted as a Special Protocol Assessment (SPA) on 11/4/2011, and an agreement letter was issued on 12/16/2011. The Agency and sponsor reached agreement on the study design and one of the primary endpoints (at least 2 grades reduction on both the CR-SMFRS and PR-SMFRS). The Agency did not provide agreement on the '1-grade reduction' endpoint. After receiving the SPA response, the sponsor revised the statistical analysis plan to address comments in the letter regarding missing data handling, analysis centers, and pooling of centers. The sponsor maintained the design with two co-primary endpoints (1-grade and 2-grade reduction). Protocol 23 was of identical design to Protocol 22.

## **2.2 Data Sources**

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The analysis datasets used in this review are archived at <\\cdsesub1\evsprod\nda206333\0000\m5\datasets>.

## **3 Statistical Evaluation**

### **3.1 Data and Analysis Quality**

The databases for the studies required some data management prior to performing analyses. For the LOCF imputation (which was a secondary method of missing data imputation), the applicant's definition of LOCF only imputed responses for subjects who had at least one assessment at either the 5<sup>th</sup> treatment session or the 4-week post-treatment visit. Subjects who did not attend at least one of these visits were ignored and not accounted for in the analysis. This reviewer needed to recreate LOCF analyses that included all ITT subjects randomized.

The Agency also requested additional datasets and statistical programs during the review cycle. The Agency requested the SAS programs for conducting the multiple imputation analyses. The Agency also requested new datasets for the MRI assessments. Following database lock, the applicant discovered that the imaging vendor did not provide the baseline MRI measurements for any subject who did not have a post-treatment MRI conducted. The affected MRIs were eventually read, but the outcomes were not included in the database submitted with the original application. The Agency requested updated datasets that included the missing MRI assessments.

### **3.2 Evaluation of Efficacy**

#### **3.2.1 Study Design and Statistical Analysis**

Studies 22 and 23 were identically designed, randomized, double-blind, placebo-controlled studies of the efficacy and safety of deoxycholic acid for the reduction of submental fat (SMF). Studies 22 and 23 enrolled subjects age 18 to 65 with scores of 2-3 on the clinician and patient scales (moderate to severe submental convexity on the clinician-reported submental fat rating scale (CR-SMFRS) and moderate to large amount

of chin fat on the patient-reported submental fat rating scale (PR-SMFRS).) Subjects were also to express dissatisfaction with the submental area (extremely dissatisfied, dissatisfied, or slightly dissatisfied on a 7 point scale). Subjects were randomized in a 1:1 ratio to deoxycholic acid or placebo. Treatment was injected in up to 6 treatment sessions at 28-day intervals. Each treatment session involved up to 50 injections (0.2 mL each) spaced on a 1-cm grid. Subjects could stop treatment if they lacked sufficient tissue for injection or were satisfied with the reduction in SMF. Subjects were evaluated at screening, baseline, and Weeks 1, 4, 5, 8, 9, 12, 13, 16, 17, 20, 21, 24 (or 4 weeks post-treatment), 32 (or 12 weeks post-treatment), and 44 (or 24 weeks post-treatment). Treatments could be administered at Weeks 0, 4, 8, 12, 16, and 20. The primary efficacy timepoint was 12 weeks after the last treatment.

Efficacy was assessed through a variety of clinician and patient scales and measurements. The primary efficacy assessments were based on the clinician-reported submental fat rating scale (CR-SMFRS) and the patient-reported submental fat rating scale (PR-SMFRS). The CR-SMFRS and the PR-SMFRS instruments were as follows:

**Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)**

<b>Score</b>	<b>SMF Description</b>
<b>0</b>	Absent Submental Convexity: No localized submental fat evident.
<b>1</b>	Mild Submental Convexity: Minimal, localized submental fat.
<b>2</b>	Moderate Submental Convexity: Prominent, localized submental fat.
<b>3</b>	Severe Submental Convexity: Marked, localized submental fat.
<b>4</b>	Extreme Submental Convexity.

Each level of the CR-SMFRS was accompanied by representative photographs.

**Patient-Reported Submental Fat Rating Scale (PR-SMFRS)**

Please look in the mirror at **the area under your chin** to help you answer the following question:

<b>How much fat do you have under your chin right now?</b>	
Mark <input checked="" type="checkbox"/> in one box below	
<input type="checkbox"/>	No chin fat at all
<input type="checkbox"/>	A slight amount of chin fat
<input type="checkbox"/>	A moderate amount of chin fat
<input type="checkbox"/>	A large amount of chin fat
<input type="checkbox"/>	A very large amount of chin fat

Each level of the PR-SMFRS was accompanied by representative line drawings. The PR-SMFRS and CR-SMFRS were assessed at screening and Weeks 4, 8, 12, 16, 20, and 4 weeks post-treatment, 12 weeks post-treatment, and 24 weeks post-treatment.

At selected centers approximately 200 subjects were to have MRI assessments (SMF area and volume). MRI assessments were conducted at screening and the 12 weeks post-treatment visit.

The patient-reported submental fat impact scale (PR-SMFIS) was assessed at baseline and Weeks 16, 4 weeks post-treatment, 12 weeks post-treatment, and 24 weeks post-treatment. The PR-SMFIS is comprised of 6 elements which assess how unhappy, bothered, self-conscious, embarrassed, older, and overweight the subject feels due to chin fat. The scores from the 6 elements are averaged to compute the total score. The scale is presented in the Appendix.

Caliper measurements (in mm) and the submental skin laxity grade (SMSLG) were taken at baseline and Weeks 16, 4 weeks post-treatment, 12 weeks post-treatment, and 24 weeks post-treatment. The scale for the SMSLG, which assesses skin wrinkling, adherence to underlying neck structure (bone and muscle), and redundancy (horizontal and vertical folds), is also presented in the Appendix.

The protocols defined two co-primary endpoints based on improvement on both the CR-SMFRS and the PR-SMFRS. The first co-primary endpoint was defined as at least a 1-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The second co-primary endpoint was defined as at least a 2-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The protocols also defined two secondary endpoints: MRI responder (at least 10% reduction in volume from baseline to 12 weeks post-treatment) and change from baseline to 12 weeks post-treatment in PR-SMFIS total score (average of the 6 elements).

The responder endpoints (1-grade composite response, 2-grade composite response, and MRI responder) were analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified on center. Change in PR-SMFIS was analyzed with ANCOVA with baseline included as a covariate. Multiple imputation was used as the principle method of handling missing data. Both co-primary endpoints were required to demonstrate statistical significance. Multiplicity for the two secondary endpoints was handled using Holm's method.

Small centers were combined into analysis centers for the CMH analyses. The smallest sites were to be pooled together until the analysis center had at least 8 subjects per treatment arm. The next larger centers were then pooled together to reach at least 8 subjects per treatment arm, etc. until all analysis centers had at least 8 subjects per treatment arm. Consistency of treatment response across analysis centers for the primary endpoint was assessed by plotting the proportion of responders on the deoxycholic acid arm versus the proportion of responders on the placebo arm by center.

The ITT population was defined as all randomized subjects. The ITT-MRI population was defined as all randomized subjects in the MRI cohort. The ITT population was the primary analysis population for all efficacy endpoints except for MRI response, where the ITT-MRI population was the primary analysis population.

The primary method of handling missing data was multiple imputation. The sensitivity analyses include (1) multiple imputation while imputing all missing subjects as if they had received deoxycholic acid, (2) multiple imputation while imputing all missing subjects as if they had received placebo, and (3) LOCF.

### **3.2.2 Subject Disposition**

Study 22 randomized 256 subjects to deoxycholic acid and 250 subjects to placebo. One subject randomized to placebo never received treatment. Study 23 randomized 258 subjects to deoxycholic acid and 258 subjects to placebo. One subject on each treatment arm did not receive treatment. The subjects who were randomized but did not receive treatment are included in the ITT population, but not the safety population. Slightly higher proportions of deoxycholic acid subjects did not return for the 12 weeks post-treatment visit than placebo subjects (10% vs. 6% in Study 22, and 16% vs. 11% in Study 23). The most common reasons for discontinuing the study prior to the 12 weeks post-treatment visit were ‘withdrawal of consent due to subject convenience’ and ‘lost to follow-up’. Subjects could discontinue treatment before completing 6 treatment sessions. The most common reasons for discontinuing treatment were ‘insufficient SMF’ and ‘adverse events’. See Table 6.

