FDA Briefing Document

Dermatologic and Ophthalmic Drugs Advisory Committee
Meeting

March 9, 2015
Morning Session

BACKGROUND PACKAGE FOR NDA 206333
DEOXYCHOLIC ACID INJECTION

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS
DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought deoxycholic acid injection (DCA), also referred to as ATX-101, to this Advisory Committee in order to gain the Committee’s insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation, but instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
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Division Director Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental Products

MEMORANDUM

Date: January 29, 2015

From: Kendall A. Marcus, MD
Director, Division of Dermatology and Dental Products
Office of Drug Evaluation III, CDER, FDA

To: Chair, Members and Invited Guests
Dermatologic and Ophthalmic Drugs Advisory Committee
(DODAC)

Subject: Overview of the March 9, 2015 DODAC meeting

Deoxycholic acid for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults

The drug is injectable 1% deoxycholic acid (DCA) for subcutaneous use. DCA is a new molecular entity that is structurally identical to endogenous deoxycholic acid, a secondary bile acid which assists in lipid absorption in the gut. The physiologic effect of the drug involves cytolytic effects on cells in the submental fat tissue at the site of injection.

The Applicant is seeking approval for DCA for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

The proposed dosing regimen is up to 6 treatment sessions at 28-day intervals. Each treatment session involves up to 50 injections of 1% DCA solution (0.2 mL each) into submental fat, spaced on a 1-cm grid (area adjusted dose of 2 mg/cm²). The product is proposed to be marketed in a 2 mL single patient use vial.

If approved, DCA will be the first drug treatment for submental fat reduction, and provide an alternative to surgical treatments for this aesthetic condition.
I. INTRODUCTION

This document provides the Dermatologic and Ophthalmic Drugs Advisory Committee with a summary of FDA analyses of the data submitted by Kythera Biopharmaceuticals to support an indication for DCA for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. During the scheduled March 9, 2015 Advisory Committee meeting, the Committee will be asked to consider the safety and efficacy data submitted in support of the DCA application.

The background materials provided represent the preliminary findings and opinions of the multidisciplinary review team and are based on their reviews of the Applicant’s submissions. Please note that the FDA analyses presented herein may differ somewhat from those presented by the Applicant. This document represents the review team’s preliminary findings to date. No regulatory decision has been made on the status of the application.

The proposed indication, the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults, is supported by 44-week safety and efficacy data from two Phase 3 trials ATX-101-11-22 and ATX-101-11-23 (hereafter referred to as 22 and 23, respectively in our document). Two additional Phase 3 trials (for European registration), three Phase 2 trials and seven Phase 1 trials have been conducted using various formulations and/or dosing regimens. One open label trial with 12 months of safety follow up was also submitted and reviewed. A 120-day safety update trial report was also provided in support of the application.

The two pivotal Phase 3 trials are summarized in the table below:

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Trial 22 (N=506)</th>
<th>Trial 23 (N=516)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms and sample size</td>
<td>1% DCA: 256 Placebo: 250</td>
<td>1% DCA: 258 Placebo: 258</td>
</tr>
<tr>
<td>Injection Pattern</td>
<td>Up to 50 injections (0.2 mL each) spaced on a 1 cm grid</td>
<td>Up to 50 injections (0.2 mL each) spaced on a 1 cm grid</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Every 4 weeks, up to a maximum of 6 treatment sessions</td>
<td>Every 4 weeks, up to a maximum of 6 treatment sessions</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Adults age 18 to 65 with scores of 2 or 3 on both the CR-SMFRS(^1) and PR-SMFRS(^2) and a history of stable body weight.</td>
<td>Adults age 18 to 65 with scores of 2 or 3 on both the CR-SMFRS(^1) and PR-SMFRS(^2) and a history of stable body weight.</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>- At least 2 grade reduction on both the CR-SMFRS and PR-SMFRS - At least 1 grade reduction on both the CR-SMFRS and PR-SMFRS</td>
<td>- At least 2 grade reduction on both the CR-SMFRS and PR-SMFRS - At least 1 grade reduction on both the CR-SMFRS and PR-SMFRS</td>
</tr>
<tr>
<td>Study location</td>
<td>US, Canada</td>
<td>US, Canada</td>
</tr>
</tbody>
</table>

