Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

Morning Session

FDA Introductory Remarks

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products

March 9, 2015
Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

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

March 9, 2015
Efficacy and Safety of Deoxycholic Acid

FDA Speakers

Milena Lolic, MD, MS
Medical Officer
Division of Dermatology and Dental Products

Elektra Papadopoulos, MD, MPH
Acting Associate Director
Study Endpoints

Kathleen Fritsch, PhD
Statistical Reviewer
Office of Biostatistics
Overview

• Background
• Efficacy Endpoints
• Summary of Efficacy
• Summary of Safety
• Questions
Background

Milena Lolic, MD, MS
Medical Officer
Division of Dermatology and Dental Products
Submental Fat Reduction

- Submental convexity contouring
- Aesthetic indication
  - Minimal physical morbidity
  - Individual values
- No approved drug treatments
- No established endpoints
Endpoint Selection

**Observable**

- Clinical judgment
  - No
    - Self-report?
      - Yes
        - PRO*
  - Yes

**Non-observable**

- Physiologic or lab findings that can be measured without human assessment
  - PRO

**Biomarker**

*PRO-Patient reported outcome
**ClinRO-Clinician reported outcome
Endpoints Development

Ph 1-2 Study 03 (n=85)
Safety & Efficacy
(Dose escalation)

- **ClinRO**
  - *CR-SMFRS*
- **PRO**
  - *SSRS*
  - *PGIC*

Ph 2 Study 07 (n=73)
Safety & Efficacy
(Injection paradigms)

- **ClinRO**
  - *CR-SMFRS*
- **PRO**
  - *SSRS*
  - *PGIC*

*(CR-SMFRS)*- Clinicians Reported Submental Fat Rating Scale
*(SSRS)*- Subject Self Rating Scale
*(PGIC)*- Patient Global Impression of Change
FDA Advice for Phase 2b

a) continue clinician assessment (CR-SMFRS)
b) include relevant patient assessment
c) add objective assessment (biomarker)
## Applicant-Proposed Endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Concept</th>
<th>Instrument (Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Amount of Submental Fullness</td>
<td>PR-SMFRS (PRO) CR-SMFRS (ClinRO)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Submental Fat Volume</td>
<td>MRI (Biomarker)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Impact of Submental Fullness</td>
<td>Submental Fat Impact Scale (PRO)</td>
</tr>
</tbody>
</table>
Endpoints Development

Ph2b Study 15 (n=129)
Safety & Efficacy
(ClinRO, PRO measures, MRI)
Endpoints Development (almost there)

- ClinRO and PRO rating scales with similar categories
- PRO impact scale becomes separate measure
- MRI data supportive of submental fat reduction
Endpoints Development (almost there)

- Improved correlation between PRO and ClinRO assessment for a single subject needed
  - Standardized subject positioning
  - Assistance for PRO (graphic tool)
Endpoints Development

- Improved correlation between PRO and ClinRO assessment for a single subject needed
  - Standardized subject positioning
  - Assistance for PRO (graphic tool)

- Composite endpoint
Primary Efficacy Endpoint:

- Based on Submental Fat Rating Scale (SMFRS) Measures:
  - Clinician-reported Submental Fat Rating Scale (CR-SMFRS)
  - Patient-reported Submental Fat Rating Scale (PR-SMFRS)

Secondary Efficacy Endpoints

- Magnetic resonance imaging (MRI)
- Patient-reported Submental Fat Impact Scale (PR-SMFIS)
Efficacy Endpoints

Elektra Papadopoulos, MD, MPH
Acting Associate Director
Study Endpoints
## Clinician Assessment

### Clinician-Reported Submental Fat Rating Scale (SMF)

<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 mass</td>
</tr>
<tr>
<td>1</td>
<td>Mild Submental Convexity: Minimal, localized submental fat mass</td>
</tr>
<tr>
<td>2</td>
<td>Moderate Submental Convexity: Prominent, localized submental fat mass</td>
</tr>
<tr>
<td>3</td>
<td>Severe Submental Convexity: Marked, localized submental fat mass</td>
</tr>
<tr>
<td>4</td>
<td>Extreme Submental Convexity</td>
</tr>
</tbody>
</table>
Positioning Grid for CR-SMFRS

Source: NDA 206333 original submission; Kythera Biopharmaceuticals, Inc.
CR-SMFRS Training & Scoring Photoguide