**Table 6 – Disposition of Subjects in Studies 22 and 23**

	Study 22		Study 23	
	Deoxycholic acid	Placebo	Deoxycholic acid	Placebo
Subjects randomized (ITT)	256	250	258	258
Subjects treated (Safety)	256 (100%)	249 (>99%)	257 (>99%)	257 (>99%)
Subjects in ITT-MRI population	113 (44%)	111 (44%)	113 (44%)	112 (44%)
Subjects completing 12-week post-treatment visit (primary efficacy timepoint)	230 (90%)	234 (94%)	218 (84%)	230 (89%)
<i>Reasons for discontinuing study prior to the 12-week post-treatment visit</i>				
Withdrawal of consent due to subject convenience	18 (7%)	7 (3%)	15 (6%)	14 (5%)
Administrative decision	0	2 (1%)	0	0
Subject noncompliance	1 (<1%)	0	1 (<1%)	0
Adverse event	2 (1%)	2 (1%)	6 (2%)	3 (1%)
Lost to follow-up	5 (2%)	5 (2%)	16 (6%)	11 (4%)
Other	0	0	2 (1%)	0
<i>Reasons for discontinuing treatment</i>				
Insufficient SMF	33 (13%)	5 (2%)	44 (17%)	12 (5%)
Subject satisfaction with SMF reduction	9 (4%)	2 (1%)	12 (5%)	1 (<1%)
Withdrawal of consent for further treatments due to discomfort with procedure	4 (2%)	0 (0%)	11 (4%)	2 (1%)
Withdrawal of consent for further treatments due to subject convenience	14 (5%)	6 (2%)	13 (5%)	16 (6%)
Adverse events	19 (7%)	3 (1%)	17 (7%)	3 (1%)
Administrative decision	5 (2%)	4 (2%)	9 (3%)	3 (1%)
Lost to follow-up	5 (2%)	5 (2%)	12 (5%)	5 (2%)
Pregnancy	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Other	3 (1%)	12 (5%)	1 (<1%)	16 (6%)
<i>Number of treatments completed</i>				
6	164 (64%)	213 (85%)	140 (54%)	199 (77%)
5	21 (8%)	7 (3%)	19 (7%)	12 (5%)
4	17 (7%)	6 (2%)	31 (12%)	15 (6%)
3	11 (4%)	8 (3%)	22 (9%)	8 (3%)
2	14 (5%)	11 (4%)	15 (6%)	10 (4%)
1	29 (11%)	4 (2%)	30 (12%)	13 (5%)
0	0 (0%)	1 (<1%)	1 (<1%)	1 (<1%)

Source: pg 63-64 of atx-101-11-22-body.pdf and pg 62-63 of atx-101-22-23.pdf and reviewer analysis.

The applicant noted that all subjects who discontinued treatment due to ‘other’ reasons were due to ‘dissatisfaction with treatment results’ except for one subject (randomized to deoxycholic acid) who never received treatment. However, the verbatim comments from the CRF corresponding to the treatment discontinuation reason of ‘other’ were not included in the electronic database. The other two subjects who never received any treatment were classified as discontinuing the study due to ‘withdrawal of consent due to subject convenience’.

Two subjects who were randomized to placebo incorrectly received one treatment with deoxycholic acid during the study. Subject 124-009 in Study 22 received deoxycholic acid at Week 8 and Subject 533-006 in Study 23 received deoxycholic acid at baseline. Because these two subjects received a dose of deoxycholic acid, the applicant included these subjects in adverse event tables as having received deoxycholic acid. However, for all efficacy and safety analyses in this review, these two subjects will be analyzed and presented per the randomization, that is, as subjects on the placebo arm.

### 3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies. The mean age was 49 years in Study 22 and 48 years in Study 23. Most subjects were female (83% in Study 22 and 87% in Study 23) and white (88% in Study 22 and 86% in Study 23). The majority of the subjects were enrolled in the U.S. with about 13% enrolled in Canada. See Table 7.

**Table 7 – Demographics in Studies 22 and 23**

	Study 22		Study 23	
	Deoxy. acid N=256	Placebo N=250	Deoxy. acid N=258	Placebo N=258
<i>Age (years)</i>				
Mean	49.5	49.4	48.2	47.6
Range	19 - 65	21 - 65	19 - 65	21 - 64
<i>Gender</i>				
Male	43 (17%)	42 (17%)	37 (14%)	34 (13%)
Female	213 (83%)	208 (83%)	221 (86%)	224 (87%)
<i>Race</i>				
White	218 (85%)	227 (91%)	222 (86%)	222 (86%)
Black or Afric.-Amer.	24 (9%)	13 (5%)	24 (9%)	21 (8%)
Amer. Ind./AK Native	0 (0%)	2 (<1%)	1 (<1%)	2 (<1%)
Asian	7 (3%)	5 (2%)	4 (2%)	5 (2%)
Native HI/Pac. Islander	0 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Other	5 (2%)	2 (<1%)	2 (<1%)	7 (3%)
<i>Ethnicity</i>				
Hispanic or Latino	28 (11%)	17 (7%)	40 (16%)	39 (15%)
Not Hispanic or Latino	228 (89%)	233 (93%)	218 (84%)	219 (85%)
<i>Country</i>				
United States	223 (87%)	217 (87%)	228 (88%)	227 (88%)
Canada	33 (13%)	33 (13%)	30 (12%)	31 (12%)

Source: pg 67 of atx-101-11-22-body.pdf, pg 66 of atx-101-11-23-body.pdf, and reviewer analysis.

To be enrolled in the study, subjects were to have scores of moderate to severe (2 or 3) on the CR-SMFRS and scores of moderate to large (2 or 3) on the PR-SMFRS. Both scales had a range from 0 to 4. Approximately half of the subjects were rated by the investigator as having moderate submental fat, while approximately 63% of subjects rated themselves as having moderate chin fat. See Table 8.

**Table 8 – Baseline Disease Characteristics in Studies 22 and 23**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
<i>CR-SMFRS</i>				
Moderate	130 (51%)	130 (52%)	127 (49%)	132 (51%)
Severe	126 (49%)	120 (48%)	131 (51%)	126 (48%)
<i>PR-SMFRS</i>				
Moderate	164 (64%)	157 (63%)	163 (63%)	161 (62%)
Large	92 (36%)	92 (37%)	95 (37%)	97 (38%)
Very large	--	1 (<1%)	--	--
<i>SMF Volume (MRI)</i>	N=113	N=110	N=113	N=112
Mean (SD)	7012.2 (1523.8)	7047.1 (1529.5)	7186.6 (1763.6)	7051.8 (1774.7)

Source: reviewer analysis

### 3.2.4 Primary Efficacy Endpoints

Deoxycholic acid was superior to placebo for both responder definitions based on the CR-SMFRS and the PR-SMFRS (at least one grade improvement on both scales and at least 2 grades improvement on both scales) in both studies ( $p \leq 0.001$ ). The primary endpoints were analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified on analysis center. Both responder definitions needed to demonstrate statistical significance. The Agency provided agreement to the applicant regarding use of the 2-grade improvement endpoint as a primary endpoint in the SPA review. See Table 9.

**Table 9 – Primary Efficacy Endpoints at 12 Weeks Post-Treatment in Studies 22 and 23 (ITT)**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
2-grades improvement CR-SMFRS / PR-SMFRS	34.3/256 (13.4%)	0.1/250 (<0.1%)	48.0/258 (18.6%)	7.7/258 (3.0%)
	$p < 0.001$		$p < 0.001$	
1-grade improvement CR-SMFRS / PR-SMFRS	179.3/256 (70.0%)	46.6/250 (18.6%)	171.6/258 (66.5%)	57.3/258 (22.2%)
	$p < 0.001$		$p < 0.001$	

Source: pg 73 of atx-101-11-22-body.pdf, pg 72 of atx-101-11-23-body.pdf, and reviewer analysis.

Missing data was handled using multiple imputation. For the imputation, 100 datasets were generated and the CMH test conducted on each imputed dataset. The imputed values were generated using the logistic regression method in PROC MI. The imputation model used the ‘core’ variables sex, age, race/ethnicity categories, baseline BMI, treatment received, treatment discontinuation, and number of treatments received in all models. Missing CR-SMFRS and PR-SMFRS values at the 4-week and 12-week post-treatment visits were imputed jointly. The imputation method allowed for imputing missing baseline CR-SMFRS and PR-SMFRS values, but this step was not needed. First missing data at the 4-week post-treatment visit were imputed as follows:

1. Impute CR-SMFRS using the PROC MI logistic regression method based on the core variables, baseline CR-SMFRS, baseline PR-SMFRS, last known CR-SMFRS, and last known PR-SMFRS.
2. Impute PR-SMFRS using the PROC MI logistic regression method based on the core variables, baseline CR-SMFRS, baseline PR-SMFRS, last known PR-SMFRS, and 4-week post-treatment CR-SMFRS.

Next missing data from the 12-week post-treatment were imputed similarly as follows:

1. Impute CR-SMFRS using the PROC MI logistic regression method based on the core variables, baseline CR-SMFRS, baseline PR-SMFRS, 4-week post-treatment CR-SMFRS, and 4-week post-treatment PR-SMFRS.
2. Impute PR-SMFRS using the PROC MI logistic regression method based on the core variables, baseline CR-SMFRS, baseline PR-SMFRS, 4-week post-treatment PR-SMFRS, 4-week post-treatment CR-SMFRS, and 12-week post-treatment CR-SMFRS.

Each imputed dataset was analyzed with the CMH test stratified on analysis center. The values of the general association test statistic from the CMH analysis were transformed using the Wilson-Hilferty transformation to create a more normally distributed statistic:

$$z = \frac{(\text{CMH})^{(1/3)} - (7/9)}{(2/9)^{(1/2)}}$$

The resulting transformed values were combined using PROC MIANALYZE in SAS to yield the corresponding p-values.

As sensitivity analyses, the applicant conducted an LOCF analysis and two additional multiple imputation analyses where subjects with missing data were imputed assuming subjects had received deoxycholic acid and an analysis where subjects with missing data were imputed assuming subjects had received placebo. Note that the applicant’s LOCF analysis did not impute data for all subjects with missing data. Only subjects who had at least one assessment at either the 5<sup>th</sup> treatment session (Week 16) or the 4-week post-treatment visit had data imputed for the 12-week post-treatment visit. Subjects who did not attend at least one of these visits are ignored. The applicant did not provide a rationale for only imputing data for some of the subjects under LOCF or why the 5<sup>th</sup> treatment session was selected. A full LOCF analysis imputing data for all subjects was conducted by this reviewer.