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale (Range: 0 to 4)
PR-SMFRS = Patient-Reported Submental Fat Rating Scale (Range: 0 to 4)

The Phase 2 trials and European Phase 3 trials evaluated concentration levels of 0.5% 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 two supportive Phase 3 trials conducted for European registration, using a different formulation, are summarized in the table below:

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Trial 16 (N=363)</th>
<th>Trial 17 (N=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms and sample size</td>
<td>0.5% DCA: 120 1% DCA: 121 Placebo: 122</td>
<td>0.5% DCA: 121 1% DCA: 122 Placebo: 117</td>
</tr>
<tr>
<td>Injection Pattern</td>
<td>Up to 50 injections (0.2 mL each) spaced on a 1 cm grid</td>
<td>Up to 50 injections (0.2 mL each) spaced on a 1 cm grid</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Every 4 weeks, up to a maximum of 4 treatment sessions</td>
<td>Every 4 weeks, up to a maximum of 4 treatment sessions</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>– At least 1 grade reduction on the CR-SMFRS – Score of 4 or higher on the SSRS</td>
<td>– At least 1 grade reduction on the CR-SMFRS – Score of 4 or higher on the SSRS</td>
</tr>
<tr>
<td>Study location</td>
<td>Belgium, France, Germany, Spain, UK</td>
<td>Belgium, France, Germany, Spain, Italy, UK</td>
</tr>
</tbody>
</table>

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale
SSRS = Subject Self Rating Scale

Three Phase 2 trials were performed to support dose selection for Phase 3 per the following summary table:

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Trial 3 (N=85)</th>
<th>Trial 7 (N=57)</th>
<th>Trial 15 (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms and sample size</td>
<td>0.5% DCA: 21 1% DCA: 20 2% DCA: 22 Placebo: 22</td>
<td>(±Inj./Vol./Grid/Conc.)</td>
<td>0.5% DCA: 41 1% DCA: 43 Placebo: 45</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.5% DCA, 1% DCA, 2% DCA, placebo</td>
<td>1% DCA, placebo</td>
<td>0.5% DCA, 1% DCA, placebo</td>
</tr>
<tr>
<td>Injection Pattern</td>
<td>Up to 24 injections (0.2 mL each) spaced on a 1 cm grid</td>
<td>– Up to 48 injections (0.2 mL each) spaced on a 0.7 cm grid</td>
<td>Up to 50 injections (0.2 mL each) spaced on a 1 cm grid</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Every 4 weeks, up to a maximum of 4 treatment sessions</td>
<td>Every 4 weeks, up to a maximum of 4 treatment sessions</td>
<td>Every 4 weeks, up to a maximum of 6 treatment sessions</td>
</tr>
<tr>
<td>Study location</td>
<td>England, Australia, Canada</td>
<td>England, Australia, Canada</td>
<td>United States</td>
</tr>
</tbody>
</table>

II.  EFFICACY ENDPOINTS

The improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults is a novel drug indication, without previously established endpoints. One of the significant challenges in this product’s development was the determination of clinically meaningful efficacy endpoints. Multiple discussions were conducted with the Applicant to refine clinician and patient rating scales and also to evaluate what changes in those scales would represent a clinically meaningful outcome that could be adequately described in product labeling.
For aesthetic conditions, the Agency typically recommends that assessments of the concept of interest for which the treatment is administered be conducted from the perspective of both the investigator as well as the patient. The patient’s perspective is particularly important in evaluating the success of aesthetic treatments, because the patient is the ultimate consumer of the medical product and is in the best position to provide assurance that the endpoint is clinically meaningful.

For aesthetic indications, study success criteria should define a “treatment responder” as any patient who has demonstrated a clinically meaningful improvement on both the clinician-rated scale and a patient-reported scale.

