ATX-101 Deoxycholic Acid (DCA) Injection Submental Contouring Injectable Drug for the Reduction of Submental Fat

March 9, 2015

FDA Dermatologic and Ophthalmic Drugs Advisory Committee

KYTHERA Biopharmaceuticals, Inc.
Introduction

Frederick C. Beddingfield III, MD, PhD, FAAD
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KYTHERA Biopharmaceuticals, Inc.
Clinical Associate Professor of Medicine,
Division of Dermatology
University of California at Los Angeles
Background on Submental Fat

- Disproportionate/excess convexity or fullness
- Causes
  - Genetics
  - Lifestyle
  - Aging
- Can be resistant to weight loss
Current and/or Off-Label Treatment Options

- Aesthetic surgical procedures
- Targeted liposuction
- Unlicensed and/or compounded lipolytic drugs
  - FDA warning letters regarding compounded lipolytic drugs
Rationale for FDA-approved and Regulated Product

- Provide healthcare practitioners and patients with less invasive choice
- Reduce use of compounded products
- Quality manufacturing and safety monitoring
ATX-101 is a Pure Synthetic Version of Naturally Occurring DCA

- DCA emulsifies fats for absorption in intestine
- ATX-101 is biologically indistinguishable from endogenous DCA
- Temporarily increases DCA exposure
  - Levels within typical endogenous range
  - Return to baseline within 24 hours
Sodium Deoxycholate Used as Solubilizing Excipient for > 20 Years

- United States
  - Antifungal Amphotericin B (Amphocin®)
  - Influenza vaccines (Fluarix® and Flulaval®)
- Ex-US
  - Solubilizing excipient for phosphatidylcholine
  - Treatment of fat emboli
ATX-101: Corrective Procedure, Less Invasive Than Surgical Options

- Acute intermittent ATX-101 exposure
  - Subcutaneous injections
  - Up to 6 treatments
  - At least 4 weeks between treatments
- Gradual, incremental reduction
- Treatment tailored to each patient
ATX-101 MOA: DCA Disrupts Cell Membrane of Adipocytes, Causing Destruction of Fat Cells

Before Treatment

+1 Day

+2 Days

+5 Days

+1 Week

+3 Weeks

+4 Weeks

Multiple Treatments

Direct Effects

Healthy Adipocytes

Adipocytolysis
Destruction of Fat Cells

Local Tissue Response

Macrophage Infiltration,
Phagocytosis and Fibroblast Recruitment

Minimal Residual Inflammation and Neocollagenesis
Requested Indication

ATX-101 (deoxycholic acid injection) is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATX-101 Administration</td>
<td>Derek H. Jones, MD, FAAD</td>
<td>Skincare &amp; Laser Physicians, Los Angeles</td>
</tr>
<tr>
<td>Study Design</td>
<td>Todd M. Gross, PhD</td>
<td>KYTHERA Biopharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Efficacy Results</td>
<td>Frederick C. Beddingfield III, MD PhD, FAAD</td>
<td>KYTHERA Biopharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Safety Results</td>
<td>Paul F. Lizzul, MD PhD, FAAD</td>
<td>KYTHERA Biopharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Post Approval Training Program &amp; Concluding Remarks</td>
<td>Frederick C. Beddingfield III, MD PhD, FAAD</td>
<td>KYTHERA Biopharmaceuticals, Inc.</td>
</tr>
</tbody>
</table>
Additional Subject Matter Experts

- Valerie Callender, MD, FAAD  
  Dermatologist, Callender Dermatology & Cosmetic Center

- Steven Fagien, MD, FACS  
  Oculoplastic Surgeon  
  Private Practice  
  Boca Raton Regional Hospital

- Thomas Fuerst, PhD  
  Chief Science Officer  
  BioClinica, Inc.