The applicant presented the results of their missing data sensitivity analyses graphically and did not include any tabular representations of the results under various missing data assumptions. Table 10 and presents the CR-SMFRS/PR-SMFRS improvement results for observed data, multiple imputation (the primary method), and LOCF using both the applicant's and reviewer's analyses. The applicant's missing data sensitivity analysis results plots (including the two additional multiple imputation analyses) are consistent with the analyses presented in Table 10. The results are consistent across all methods of handling missing data.

**Table 10 – Efficacy Outcomes under Missing Data Handling Methods in Studies 22 and 23**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
<b>2-grades improvement CR-SMFRS / PR-SMFRS</b>				
Observed Case Responders	34/233 (14.6%)	0/233 (0%)	45/221 (20.4%)	7/230 (3.0%)
Imputed Responders (MI) <sup>a</sup>	34.3/256 (13.4%)	0.1/250 (<0.1%)	48.0/258 (18.6%)	7.7/258 (3.0%)
Imputed Responders (LOCF – Applicant definition) <sup>b</sup>	34/241 (14.1%)	0/240 (0%)	47/235 (20.0%)	7/246 (2.9%)
Imputed Responders (LOCF – all subjects)	34/256 (13.3%)	0/250 (0%)	47/258 (18.2%)	7/258 (2.7%)
<b>1-grade improvement CR-SMFRS / PR-SMFRS</b>				
Observed Case Responders	172/233 (73.8%)	44/233 (18.9%)	156/221 (70.6%)	51/230 (22.2%)
Imputed Responders (MI) <sup>a</sup>	179.3/256 (70.0%)	46.6/250 (18.6%)	171.6/258 (66.5%)	57.3/258 (22.2%)
Imputed Responders (LOCF – Applicant definition) <sup>b</sup>	175/241 (72.6%)	45/240 (18.8%)	164/235 (69.8%)	55/246 (22.4%)
Imputed Responders (LOCF – all subjects)	175 /256 (68.4%)	47/250 (18.8%)	167/258 (64.7%)	56/258 (21.7%)

<sup>a</sup> Mean of 100 imputations (primary analysis)

<sup>b</sup> Only subjects who had at least one assessment at either the 5<sup>th</sup> treatment session (Week 16) or the 4-week post-treatment visit had data imputed for the 12-week post-treatment visit

Source: reviewer analysis

### 3.2.5 Secondary Endpoints

The two key secondary endpoints were MRI responder (at least 10% reduction in volume from baseline to 12 weeks post-treatment) and change from baseline to 12 weeks post-treatment in patient-reported submental fat impact score (PR-SMFIS) total score (the average of 6 impact elements each scored from 0 to 10). Multiplicity was controlled for

the two secondary endpoints (after demonstrating significance on both co-primary endpoints) using Holm's method.

MRIs were conducted on only a subset of the subjects enrolled in the trial. Selected centers were identified as MRI centers at the beginning of the study. All subjects at the selected centers were to undergo MRI assessments until approximately 200 subjects were enrolled at these centers. Study 22 enrolled 224 subjects in the MRI cohort and Study 23 enrolled 225 subjects in the MRI cohort. MRIs were conducted at screening and 12 weeks post-treatment.

The applicant reported that the vendor reading the MRIs did not originally read the baseline MRIs of 30 subjects (19 deoxycholic acid and 11 placebo) who did not return for the post-treatment MRI in Study 22 and 29 subjects (19 deoxycholic acid and 10 placebo) who did not return for the post-treatment MRI in Study 23. In addition, in each study there was one subject who had both baseline and post-treatment MRIs conducted but the post-treatment MRI was not read by the vendor. Both subjects were on the placebo arm and were non-responders on the MRI endpoint. The applicant did not provide any explanation for why the two post-treatment MRIs were not initially read. The original study reports treated all of these subjects as having missing data and the outcomes were imputed. The primary method of imputation for MRI results was multiple imputation and each missing assessment was imputed 100 times. The imputation procedure for missing MRI assessments was conducted similarly to the multiple imputation procedure for the CR-SMFRS and PR-SMFRS as follows, with a step included for imputing missing baseline MRI assessments.

1. Missing baseline MRI volumes were imputed using PROC MI regression based on age, sex, race/ethnicity, baseline BMI, and baseline caliper measurement.
2. Missing values of the post-treatment MRI volume were imputed using PROC MI regression based on the core variables (sex, age, race/ethnicity categories, baseline BMI, treatment received, treatment discontinuation, and number of treatments received), baseline MRI volume, baseline MRI thickness, baseline CR-SMFRS, last available CR-SMFRS at or before the 12-week post-treatment visit, baseline PR-SMFRS, last available PR-SMFRS at or before the 12-week post-treatment visit, baseline caliper measurement, and last available caliper measurement at or before the 12-week post-treatment visit.

After the MRI results that were originally ignored were read, the two missed post-treatment assessments no longer required imputation, and the subjects with missing post-treatment assessments now had their post-treatment responses imputed using observed baseline MRI results rather than imputed baseline results. These changes to the amount of imputation needed led to very minor changes (<0.3%) in the estimated results depending on whether the original or updated databases were used.

The proportions of MRI responders who had at least a 10% reduction in volume from baseline to 12 weeks post-treatment using the original database and multiple imputation (from the study report) the updated database and multiple imputation (from the supplementary report), and a sensitivity analyses using the updated database treating

missing as failure (reviewer analysis) are presented in Table 11. The MRI responder endpoint is statistically significant with multiplicity adjustments based on Holm’s method ( $p < 0.025$ ).

**Table 11 – At Least 10% Reduction in MRI Volume in Studies 22 and 23**

	Study 22		Study 23	
	Deoxycholic acid N=113	Placebo N=111	Deoxycholic acid N=113	Placebo N=112
<b>≥ 10% reduction in volume</b>				
MI in original database	52.3 (46.3%) $p < 0.001$	5.9 (5.3%)	45.5 (40.2%) $p < 0.001$	5.8 (5.2%)
MI in updated database	52.0 (46.0%) $p < 0.001$	5.9 (5.3%)	45.8 (40.5%) $p < 0.001$	5.8 (5.2%)
Missing as failure	48 (42.5%) $p < 0.001$	5 (4.5%)	38 (33.6%) $p < 0.001$	5 (4.5%)

Source: pg 516 of atx-101-11-22-body.pdf, pg 34 of atx-101-11-22-e3-16-1-13.pdf, pg 516 of atx-101-11-23-body.pdf, pg 34 of atx-101-11-23-e3-16-1-13.pdf, and reviewer analysis.

The other secondary endpoint was change from baseline in the patient-reported submental fat impact score (PR-SMFIS). The PR-SMFIS assessed how happy, bothered, self-conscious, embarrassed, older, and overweight the subject feels due to chin fat. Each element was evaluated on an 11-point scale where 0 = ‘not at all’ and 10 = ‘extremely’. The full instrument is presented in the Appendix. The PR-SMFIS was assessed at baseline, Week 16 and at 4, 12, and 24 weeks post-treatment. The primary assessment timepoint was 12 weeks post-treatment. Note that the PR-SMFIS evaluates one ‘positive’ impact (happy) and five ‘negative’ impacts (bothered, self-conscious, embarrassed, older, and overweight). For all analyses, the happiness element is transformed into an ‘unhappiness’ element by subtracting the observed score from 10 (unhappy = 10 - happy). The scores on each element were averaged to get the total score. The mean change from baseline to 12 weeks post-treatment was analyzed with ANCOVA with terms for baseline and baseline PR-SMFIS score. Missing data was handled with multiple imputation. The results for the total score (average) are presented in Table 12. The results were significant when adjusted for multiplicity using Holm’s method ( $p < 0.025$ ).

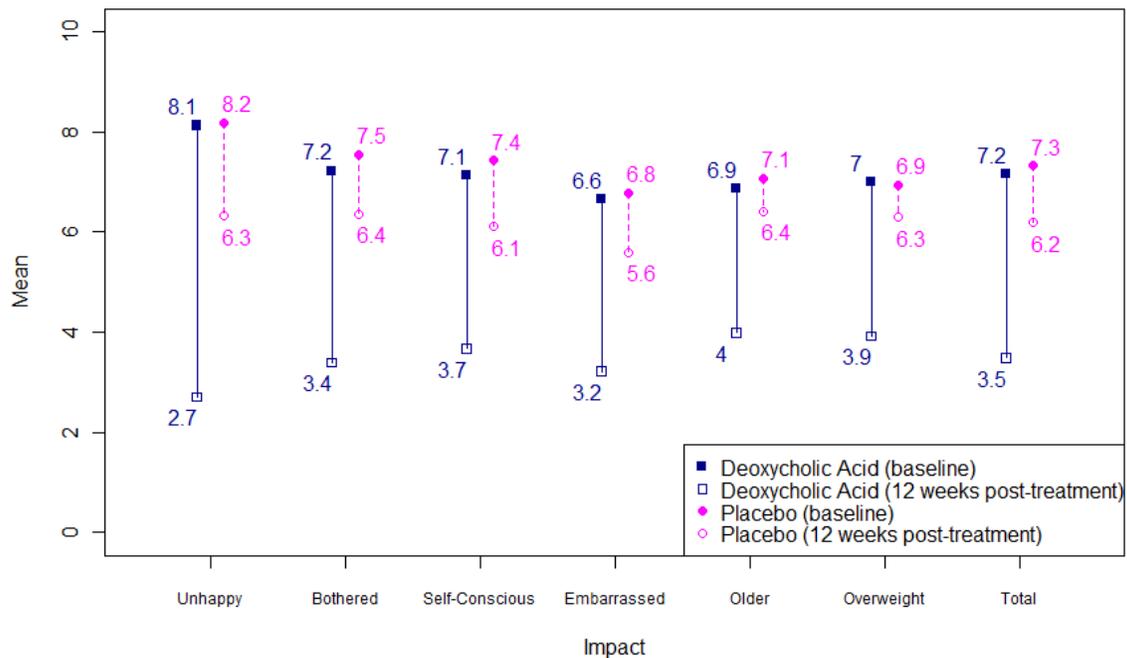
**Table 12 – Change from Baseline in Total PR-SMFIS in Studies 22 and 23 (Multiple Imputation)**