At the time of this product’s development, there were no known existing measures of submental fullness. Therefore, the Applicant, with advice from the Agency, developed parallel patient-reported and clinician-reported scales for use within their drug development program for use as a composite primary endpoint measure. The Applicant incorporated instructions for standardization of patient positioning (i.e., a positioning grid) to minimize variability of measurement and improve reliability and validity of the assessment (see Appendix A), for both the clinician and patient-reported scales. The resultant instruments were deemed fit for purpose in the targeted patient population and clinical trial context of use.

Briefly, the clinician-reported scale included 5 grades ranging from 0 (absent submental convexity) to 4 (extreme submental convexity). The clinician-reported scale included exemplar photographs as well as verbal descriptors (see Appendix B and CR-SMFRS table below).

The patient-reported scale was in parallel with the clinician-reported scale and also ranged from 0-4 (see Appendix C and PR-SMFRS table below). The patient-reported scale included line drawings as well as verbal descriptors (see Appendix D). Copies of these instruments are appended.

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

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

<table>
<thead>
<tr>
<th>How much fat do you have under your chin right now?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark ☐ in one box below</td>
</tr>
<tr>
<td>☐ No chin fat at all</td>
</tr>
<tr>
<td>☐ A slight amount of chin fat</td>
</tr>
<tr>
<td>☐ A moderate amount of chin fat</td>
</tr>
<tr>
<td>☐ A large amount of chin fat</td>
</tr>
<tr>
<td>☐ A very large amount of chin fat</td>
</tr>
</tbody>
</table>

Because the clinician and patient scales do not directly measure fat in the submental area, an objective measure (i.e., imaging) of submental fat reduction was recommended to verify the purported effects of the proposed drug treatment.

The applicant provided MRI measurement of submental fat volume in a subset of subjects (those enrolled at selected centers with access to MRI facilities). MRI of the chin/neck area was performed similarly to standard, non-contrast, high field clinical MRI examination. Instructions for imaging included standardized subject positioning, anatomical coverage, and image parameter settings. All images were subject to centralized independent and blinded review of image data. MRIs were performed on approximately 400 subjects from 44 selected centers. The proportion of subjects who had at least a 10% reduction in submental fat volume at the same time point as the primary endpoint was a key secondary endpoint.

The Applicant developed a 6-item patient-reported impact scale, the Patient-Reported Submental Fat Impact Scale (PR-SMFIS), as another secondary endpoint. The total score is the average of the 6 individual scores, each of which ranges from 0 to 10 (see below).

The PR-SMFIS items were as follows:

1. How happy are you with the appearance of your chin fat? (0 = not happy at all; 10 = extremely happy)
2. How bothered are you by the appearance of your chin fat? (0 = not bothered at all; 10 = extremely bothered)
3. How self-conscious are you about the appearance of your chin fat? (0 = not self-conscious at all; 10 = extremely self-conscious)
4. How embarrassed are you about the appearance of your chin fat? (0 = not embarrassed at all; 10 = extremely embarrassed)
5. How much older do you look because of your chin fat? (0 = not older at all; 10 = very much older)
6. How much overweight do you look because of your chin fat? (0 = not overweight at all; 10 = extremely overweight)
III. SUMMARY OF EFFICACY

The efficacy of DCA for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat was assessed in two placebo-controlled Phase 3 trials. Trials 22 and 23 enrolled subjects aged 18 to 65 years with scores of moderate to severe submental convexity on the clinician-reported submental fat rating scale (CR-SMFRS) and scores of 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 primary efficacy endpoints were based on the CR-SMFRS and PR-SMFRS scales. Each grade of the CR-SMFRS was accompanied by representative photographs, while each grade of the PR-SMFRS was accompanied by representative line drawings.

The protocols defined success based on improvement on both the CR-SMFRS and the PR-SMFRS. Success was defined as achieving at least a 2-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. Success defined as achieving at least a 1-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS was also assessed.

DCA was superior to placebo (p<0.001) for both primary endpoints. The efficacy results from Trials 22 and 23 are presented in Table 1.