- Dee Anna Glaser, MD, FAAD  
  Professor and Vice Chair, Dermatology, St. Louis University School of Medicine

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  Pharmacology and Pharmacokinetics Consultant  
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- David Sarwer, PhD  
  Professor of Psychology  
  Perelman School of Medicine  
  University of Pennsylvania
ATX-101 Administration

Derek H. Jones, MD, FAAD
Founder and Director
Skincare & Laser Physicians
Clinical Associate Professor of Medicine,
Division of Dermatology
University of California at Los Angeles
Many patients are dissatisfied with excess SMF
Some patients will seek corrective treatment
ATX-101 Administration

Physician palpates submental fat pad and examines surrounding area

Administered via 30G needle, 1 mL syringe

Temporary grid applied to SMF to control spacing of injections

Subcutaneous injections into SMF using grid
Not All Patients Are Candidates for ATX-101

- **Careful Consideration**
  - Thyromegaly
  - Cervical lymphadenopathy
  - Inferiorly located submandibular glands
  - Prominent platysmal bands
  - Excessive skin laxity

- **Caution advised**
  - History of dysphagia
  - Facial neuropraxia
  - Inflammation or induration in treatment area
  - Scar tissue
  - Prior surgical or aesthetic procedures in treatment area
  - Antiplatelet or anticoagulant

- **Contraindications**
  - Infection at injection site
Representative Photos of Typical ATX-101 Patient

Moderate  Severe

Enrolled Patients
Summary

- Patients are currently seeking treatment for submental fat
- Patients want less invasive options
- ATX-101 injection procedure is relatively straightforward for healthcare providers familiar with other facial injectable products
Pivotal Clinical Study Design

Todd M. Gross, PhD
Vice President, Clinical Development, Biostatistics, and Data Management
KYTHERA Biopharmaceuticals, Inc.
Associate Professor of Statistics
University of California, Santa Barbara
Key Study Design Elements: Phase 3 Studies (Studies 22 and 23)

- Identical
- Independent
- Double-blind
- Randomized
- Placebo-controlled (vehicle)
- All sites located in US or Canada
Key Enrollment Criteria

- Moderate or severe submental fat (SMF) as assessed by clinician and patient scales
- Dissatisfied with appearance of SMF
- 18 - 65 years old
- Stable body weight and BMI ≤ 40 kg/m²
- No prior intervention for submental fat
- No excess skin laxity
Pivotal Study Design

Study Visits

- Safety evaluations took place 7 days after each treatment session
- Efficacy endpoints based on the change from baseline to 12 weeks after the last treatment

**Screening, Baseline and Randomization**

1:1

**Placebo**

**Treatment Phase**

≤ 6 Treatments
1 Month Apart\(^a\)

**Follow-up Phase**

Began After
Last Treatment For Each Patient

- **Primary Endpoint**
  - 12 Weeks After Last Treatment

- **End of Study**
  - 24 Weeks After Last Treatment

\(^a\) Safety evaluations took place 7 days after each treatment session
\(^b\) Efficacy endpoints based on the change from baseline to 12 weeks after the last treatment
Design Elements of Pivotal Trials

- Active and placebo substances are identical in appearance and physical properties
- Independently labeled and coded product
- Automated randomization and kit assignment
- Independent assessments by clinician and patient without reference to previous assessments
- MRI as objective measure to support rating scales
Clinician and patient scales for SMF and perceived impact
  - CR-SMFRS, PR-SMFRS, PR-SMFIS
Based on patient interviews and expert input
Assessed reliability and validity in Phase 2 and non-treatment studies
Confirmed in pivotal trials
Validated Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)

<table>
<thead>
<tr>
<th>Scale</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submental Convexity</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td>Description</td>
<td>No Localized Submental Fat Evident</td>
<td>Minimal Localized Submental Fat</td>
<td>Prominent Localized Submental Fat</td>
<td>Marked Localized Submental Fat</td>
<td>Extreme Submental Convexity</td>
</tr>
</tbody>
</table>

Representative Photographs
Validated 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>
<th>Mark □ in one box below</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No chin fat at all</td>
<td></td>
</tr>
<tr>
<td>□ A slight amount of chin fat</td>
<td></td>
</tr>
<tr>
<td>□ A moderate amount of chin fat</td>
<td></td>
</tr>
<tr>
<td>□ A large amount of chin fat</td>
<td></td>
</tr>
<tr>
<td>□ A very large amount of chin fat</td>
<td></td>
</tr>
</tbody>
</table>
Co-Primary Efficacy Endpoints

- Composite 2-grade responders
  - ≥ 2-grade improvement* on CR-SMFRS
  - AND
  - ≥ 2-grade improvement* on PR-SMFRS