**Score = 0**
Absent Submental Convexity: No localized submental fat evident.

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

Source: NDA 206333 original submission; Kythera Biopharmaceuticals, Inc.
CR-SMFRS Training & Scoring Photoguide

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

**Score = 3**
Severe Submental Convexity: Marked, localized submental fat.

Source: NDA 206333 original submission; Kythera Biopharmaceuticals, Inc.
CR-SMFRS Training & Scoring Photoguide

Score = 4

Extreme Submental Convexity

Source: NDA 206333 original submission; Kythera Biopharmaceuticals, Inc.
Patient-Reported Submental Fat Rating Scale (PR-SMF)

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

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

Mark ☐ in one box below

<table>
<thead>
<tr>
<th>☐</th>
<th>No chin fat at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>A slight amount of chin fat</td>
</tr>
<tr>
<td>☐</td>
<td>A moderate amount of chin fat</td>
</tr>
<tr>
<td>☐</td>
<td>A large amount of chin fat</td>
</tr>
<tr>
<td>☐</td>
<td>A very large amount of chin fat</td>
</tr>
</tbody>
</table>
Grade 4
Patient Impact Assessment
Secondary Endpoint

The PR-SMFIS items were as follows:

1. How happy are you with the appearance of your chin fat?
   \(0 = \text{not happy at all}; 10 = \text{extremely happy}\)

2. How bothered are you by the appearance of your chin fat?
   \(0 = \text{not bothered at all}; 10 = \text{extremely bothered}\)

3. How self-conscious are you about the appearance of your chin fat?
   \(0 = \text{not self-conscious at all}; 10 = \text{extremely self-conscious}\)

4. How embarrassed are you about the appearance of your chin fat?
   \(0 = \text{not embarrassed at all}; 10 = \text{extremely embarrassed}\)

5. How much older do you look because of your chin fat?
   \(0 = \text{not older at all}; 10 = \text{very much older}\)

6. How much overweight do you look because of your chin fat?
   \(0 = \text{not overweight at all}; 10 = \text{extremely overweight}\)

Source: NDA 206333 original submission; Kythera Biopharmaceuticals, Inc.
Applicant-Proposed Responder Definitions

- 1-grade improvement in both 5-point SMFRS rating scales (CR-SMFRS and PR-SMFRS)

- 3-point improvement in the 11-point patient-reported submental fat impact scale (PR-SMFIS)
Summary of Efficacy

Kathleen Fritsch, PhD
Biostatistical Reviewer
Division of Biometrics III
Phase 3 Trials

- Trial Design (22 and 23)
  - Randomized, double blind, placebo controlled
  - 1% DCA or placebo up to 6 sessions one month apart
  - 24 weeks of follow-up after last treatment

- Sample Size
  - 22- 506 subjects
  - 23- 516 subjects

- Subjects characteristics
  - 18-65 years old
  - Moderate to severe submental fullness
## Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint (Evaluated at 12 Weeks Post-treatment)</th>
<th>Protocol Designation</th>
<th>SPA Agreement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 grades reduction on both the CR-SMFRS and the PR-SMFRS</td>
<td>Co-Primary</td>
<td>Yes</td>
</tr>
<tr>
<td>At least 1 grade reduction on both the CR-SMFRS and the PR-SMFRS</td>
<td>Co-Primary</td>
<td>No</td>
</tr>
<tr>
<td>At least 10% reduction in MRI volume</td>
<td>Secondary</td>
<td>Yes</td>
</tr>
<tr>
<td>PR-SMFIS total score</td>
<td>Secondary</td>
<td>No</td>
</tr>
</tbody>
</table>
## Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Trial 22</th>
<th></th>
<th>Trial 23</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCA</td>
<td>Placebo</td>
<td>DCA</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=256</td>
<td>N=250</td>
<td>N=258</td>
<td>N=258</td>
</tr>
<tr>
<td>2-grade improvement CR-SMF / PR-SMF</td>
<td>13%</td>
<td>&lt;0.1%</td>
<td>19%</td>
<td>3%</td>
</tr>
<tr>
<td>1-grade improvement CR-SMF / PR-SMF</td>
<td>70%</td>
<td>19%</td>
<td>67%</td>
<td>22%</td>
</tr>
</tbody>
</table>