The protocols also defined two secondary endpoints: MRI responder (at least 10% reduction in submental fat volume from baseline to 12 weeks post-treatment) and change from baseline to 12 weeks post-treatment in patient-reported submental fat impact scale (PR-SMFIS) total score. DCA was superior to placebo (p<0.001) for both secondary endpoints.
### Table 1 – Primary and Secondary Efficacy Endpoints in Trials 22 and 23 (ITT)

| Endpoint | Trial 22 | | | Trial 23 | | |
|----------|---------|--------|--------|---------|--------|
|          | DCA N=256 | Placebo N=250 | DCA N=258 | Placebo N=258 | |
| 2-grade improvement CR-SMFERS / PR-SMFERS<sup>a</sup> | 13.4% | <0.1% | 18.6% | 3.0% | |
| | p<0.001 | | p<0.001 | | |
| 1-grade improvement CR-SMFERS / PR-SMFERS<sup>a</sup> | 70.0% | 18.6% | 66.5% | 22.2% | |
| | p<0.001 | p<0.001 | | |

**Secondary Endpoints**

| Endpoint | Trial 22 | | | Trial 23 | | |
|----------|---------|--------|--------|---------|--------|
| ≥10% reduction in MRI volume<sup>b</sup> | (N=113) | 46.0% | (N=111) | 5.3% | |
| | p<0.001 | | p<0.001 | | |

| Endpoint | Trial 22 | | | Trial 23 | | |
|----------|---------|--------|--------|---------|--------|
| PR-SMFIS<sup>b</sup> | Baseline [mean (SD)] | 7.17 (1.69) | 7.33 (1.62) | 7.37 (1.72) | 7.24 (1.68) | |
| | Change from baseline [LSmeans (SE)] | -3.61 (0.143) | -1.10 (0.143) | -3.44 (0.158) | -1.46 (0.156) | |
| | | p<0.001 | p<0.001 | p<0.001 | |

<sup>a</sup> Primary endpoints. P-values based on Cochran-Mantel-Haenszel tests stratified on analysis centers.

<sup>b</sup> Secondary endpoints. Multiplicity among the secondary endpoints was handled with Holm’s method (smaller p-value <0.025 and larger p-value <0.05). P-values based on Cochran-Mantel-Haenszel tests stratified on analysis centers (MRI reduction) and ANCOVA with baseline PR-SMFIS score as a covariate.

SD= standard deviation; LSMeans = least squares means; SE = standard error

### IV. SUMMARY OF SAFETY

The clinical program used for safety assessment consists of 13 clinical trials in which a total of 1547 subjects received at least 1 dose of DCA and 877 subjects received placebo. This section will primarily focus on review of the safety data through Week 44 from Trials 22 and 23.

The Division’s primary safety analyses (N=1019) evaluated deaths, serious AEs (SAEs), adverse events (AEs), and laboratory abnormalities in the pivotal Phase 3 trials. Safety review of the total safety database provides supportive data.

In general, the Division agrees with the Applicant’s safety assessments. General aspects pertaining to the safety of DCA as compared to placebo are described below.

#### A. Deaths

Deaths occurred infrequently in the clinical trials and in all cases were assessed by investigators as unrelated to study drug. A total of 5 deaths have been reported in the DCA development program, two of which were from the pivotal Phase 3 trials: 1) heroin overdose (placebo), and 2) head trauma due to a motor vehicle accident (DCA). The reported causes of death from other trials included the following: 1) cholangiocarcinoma (DCA); 2) myocardial infarction (DCA); and 3) pancreatic cancer (placebo).
The Agency concurs that none of the deaths are likely to be related to the study drug. In the case of death from cholangiocarcinoma, it appears likely that the malignancy pre-existed any treatment with study drug.

B. Serious Adverse Events (SAE’s)

In the pivotal Phase 3 trials, there were 21 subjects (4%) in the DCA arm and 25 subjects (5%) in the placebo arm who reported SAEs, none of which was considered related to the treatment by either the Applicant or the Agency.