Total PR-SMFIS	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
Baseline [mean (SD)]	7.17 (1.69)	7.33 (1.62)	7.37 (1.72)	7.24 (1.68)
12 week post-treatment [mean (SD)]	3.61 (2.36)	6.17 (2.10)	3.90 (2.64)	5.82 (2.30)
Change from baseline [LSmeans (SE)]	-3.61 (0.143)	-1.10 (0.143)	-3.44 (0.158)	-1.46 (0.156)
p-value	<0.001		<0.001	

Source: pg 518-519 of atx-101-11-22-body.pdf, pg 518-519 of atx-101-11-23-body.pdf

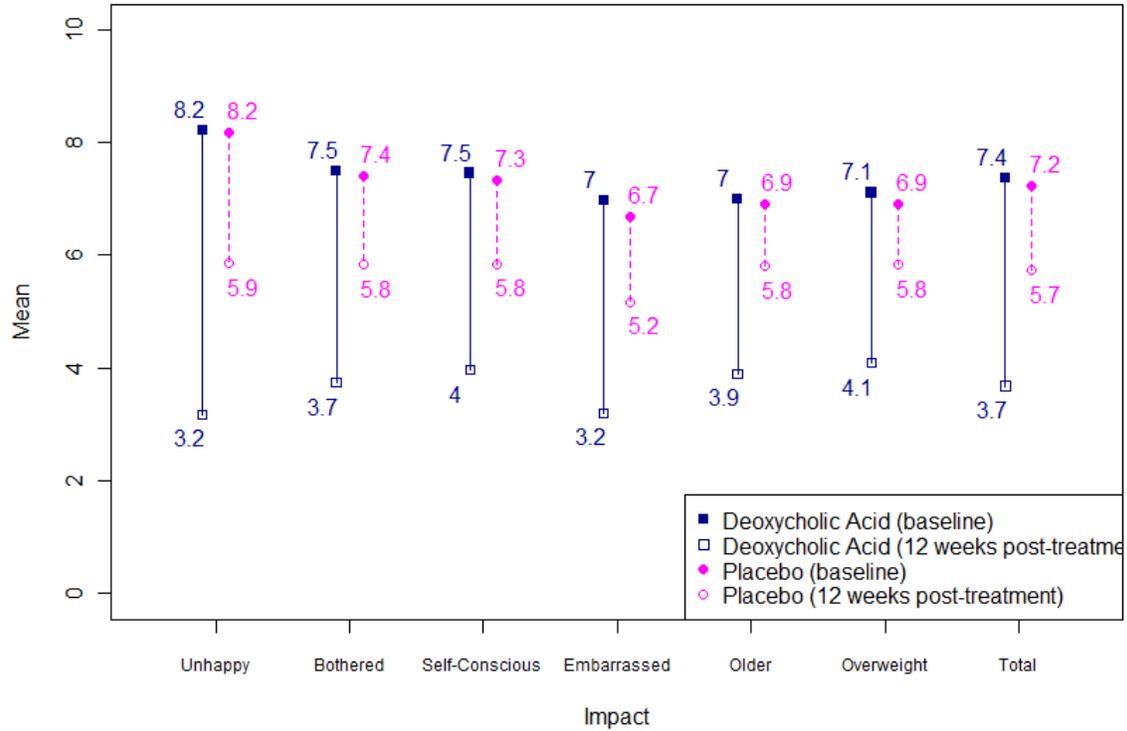
The mean baseline and 12 weeks post-treatment scores for the individual impacts are presented in Figure 1 and Figure 2 (observed data). The treatment effects (change from baseline for deoxycholic acid minus placebo) for all of the individual impacts had magnitudes in the range of about 2 to 3.5 units. The ‘unhappiness’ impact had the largest mean change from baseline to post-treatment of all of the impacts. Note that the ‘unhappiness’ impact was actually assessed as a ‘happiness’ impact where 0 = ‘not happy at all’ and 10 = ‘extremely happy’, while the other impacts measured negative outcomes. The difference in the way this element was assessed may impact the results.

**Figure 1 – Baseline and 12 Weeks Post-Treatment Means on the PR-SMFIS Individual Impacts in Study 22 (Observed Cases)**



Note: ‘Unhappy’ impact is transformed as 10 - ‘happy’ impact score prior to analysis.  
Source: Reviewer analysis.

**Figure 2 – Baseline and 12 Weeks Post-Treatment Means on the PR-SMFIS Individual Impacts in Study 23 (Observed Cases)**

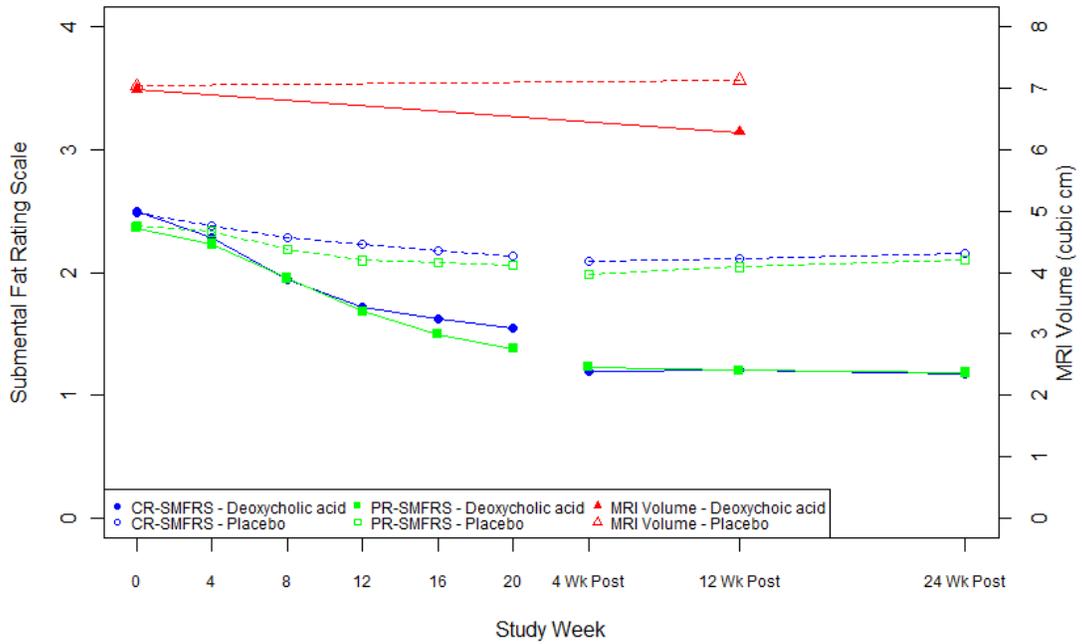


Note: ‘Unhappy’ impact is transformed as 10 - ‘happy’ impact score prior to analysis.  
Source: Reviewer analysis.

### 3.2.6 Efficacy over Time

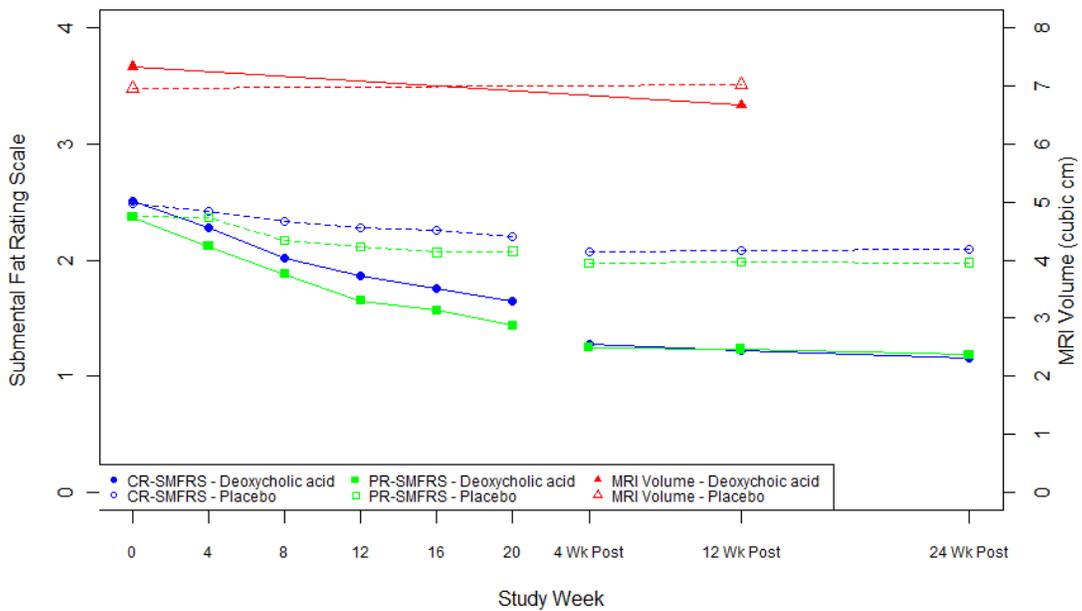
The mean PR-SMFRS and CR-SMFRS scores improved over the treatment period with greater improvement on the deoxycholic acid arm than the placebo arm. The improvements on the patient and clinician scales were similar. During the post-treatment period, the mean scores remained relatively constant through 24 weeks post-treatment. The mean MRI volume decreased on the deoxycholic acid arm from baseline to 12 weeks post-treatment and was relatively constant on the placebo arm. See Figure 3 and Figure 4.