All p-values < 0.001
Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Trial 22</th>
<th>Trial 23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCA N=256</td>
<td>DCA N=258</td>
</tr>
<tr>
<td></td>
<td>Placebo N=250</td>
<td>Placebo N=258</td>
</tr>
<tr>
<td><strong>≥ 10% reduction in</strong></td>
<td>(N=113) 46%</td>
<td>(N=113) 41%</td>
</tr>
<tr>
<td><strong>MRI volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR-SMFIS</strong></td>
<td>7.2 - 3.6</td>
<td>7.4 - 3.4</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>-3.6</td>
<td>-3.4</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td>-1.1</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

All p-values < 0.001
# Comparison of Clinician and Patient Ratings (Study 22)

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 2 grades Impr.</td>
<td>1 grade Impr.</td>
<td>No change/Worse</td>
</tr>
<tr>
<td>Clinician</td>
<td>DCA</td>
<td>≥ 2 grades Impr.</td>
<td>1 grade Impr.</td>
<td>No change/Worse</td>
</tr>
<tr>
<td></td>
<td>N=233</td>
<td>15%</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>41%</td>
<td>14%</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>18%</td>
<td>2%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>31%</td>
<td>53%</td>
<td>16%</td>
</tr>
<tr>
<td>Clinician</td>
<td>Placebo</td>
<td>≥ 2 grades Impr.</td>
<td>1 grade Impr.</td>
<td>No change/Worse</td>
</tr>
<tr>
<td></td>
<td>N=233</td>
<td>0%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>2%</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>31%</td>
<td>4%</td>
<td>16%</td>
<td>44%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>6%</td>
<td>33%</td>
<td>61%</td>
</tr>
</tbody>
</table>
Efficacy Outcomes over Time

Efficacy Outcomes (Study 22)

- Placebo (dashed)
- CR-SMFRS
- DCA (solid)
Efficacy Outcomes over Time
Efficacy Outcomes over Time

Efficacy Outcomes (Study 22)

- Placebo (dashed)
- MRI
- DCA (solid)
- CR-SMFRS
- PR-SMFRS

Submental Fat Rating Scale (Mean Score) vs. Study Week

MRI Volume (cubic cm) vs. Study Week

Study Week:
- 0
- 4 Wks
- 8 Wks
- 12 Wks
- 20 Wks
- +4 Wks
- +12 Wks
- +24 Wks
Summary of Safety

Milena Lolic, MD, MS
Medical Officer
Division of Dermatology and Dental Products
Safety Database

• 13 trials (N=2424)

• 7 RCT (N=2019)

• 2 US Pivotal trials (N=1019)
Adverse Event (AE) Assessment

• Deaths
  – 3 deaths reported on DCA treatment, 2 on placebo
  – No death was considered treatment-related

• Serious AEs
  – No SAE was reported with greater than 1% frequency
  – One SAE treatment related (MMN* injury in EU trials)

• Common AEs
  – Imbalance in total AEs was mainly due application site reactions

• AEs of special interest

* marginal mandibular nerve
Common Adverse Events
Injection site reactions

- Edema/Swelling
- Hematoma
- Pain
- Numbness
- Erythema
- Induration

**Percent of Subjects**

- DCA
- Placebo
Adverse Events of Special Interest
Marginal Mandibular Nerve injury

• 4% DCA-treated v. <1% placebo

• Duration 1-298 days (DCA median= 45 days)

• All resolved
Adverse Events of Special Interest

Dysphagia

• 2% DCA treated v. <1% placebo treated

• Duration 1-81 days (DCA median=3 days)

• One subject did not recover at the time of trial discontinuation
Adverse Events of Special Interest
Allergic Reactions

- No cases of anaphylactic reactions
- Rare cases of injection site urticaria
- All resolved (some with antihistamines)
# Effects on Liver

**LFT >2xUNL**

<table>
<thead>
<tr>
<th></th>
<th>DCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
AEs Over Time per Subject

Number AEs

Cycle 1  Cycle 2  Cycle 3  Cycle 4  Cycle 5  Cycle 6

DCA

placebo
Questions?
Questions for Committee

1. **VOTE**: 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?

   a. If not, what additional studies/analyses are needed?

Background Information for Consideration (Issue 1a):
As the question states, we are asking the Committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, does not mean that one must agree with proposed dosing recommendations or proposed labeling. If your answer is “No”, please consider what additional studies should be recommended?
Questions for Committee

2. **DISCUSSION:** Do the members of the committee have any comments on the approach which was developed for evaluation of safety and efficacy for this novel indication?