An overview of SAEs in the total safety database revealed 58 subjects with 75 SAEs: 29 subjects (2%) in the DCA group and 28 subjects (3%) in the placebo group reported at least 1 SAE (one subject did not have an assigned treatment arm). No SAE was reported in any MedDRA System Organ Class (SOC) with greater than 1% frequency. SAEs were considered unrelated to DCA with the exception of one case of mandibular nerve injury that occurred in a subject from a European Phase 3 trial. The outcome of the event was reported as “recovered.” The applicant has proposed product labeling and an instructions for use manual with anatomical diagrams to mitigate this risk.

C. Common Adverse Events

In the pivotal Phase 3 trials, at least one adverse event was reported by 97% of DCA treated subjects and 90% of placebo treated subjects. The imbalance in total AEs was mainly due to AEs of administration site reactions and will be discussed further below.

Adverse events that occurred in ≥2% of DCA treated subjects and at greater incidence than placebo are shown in Table 2 below:

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>DCA (N=513) n(%)</th>
<th>Placebo (N=506) n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site hematoma</td>
<td>368 (72%)</td>
<td>353 (70%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>356 (70%)</td>
<td>160 (32%)</td>
</tr>
<tr>
<td>Injection site anesthesia</td>
<td>341 (66%)</td>
<td>29 (6%)</td>
</tr>
<tr>
<td>Injection site edema</td>
<td>311 (61%)</td>
<td>147 (30%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>170 (33%)</td>
<td>80 (16%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>136 (27%)</td>
<td>91 (18%)</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>120 (23%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Injection site paresthesia</td>
<td>70 (14%)</td>
<td>20 (4%)</td>
</tr>
<tr>
<td>Injection site nodule</td>
<td>68 (13%)</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>64 (12%)</td>
<td>30 (6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (8%)</td>
<td>20 (4%)</td>
</tr>
<tr>
<td>Skin tightness</td>
<td>24 (5%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Injection site warmth</td>
<td>22 (4%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>
### Table 3: Most Frequent Adverse Reactions with ≥ 30 Days Duration

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>DCA (N=513)</th>
<th>Placebo (N=506)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site anesthesia</td>
<td>213 (42%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>80 (16%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>67 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site edema</td>
<td>54 (11%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>43 (8%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Injection site nodule</td>
<td>32 (6%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Injection site paresthesia</td>
<td>20 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site hematoma</td>
<td>16 (3%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>14 (3%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

The longest duration of any adverse reaction was a single case of injection site anesthesia (numbness) that started after Cycle 1 and lasted 349 days.

### 2. Mandibular Nerve Injuries

The marginal mandibular nerve (MMN) is a branch of the facial nerve. Muscles supplied by this nerve are responsible for facial symmetry, facial expressions and phonation. The cervical portion of the nerve is vulnerable to injury in procedures involving the submandibular triangle. Injury to this nerve can result in facial asymmetry, deviation of the angle of the mouth, drooling, and difficulty with speech and chewing.
MMN injury is a well-recognized complication of surgical interventions involving the face and neck. The potential for MMN injury was identified early in the DCA development program. The MMN and its branches exhibit wide anatomical variations and bear an important relationship with the inferior border of the mandible which is part of the treatment area.

In the pivotal Phase 3 trials, twenty subjects (4%) treated with DCA and one subject (<1%) treated with placebo experienced mandibular nerve injury, described as asymmetry of the lower lip on the affected side (paresis of lip depressors). The duration of the paresis ranged from 1 day to 298 days. Dosing was interrupted for four subjects. All nerve injuries resolved completely and without treatment.

3. Dysphagia

Difficulty swallowing occurred in the context of administration site reactions, e.g., pain, swelling, and induration of the submental area and not as result of esophageal or nerve injury.

A total of 11 subjects experienced dysphagia in pivotal Phase 3 trials, and all but one were in the DCA group. Two subjects discontinued treatment because of dysphagia, one of whom had not recovered at the time of trial discontinuation. The duration of dysphagia ranged from 1-81 days.

4. Allergic reactions

There were no cases of anaphylactic reactions attributed to DCA in the clinical development program.