**Figure 3 – Mean CR-SMFRS, PR-SMFRS, and MRI Volume over Time (Study 22, observed cases)**



Source: Reviewer analysis.

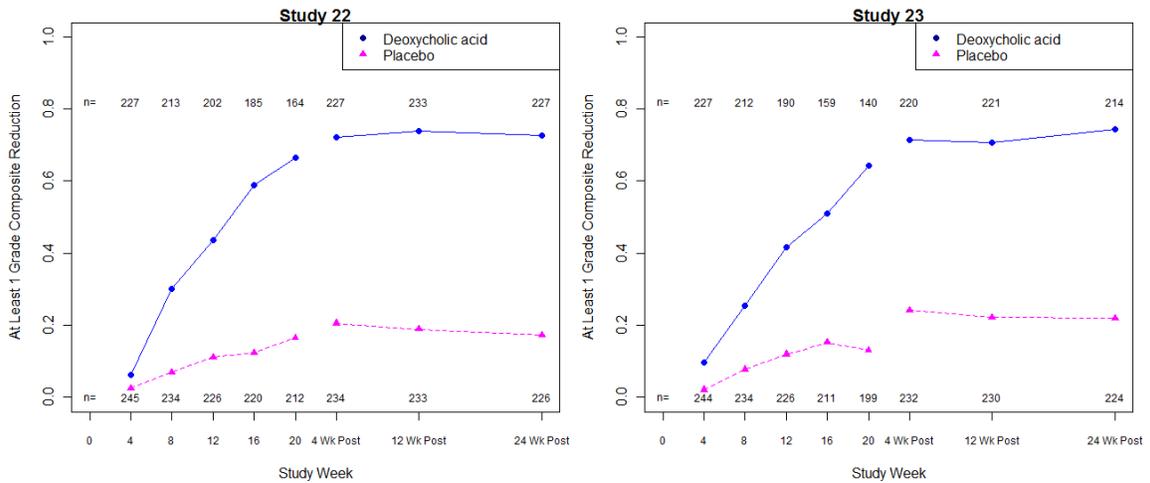
**Figure 4 - Mean CR-SMFRS, PR-SMFRS, and MRI Volume over Time (Study 23, observed cases)**



Source: Reviewer analysis.

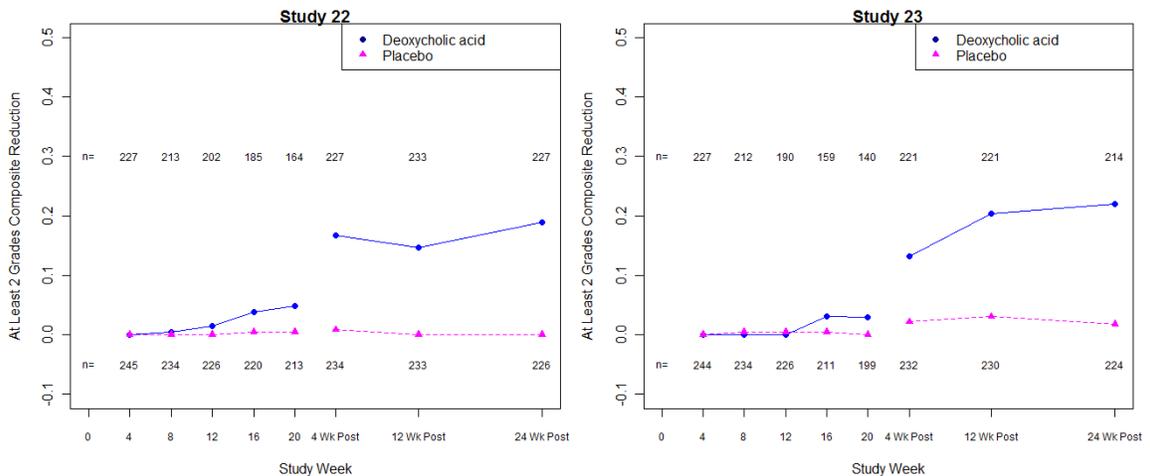
Response rates (both 1-grade and 2-grade composite reduction) increased over time during the treatment period. Response rates remained relatively constant through the post-treatment follow-up period. Note that subjects could discontinue treatment early due to insufficient SMF, subject's satisfaction with SMF reduction, withdrawal of consent for further treatments due to subject convenience, adverse events, or administrative decision. These subjects would then enter post-treatment follow-up at the next visit. See Figure 5 and Figure 6.

**Figure 5 – At Least 1 Grade Composite Reduction over Time (Studies 22 and 23; observed cases)**



Source: Reviewer analysis.

**Figure 6 - At Least 2 Grades Composite Reduction over Time (Studies 22 and 23; observed cases)**



Source: Reviewer analysis.

### 3.2.7 Concordance between Clinician and Patient Assessments

Clinicians and patients evaluated the amount of submental fat using similar scales (PR-SMFRS and CR-SMFRS), although the wording differed slightly. Crosstabulation tables of the change in CR-SMFRS and PR-SMFRS at 12 weeks post-treatment are presented in Table 13 (pooled studies). Most of the time the amount of change assessed by the investigator and the subject were within 1 unit of each other, and there was no obvious trend of one type of rater consistently assessing greater change than the other.

**Table 13 – Crosstabulation of the Change in CR-SMFRS and PR-SMFRS at 12 Weeks Post-treatment in Pooled Studies (Observed Cases)**

#### *Deoxycholic acid*

Change in CR-SMFRS	Change in PR-SMFRS						Total
	-3	-2	-1	0	1	2	
-3	6	11	11	1	0	0	29
-2	5	57	83	16	0	0	161
-1	6	49	100	18	6	3	182
0	1	10	37	25	5	0	78
1	0	0	1	2	1	0	4
2	0	0	0	0	0	0	0
Total	18	127	232	62	12	3	454

#### *Placebo*

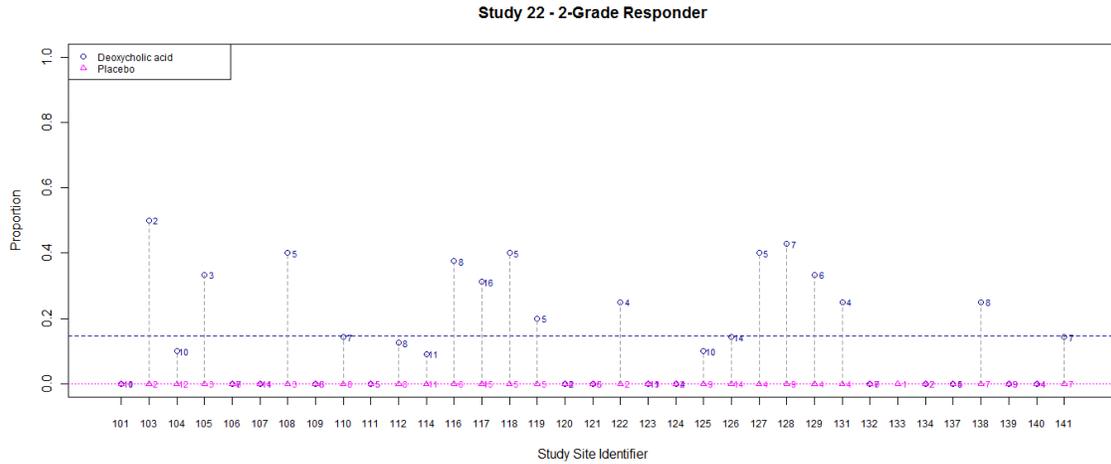
Change in CR-SMFRS	Change in PR-SMFRS						Total
	-3	-2	-1	0	1	2	
-3	0	0	0	0	0	0	0
-2	1	6	19	8	0	0	34
-1	1	13	55	53	8	0	130
0	0	11	66	172	27	2	278
1	0	0	5	14	2	0	21
2	0	0	0	0	0	0	0
Total	2	30	145	247	37	2	463

Source: reviewer analysis

### 3.2.8 Efficacy by Center

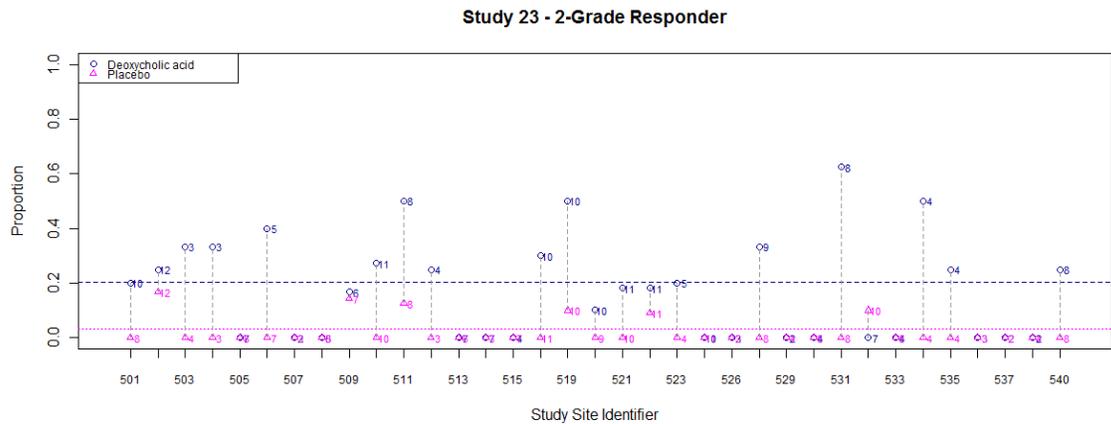
Study 22 was conducted at 35 centers in the United States (31) and Canada (4). Study 23 was conducted at 35 centers in the United States (30) and Canada (5). Because of the large number of centers and low overall response rate for the 2-grade reduction composite endpoint, no center is overly influential on the overall results. Some centers had no 2-grade responders on either arm; however, among the centers with at least one 2-grade responder, the response rate on deoxycholic acid was higher than on placebo at each center.

**Figure 7 - At Least 2 Grades Composite Reduction by Center (Study 22; observed cases)**



Source: reviewer analysis. Numbers represent the number of subjects per arm per center.

**Figure 8 - At Least 2 Grades Composite Reduction by Center (Study 23; observed cases)**



Source: reviewer analysis. Numbers represent the number of subjects per arm per center.

### 3.3 Evaluation of Safety

#### 3.3.1 Extent of Exposure

Subjects could receive up to 6 injections during the study. The majority of deoxycholic subjects (64% in Study 22 and 54% in Study 23) and placebo subjects (85% in Study 22 and 77% in Study 23) received all 6 injections. Approximately 10% of deoxycholic acid subjects and 2% of placebo subjects discontinued treatment due to adverse events or discomfort with the procedure. In addition, approximately 19% of deoxycholic acid subjects and 4% of placebo subjects had fewer than 6 treatments due to insufficient SMF or subject satisfaction with SMF reduction. See Table 6 (pg. 11), Table 14, and Table 15.

**Table 14 - Number of Treatments Received by Treatment Discontinuation Reason (Study 22)**

Number of treatments	Deoxycholic Acid N=256				Placebo N=250			
	Response <sup>a</sup>	Adverse Experience <sup>b</sup>	Other <sup>c</sup>	Completed Treatment	Response <sup>a</sup>	Adverse Experience <sup>b</sup>	Other <sup>c</sup>	Completed Treatment
6	--	--	--	164	--	--	--	213
5	20	0	1	--	3	1	3	--
4	10	3	4	--	1	1	4	--
3	5	2	4	--	1	0	7	--
2	6	3	5	--	1	1	9	--
1	1	15	13	--	1	0	3	--
0	--	--	0	--	--	--	1	--
<b>Total</b>	42 (16%)	23 (9%)	27 (11%)	164 (64%)	7 (3%)	3 (1%)	27 (11%)	213 (85%)

<sup>a</sup> Insufficient SMF into which injections may safely be given or Subject satisfaction with SMF reduction

<sup>b</sup> Adverse event or Withdrawal of consent for further treatments due to discomfort with procedure

<sup>c</sup> Administrative decision, Lost to follow-up, Withdrawal of consent for further treatments due to subject convenience, Other

Source: Reviewer analysis

**Table 15 - Number of Treatments Received by Treatment Discontinuation Reason (Study 23)**

Number of treatments	Deoxycholic Acid N=258				Placebo N=258			
	Response <sup>a</sup>	Adverse Experience <sup>b</sup>	Other <sup>c</sup>	Completed Treatment	Response <sup>a</sup>	Adverse Experience <sup>b</sup>	Other <sup>c</sup>	Completed Treatment
6	--	--	1	139	--	--	--	199
5	12	3	4	--	5	2	5	--
4	25	1	5	--	3	2	10	--
3	11	2	9	--	3	1	4	--
2	5	6	4	--	2	0	8	--
1	3	16	11	--	0	0	13	--
0	--	--	1	--	--	--	1	--
<b>Total</b>	56 (22%)	28 (11%)	35 (14%)	139 (54%)	13 (5%)	5 (2%)	41 (16%)	199 (77%)

<sup>a</sup> Insufficient SMF into which injections may safely be given or Subject satisfaction with SMF reduction

<sup>b</sup> Adverse event or Withdrawal of consent for further treatments due to discomfort with procedure

<sup>c</sup> Administrative decision, Lost to follow-up, Withdrawal of consent for further treatments due to subject convenience, Other

Source: Reviewer analysis

The average number of injections received per treatment session was 27 for deoxycholic acid and 30 for placebo. The average number of injections received at the first treatment session (32) was higher than the average received at the 6<sup>th</sup> treatment session (among subjects who received 6 treatments) (22 injections for deoxycholic acid subjects and 28 injections for placebo subjects). See Table 16.

**Table 16 – Average Number of Injections per Treatment Session**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
All sessions	28.3	30.5	26.1	29.4
Treatment 1	32.9 (N=256)	33.2 (N=249)	30.8 (N=258)	32.3 (N=256)
Treatment 6	23.7 (N=164)	27.7 (N=213)	21.4 (N=140)	27.9 (N=199)

Source: pg 132 of atx-101-22-body.pdf and 131 of atx-101-23-body.pdf.

One subject in each study who was randomized to placebo received deoxycholic acid injections at one visit. Subject 124-009 in Study 22 received deoxycholic acid at Week 8 (third treatment visit), and Subject 533-006 in Study 23 received deoxycholic acid at baseline (first treatment visit). The applicant included these two subjects in safety tables and analyses as having received deoxycholic acid. All safety tables in this review include these subjects under the randomized treatment arm (placebo), and thus differ slightly from the applicant's tables.

### 3.3.2 Adverse Events

Most subjects (>87%) experienced at least one adverse event. Approximately 7% of deoxycholic acid subjects and 1% of placebo subjects discontinued due to adverse events. See Table 17.

**Table 17 – Adverse Events in Studies 22 and 23 (Safety Population)**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=250	Deoxycholic acid N=258	Placebo N=258
Any Adverse Event	249 (97%)	216 (87%)	252 (98%)	236 (92%)
Discontinued treatment due to AEs	17 (7%)	3 (1%)	18 (7%)	4 (2%)
Discontinued study due to AEs	6 (2%)	1 (<1%)	10 (4%)	3 (1%)

Source: Reviewer analysis

The most common adverse reactions were injection site reactions. More than half of deoxycholic acid subjects experienced injection site hematomas, pain, edema, and anesthesia. More than 10% of deoxycholic acid subjects experienced injection site swelling, erythema, induration, paresthesia, pruritus, and nodule. See Table 18.

**Table 18 –Injection Site Reactions (Study 22 and 23, Safety Population)**

	Study 22		Study 23	
	Deoxycholic acid N=256	Placebo N=249	Deoxycholic acid N=257	Placebo N=257
Injection site hematoma	180 (70%)	167 (67%)	188 (73%)	186 (73%)
Injection site pain	167 (65%)	59 (23%)	189 (74%)	101 (39%)
Injection site edema	136 (53%)	54 (22%)	175 (68%)	93 (36%)
Injection site anesthesia	172 (67%)	11 (4%)	169 (66%)	18 (7%)
Injection site swelling	95 (37%)	40 (16%)	75 (29%)	40 (16%)
Injection site erythema	46 (18%)	25 (10%)	90 (35%)	66 (25%)
Injection site induration	47 (18%)	4 (2%)	73 (28%)	9 (4%)
Injection site paresthesia	33 (13%)	8 (3%)	37 (14%)	12 (5%)
Injection site pruritus	22 (9%)	9 (4%)	42 (16%)	21 (8%)
Injection site nodule	31 (12%)	3 (1%)	37 (14%)	11 (4%)
Injection site warmth	7 (3%)	2 (1%)	15 (6%)	6 (2%)

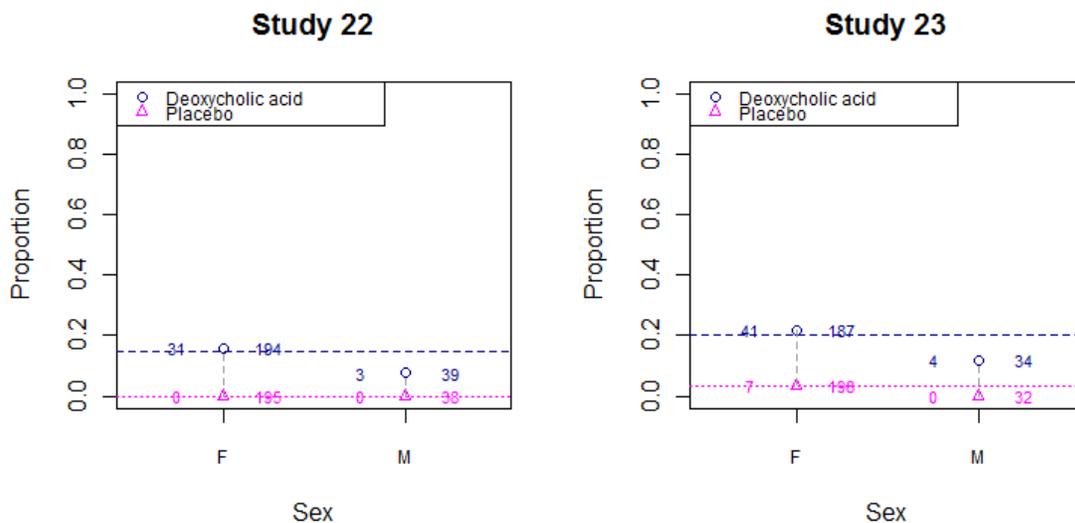
Source: Reviewer analysis.