In the pivotal Phase 3 trials, in the category of “injection site reactions” there were 4 subjects in the DCA arm and one subject in the placebo arm who had “injection site urticaria”. The rash/hives developed at the injection site from 1-40 days after treatment, and resolved in all subjects (three subjects required antihistamines) without recurrence, despite additional treatments.

5. Effects on the liver

Overall, the number of subjects with transiently elevated liver enzymes was comparable between the DCA and placebo arms. None of the elevations was considered serious or prompted study treatment change by the investigators.

The percentage of subjects with > 2 times the upper limit of normal values for individual liver enzymes was:

- ALT (alanine aminotransferase): 6% of DCA-treated subjects and 7% of placebo-treated subjects,
- AST (aspartate aminotransferase): 3% of DCA-treated subjects and 3% of placebo-treated subjects,
• Alkaline phosphatase: <1% of DCA-treated subjects and <1% of placebo-treated subjects, and
• Total bilirubin: <1% of DCA-treated subjects and <1% of placebo-treated subjects.

V.  REVIEWS BY OTHER DISCIPLINES

FDA’s review of information provided in the NDA related to Chemistry, Manufacturing, and Controls, non-clinical studies, and clinical pharmacology studies did not identify any substantive review issues.

The applicant provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The toxicity profile of DCA has been well characterized and FDA concluded that, at the proposed clinical dose, there is no significant safety concern identified in the submitted non-clinical studies.

Five studies were conducted to characterize the clinical pharmacology of DCA. Systemic exposure was assessed after subcutaneous (SC) administration into the submental fat using the maximum proposed dosing regimen that is intended for labeling. Pharmacokinetic studies demonstrated that following single treatment with DCA there was rapid, approximately three-fold increase in maximal DCA plasma concentrations followed by return to baseline levels within 24 hours.

FDA’s review of the thorough QTc trial concluded that no significant QTc prolongation effect of DCA was detected at doses representing the maximum therapeutic exposure, and 2 times the anticipated maximum therapeutic exposure. The drug-drug interaction potential of DCA was assessed in in vitro inhibition and induction studies. The results suggested that DCA is not likely to either induce or inhibit the activity of CYP enzymes.

VI.  GENERAL SUMMARY

The currently available data support a favorable benefit-risk assessment for the use of DCA for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. No major safety issues associated with the use of DCA have been identified to date.
VII. PRELIMINARY TOPICS FOR THE ADVISORY COMMITTEE

The Division is convening this meeting to solicit the Committee’s comments on the following topics. Please note, however, that these are preliminary topics and are still subject to change.

1. **Do the efficacy and safety data provided to you today support the approval of deoxycholic acid injection for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat?**

**Background Information for Consideration (Issue 1):** As the question states, we are asking the Committee to weigh the risks and benefits provided to you today in the vote for approval. Please note that a vote for approval, in general terms, does not mean that one must agree with the proposed dosing recommendations or proposed labeling. If your answer is “No”, please consider what additional studies should be recommended.
## Appendix A – CR-SMFRS Including Positioning Grid

[Reproduced from Applicant’s Clinical Trial Protocol for ATX-101-11-23]

<table>
<thead>
<tr>
<th>Score</th>
<th>SMF Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent Submental Convexity: No localized submental fat evident.</td>
</tr>
<tr>
<td>1</td>
<td>Mild Submental Convexity: Minimal, localized submental fat.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate Submental Convexity: Prominent, localized submental fat.</td>
</tr>
<tr>
<td>3</td>
<td>Severe Submental Convexity: Marked, localized submental fat.</td>
</tr>
<tr>
<td>4</td>
<td>Extreme Submental Convexity.</td>
</tr>
</tbody>
</table>
CR-SMFRS Assessment Procedures

CR-SMFRS score is based on investigator’s clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head.

Each center will be provided with the CR-SMFRS book containing the representative photographs for each score and a 2-inch by 2-inch grid poster that will be placed on the wall, with the horizontal lines parallel to the floor, in the area where ratings will be conducted.

The score is determined using the definitions in the rating scale and representative photographs associated with each score. In order to maintain a consistent posture from which the scores will be made, the final determination of the score will be made while the subject’s head is in the Frankfort plane posture. The correct posture will be achieved as in the example below using the following:

1. Position the subject standing facing to the rater’s left approximately 1 foot in front of the grid.
2. The rater will stand such that he or she can visualize the horizontal lines on the grid to be parallel to the plane from the subject’s lower orbital arch of the eye to the cephalic margin of the tragus of the ear. This is the Frankfort plane.
3. While the subject is in the correct position relative to the horizontal plane, the rater will visualize the vertical lines to line-up with the tragus and the front of the subject’s shoulder. Alternatively a vertical line can be used that aligns with the back of the subject’s head on a plane slightly posterior to the subject’s shoulder.

The score will be recorded as a whole number. At screening and baseline, the score is determined in conjunction with protocol entry criteria (e.g., absence of loose skin, diffuse submental fat, and prominent platysmal bands at rest that interfere with evaluation of localized fat).
APPENDIX B – PHOTOGUIDE FOR CR-SMFRS TRAINING

[Reproduced from Applicant’s ATX-101 Clinical Outcome Assessment Evidence Dossier]

Score = 0

Absent Submental Convexity: No localized submental fat evident.

![Image of submental area with score 0]

---

18
Score = 0

Absent Submental Convexity: No localized submental fat evident.
Score = 1

Mild Submental Convexity: Minimal, localized submental fat.
Score = 1

Mild Submental Convexity: Minimal, localized submental fat.
Score = 2

Moderate Submental Convexity: Prominent, localized submental fat.
Score = 2

Moderate Submental Convexity: Prominent, localized submental fat.
Score = 3
Severe Submental Convexity: Marked, localized submental fat.
Score = 3
Severe Submental Convexity: Marked, localized submental fat.
Score = 4
Extreme Submental Convexity
Score = 4
Extreme Submental Convexity
APPENDIX C – PR-SMFRS

[Reproduced from Applicant’s Clinical Trial Protocol for ATX-101-11-23]

Appendix D. Subject-Reported Outcome Measures

D1. Patient-Reported Submental Rating Scale (PR-SMFRS)

The subject will be instructed to position his or her head in a manner similar to that described for CR-SMFRS assessment and asked to respond to the question below.

PR-SMFRS

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

How much fat do you have under your chin right now?

Mark ☒ in one box below

- [ ] No chin fat at all
- [ ] A slight amount of chin fat
- [ ] A moderate amount of chin fat
- [ ] A large amount of chin fat
- [ ] A very large amount of chin fat
APPENDIX D – PR-SMF-LD (LINE DRAWINGS)

[Reproduced from Applicant’s Clinical Trial Protocol for ATX-101-11-23]

Product: ATX-101
Clinical Protocol ATX-101-11-23 (REFINE-2)
Date: 4 November 2011

D5: Standardized Line Drawings

Line Drawing Procedure:
Each subject will be given 10 line drawings that include 2 example line drawings representing each of the 5 SMF Scores. The drawings will be printed on cards provided by Kythera; each card will have a unique identifier. The profile depicted on each card is derived from the representative photograph’s profile view in the CR-SMFRS. The unique identifiers will not be associated with the CR-SMFRS score and will be present only on the back of the card. Subjects will not be provided with the CR-SMFRS score associated with the line drawings or any other written or verbal descriptions of the line drawing. Cards will be provided to the subject in a shuffled order. The subject will be asked to look at each line drawing and select the drawing that best represents how they believe their profile to be at the present time. The subject is to be instructed that there is no incorrect answer; they should choose the one drawing that best represents their profile.

The center will record the code corresponding to the selected line drawing. The code will be matched to a grade (0 to 4).

The person presenting the cards to the subject will read instructions to the each subject as follows: “Here are 10 profiles representing different shapes of the chin area. Please examine the cards and identify the line drawing that you believe is closest to your profile. If you are unsure, just select the overall closest match even if it is not perfect. There is no right and no wrong answer.”

The line drawings that will be presented are shown below, except that the SMF grades will not be identified on the cards.
Line Drawing Cards:

Grade 0

Grade 1