## 4 Findings in Special/Subgroup Populations

### 4.1 Gender, Race, Age, and Geographic Region

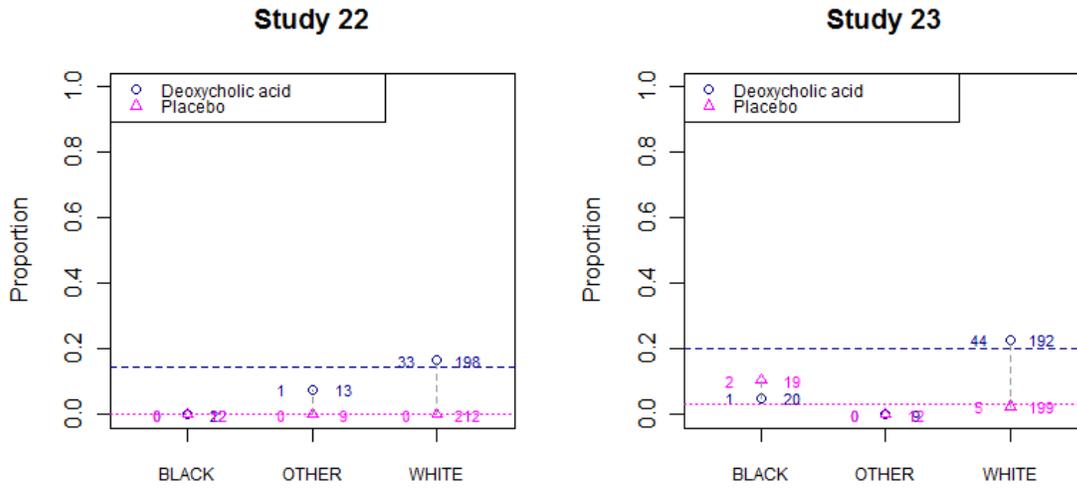
Treatment effects were generally consistent across gender, race, age, and country subgroups in Studies 22 and 23. The majority of subjects were female and white. See Figure 9 through Figure 12.

**Figure 9 - At Least 2 Grades Composite Reduction by Gender in Studies 22 and 23 (observed cases)**



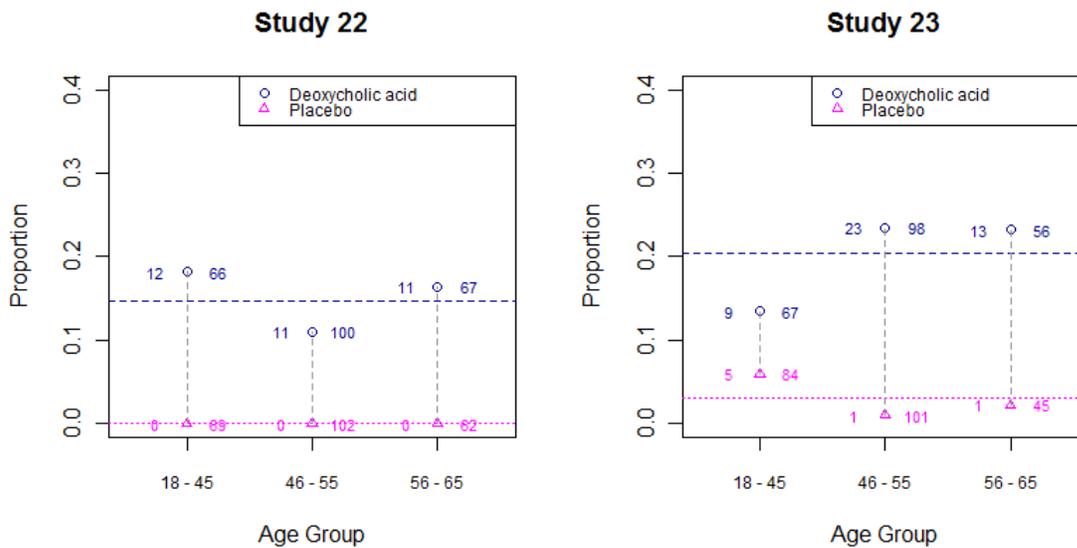
Source: Reviewer analysis. Numbers represent the number of responders and the number of subjects in the subgroup.

**Figure 10 - At Least 2 Grades Composite Reduction by Race in Studies 22 and 23 (observed cases)**



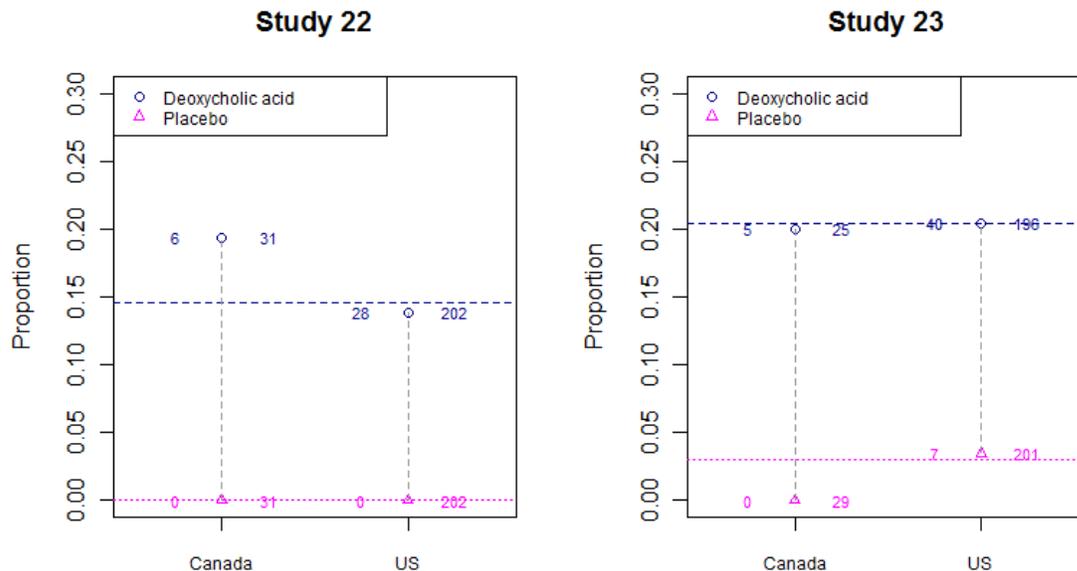
Source: Reviewer analysis. Numbers represent the number of responders and the number of subjects in the subgroup.

**Figure 11- At Least 2 Grades Composite Reduction by Age Group in Studies 22 and 23 (observed cases)**



Source: Reviewer analysis. Numbers represent the number of responders and the number of subjects in the subgroup.

**Figure 12- At Least 2 Grades Composite Reduction by Country in Studies 22 and 23 (observed cases)**



Source: Reviewer analysis. Numbers represent the number of responders and the number of subjects in the subgroup.

#### 4.2 Other Special/Subgroup Populations

None.

### 5 Summary and Conclusions

#### 5.1 Statistical Issues and Collective Evidence

The applicant has evaluated the efficacy and safety of deoxycholic acid injection for the treatment of submental fat in two placebo-controlled studies. Both studies were statistically significant for the co-primary endpoints and secondary endpoints. The treatment effects were generally consistent across subgroups and centers, and the conclusions were consistent across various assumptions regarding missing data.

Protocol 22 was submitted as a special protocol assessment. The Agency and sponsor reached agreement on the study design and one of the primary endpoints (at least 2 grades reduction on both the CR-SMFRS and PR-SMFRS). The Agency did not provide agreement on the '1-grade reduction' endpoint.

The data presentations recommended by this reviewer differ from those in the original study reports in three ways:

- The applicant's definition of LOCF (which was a secondary method of missing data imputation) only imputed responses for subjects who had at least one assessment at either the 5<sup>th</sup> treatment session or the 4-week post-treatment visit. Subjects who did not attend at least one of these visits were ignored and not accounted for in the analysis. This reviewer's LOCF analyses include all randomized ITT subjects.
- The original study report was based on a database that had some missing (unread) MRI scans (scans were conducted but the results were not included in the database). This review includes the data from the missed scans. The applicant submitted the results from the missing scans in a supplemental database and report. The majority of the unread scans were for subjects who had only baseline scans but did not have post-treatment scans. However, two of the unread scans were post-treatment scans.
- Two subjects who were randomized to placebo incorrectly received an injection of the active treatment. The applicant classified these subjects in safety tables as having received deoxycholic acid. This review includes these subjects under their randomized treatment arm (deoxycholic acid).

## **5.2 Conclusions and Recommendations**

Deoxycholic acid 1% for injection was superior to placebo in the treatment of submental fat in two studies. Studies 22 and 23 enrolled subjects aged 18 to 65 with scores of 2-3 on the clinician and patient submental fat rating scales (moderate to severe submental convexity on the clinician-reported submental fat rating scale (CR-SMFRS) and moderate to large amount of chin fat on the patient-reported submental fat rating scale (PR-SMRFS).) Subjects were treated at up to 6 treatment sessions at 28-day intervals. Each treatment session involved up to 50 injections (0.2 mL each) spaced on a 1-cm grid. Subjects could stop treatment if they lacked sufficient tissue for injection or were satisfied with the reduction in SMF. The protocols defined two co-primary responder endpoints based on improvement on both the CR-SMFRS and the PR-SMFRS. The first co-primary endpoint was defined as at least a 1-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The second co-primary endpoint was defined as at least a 2-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The 2-grade improvement responder rate was 13.4% vs. <0.1% in Study 22 and 18.6% vs. 3.0% in Study 23. The 1-grade improvement responder rate was 70.0% vs. 18.6% in Study 22 and 66.5% vs. 22.2% in Study 23. The secondary endpoints were supportive of the primary endpoints. The primary and secondary efficacy endpoints were all statistically significant ( $p < 0.001$ ).

## Appendix

### Efficacy Assessment Scales:

#### Submental Skin Laxity Grade (SMSLG)

Grade	Laxity Description
<b>1 None</b>	<ul style="list-style-type: none"> <li>No or minimal superficial wrinkling</li> <li>Skin well apposed to deeper neck structures</li> <li>No skin redundancy               <ul style="list-style-type: none"> <li>No skin draping (vertical folds)</li> <li>No skin sagging (horizontal folds)</li> </ul> </li> </ul>
<b>2 Mild</b>	<ul style="list-style-type: none"> <li>Mild superficial wrinkling</li> <li>Skin well apposed to deeper neck structures</li> <li>Minimal skin redundancy               <ul style="list-style-type: none"> <li>Slight skin draping (vertical folds)</li> <li>Slight skin sagging (horizontal folds)</li> </ul> </li> </ul>
<b>3 Moderate</b>	<ul style="list-style-type: none"> <li>May have mild to moderate superficial wrinkling</li> <li>Skin has mild to moderate separation from deeper neck structures</li> <li>Moderate skin redundancy               <ul style="list-style-type: none"> <li>Moderate skin draping (vertical folds)</li> <li>Moderate skin sagging (horizontal folds)</li> </ul> </li> </ul>
<b>4 Severe</b>	<ul style="list-style-type: none"> <li>Mild to marked superficial wrinkling</li> <li>Loose skin separated from deeper neck structures</li> <li>Marked skin redundancy               <ul style="list-style-type: none"> <li>Marked skin draping (vertical folds)</li> <li>Marked skin sagging (horizontal folds)</li> </ul> </li> </ul>

#### Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

Please look in the mirror at **the area under your chin** to help you answer the following questions:

1.

<b>How happy are you with the appearance of your chin fat?</b>	
Mark <input checked="" type="checkbox"/> in one box below and do not mark between the boxes	
Not happy at all	Extremely happy
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10	

2.

**How bothered are you by the appearance of your chin fat?**

Mark  in one box below and do not mark between the boxes

Not bothered at all Extremely bothered

0  1  2  3  4  5  6  7  8  9  10

3.

**How self-conscious are you about the appearance of your chin fat?**

Mark  in one box below and do not mark between the boxes

Not self-conscious at all Extremely self-conscious

0  1  2  3  4  5  6  7  8  9  10

4.

**How embarrassed are you about the appearance of your chin fat?**

Mark  in one box below and do not mark between the boxes

Not embarrassed at all Extremely embarrassed

0  1  2  3  4  5  6  7  8  9  10

5.

**How much older do you look because of your chin fat?**

Mark  in one box below and do not mark between the boxes

Not older at all Very much older

0  1  2  3  4  5  6  7  8  9  10

6.

<b>How much overweight do you look because of your chin fat?</b>
Mark <input type="checkbox"/> in one box below and do not mark between the boxes
Not overweight at all <span style="float: right;">Extremely overweight</span>
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10

## Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.

Date: 12/19/2014

Statistical Team Leader: Mohamed Alosch, Ph.D.

cc:

DDDP/Marcus

DDDP/Kettl

DDDP/Lolic

DDDP/White

OBIO/Patrician

DBIII/Wilson

DBIII/Alosch

DBIII/Fritsch

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/s/  
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KATHLEEN S FRITSCH  
12/19/2014

MOHAMED A ALOSH  
12/19/2014

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA/BLA Number:** 206333    **Applicant:** Kythera

**Stamp Date:** 5/13/2014

**Drug Name:** Kybella  
(deoxycholic acid)

**NDA/BLA Type:** 505(b)(1)

**Indication:** Submental fat

I. On **initial** overview of the NDA/BLA application identify and list any potential Refuse to File issues:

	<b>Content Parameter for RTF</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	<b>X</b>			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<b>X</b>			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	<b>X</b>			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	<b>X</b>			

### IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?

Yes

II. Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	<b>X</b>			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<b>X</b>			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			<b>X</b>	
Appropriate references for novel statistical methodology (if present) are included.			<b>X</b>	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	<b>X</b>			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		<b>X</b>		Need SAS programs

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

## 74-DAY LETTER/INFORMATION REQUESTS TO THE APPLICANT

1. Submit the SAS programs for creating the multiple imputation datasets and for analyzing the results for all of the primary and secondary endpoints for Studies 22 and 23. Include any necessary supporting information such as the randomization seed.
2. The file 'MRI Core Laboratory Documentation' (atx-101-11-22-e3-16-1-13.pdf) for Study 22 includes tables and listings for Study 23 instead. Submit a corrected file with tables and listings for Study 22.
3. Submit datasets comparable to ADMRI.xpt, ADMRIMI.xpt, and XM.xpt that include the MRI assessments that were originally not read by the vendor and not included in the locked database. The datasets should include all of the observations from the locked database and the observations from the subjects originally excluded from the database (30 subjects with missing baseline MRI measurements and 1 subject with missing Visit 9 measurements in Study 22 and 29 subjects with missing baseline MRE measurements and 1 subject with missing Visit 9 measurements in Study 23.)

## SUBMISSION SUMMARY

This submission contains seven studies evaluating deoxycholic acid (10 µg/mL) in the treatment of submental fat (SMF).

- Two pivotal Phase 3, placebo-controlled trials conducted in the U.S. and Canada (22, 23)
- Two supportive Phase 3 trials conducted in Europe (16, 17)
- Three Phase 2 dose-ranging studies (3, 7, 15)

The pivotal Phase 3 studies (22, 23) evaluated a dosing regimen of up to 6 treatment sessions at 28-day intervals. Each treatment session involves up to 50 injections (0.2 mL each) spaced on a 1-cm grid. Subjects could stop treatment if they lacked sufficient tissue for injection or were satisfied with the reduction in SMF. Studies 22 and 23 enrolled subjects age 18 to 65 with scores of 2-3 on the clinician and subject scales (moderate to severe submental convexity on the clinician scale (CR-SMFRS) and moderate to large amount of chin fat on the subject scale (PR-SMFRS).) Subjects were also to express dissatisfaction with the submental area (extremely dissatisfied, dissatisfied, or slightly dissatisfied on a 7 point scale).

The pivotal studies had co-primary endpoints of (1) at least 1-grade improvement on both the CR-SMFRS and PR-SMFRS, and (2) at least 2-grade improvement on the both the CR-SMFRS and PR-SMFRS. Both primary endpoints needed to be statistically significant for the study to be successful. The secondary endpoints were 'MRI responder' (>10% reduction in volume) and Change from baseline in the sum score for the patient-reported SMF impact scale (PR-SMFIS). MRIs were conducted on a subset of subjects. The primary efficacy timepoint was Week 32 or 12 weeks post-treatment. The secondary endpoints were analyzed in sequential order. Missing data for the primary and secondary endpoints was handled with multiple imputation.

Following database lock, the applicant discovered that the imaging vendor did not provide the baseline MRI measurements for any subject who did not have a Visit 9 MRI conducted (30 subjects in Study 22 and 29 subjects in Study 23). The vendor also did not provide Visit 9 MRI measurements for one subject in each study who had actually had an MRI conducted at Visit 9. The ignored MRIs were eventually read, but the outcomes were not included in the submitted database. The applicant provided pdf listings of the excluded MRI outcomes for Study 23, but appended the outcomes for Study 23 to the reports for both Study 22 and 23 (so the outcomes for Study 22 were not submitted.) The applicant did not submit corresponding datasets for the excluded outcomes.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

### Efficacy Results in Studies 22 and 23

	Study 22		Study 23	
	Deoxycholic Acid N=256	Placebo N=250	Deoxycholic Acid N=258	Placebo N=258
2-grades improvement CR-SMFRS / PR-SMFRS	13.4%	<0.1%	18.6%	3.0%
1-grade improvement CR-SMFRS / PR-SMFRS	70.0%	18.6%	66.5%	22.2%
>10% reduction in MRI volume	(N=113) 46.3%	(N=111) 5.3%	(N=113) 40.2%	(N=112) 5.2%
Change from baseline in the sum score PR-SMFIS [mean (sd)]	-3.56 (2.79)	-1.16 (2.06)	-3.48 (2.69)	-1.42 (2.45)

Note: all p-values <0.001

**ASSOCIATED IND:** 79726

**WERE PROTOCOLS REVIEWED UNDER A SPA?** Yes.

Reviewing Statistician: Kathleen Fritsch, Ph.D.  
Mathematical Statistician, Biometrics III

Supervisor/Team Leader: Mohamed Alosh, Ph.D.  
Team Leader, Biometrics III

cc:

NDA 206333 / 000

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DBIII/Alosh

DBIII/Fritsch

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KATHLEEN S FRITSCH  
06/27/2014

MOHAMED A ALOSH  
06/27/2014