- Composite 1-grade responders
  - ≥ 1-grade improvement* on CR-SMFRS
  - AND
  - ≥ 1-grade improvement* on PR-SMFRS

*Improvement at 12 weeks after last treatment compared to baseline
Co-Primary Efficacy Endpoints

- Composite 2-grade responders
  - Degree of change difficult to attain
  - Requested by FDA
  - Consistent with prior dermatologic therapies

- Composite 1-grade responders
  - Clinically meaningful response for patients
  - Not all patients desire 2-grade change
Secondary Efficacy Endpoint: Validated MRI Assessment*

- MRI sub-study (n=449)
  - Study 22: n=224
  - Study 23: n=225
- Percent of patients achieving ≥ 10% reduction in submental volume
- Objective measure of SMF change

*Change at 12 weeks after last treatment compared to baseline
MRI Assessment Provides Objective Measure of Submental Volume

Baseline

Follow-up

Measured % change in MRI submental volume under-represents actual % change in target treatment area
Secondary Endpoint: Validated Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

- PR-SMFIS Total Scale Score
  - Used to assess impact of submental fat on patient self-perceptions related to visual and emotional attributes
Patient Impact Numerical Rating Scale

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

<table>
<thead>
<tr>
<th>How bothered are you by the appearance of your chin fat?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark [ ] in one box below and do not mark between the boxes</td>
</tr>
<tr>
<td>Not bothered at all</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

How bothered are you by the appearance of your chin fat?
Secondary Endpoint: PR-SMFIS Total Scale Score

Rate yourself on a scale from 0-10

1. How happy are you with the appearance of your chin fat?
2. How bothered are you by the appearance of your chin fat?
3. How self-conscious are you about the appearance of your chin fat?
4. How embarrassed are you about the appearance of your chin fat?
5. How much older do you look because of your chin fat?
6. How much overweight do you look because of your chin fat?

PR-SMFIS Total Scale Score (average of six items)
## Disposition

<table>
<thead>
<tr>
<th></th>
<th>Study 22</th>
<th>Study 23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>ATX-101</td>
</tr>
<tr>
<td>ITT - Randomized (N)</td>
<td>250</td>
<td>256</td>
</tr>
<tr>
<td>Treated</td>
<td>99.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Completed Primary Endpoint Visit</td>
<td>93%</td>
<td>91%</td>
</tr>
<tr>
<td>Completed Study</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>Discontinued from Study</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Patient convenience</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Adverse event</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other*</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*Administrative decision; Patient noncompliance
Cochran-Mantel-Haenszel method of imputation for missing data stratified by the site
# Balanced Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study 22 Placebo N=250</th>
<th>Study 22 ATX-101 N=256</th>
<th>Study 23 Placebo N=258</th>
<th>Study 23 ATX-101 N=258</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean</strong></td>
<td>49</td>
<td>49</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>83%</td>
<td>83%</td>
<td>87%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>BMI (kg/m²), mean</strong></td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91%</td>
<td>85%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5%</td>
<td>10%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Asian</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Fitzpatrick skin type, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-III</td>
<td>75%</td>
<td>70%</td>
<td>68%</td>
<td>66%</td>
</tr>
<tr>
<td>IV-VI</td>
<td>25%</td>
<td>30%</td>
<td>32%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Baseline CR-SMFRS score %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>52%</td>
<td>51%</td>
<td>51%</td>
<td>49%</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>48%</td>
<td>49%</td>
<td>49%</td>
<td>51%</td>
</tr>
</tbody>
</table>

BMI=body mass index; CR-SMFRS=Clinician-Reported Submental Fat Rating Scale
Efficacy

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Efficacy Agenda

Primary Efficacy Endpoints:
• Composite (CR- and PR-SMFRS) 2-grade Responders
• Composite (CR- and PR-SMFRS) 1-grade Responders

Secondary Endpoints:
• MRI Assessment
• Improvement in Visual and Emotional Impact (PR-SMFIS)

Examples of Patient Photographs of 2-grade and 1-grade Responders
2-Grade Composite Responder Rate Achieved

Responder Rate
12 Weeks After Last Treatment

ATX-101 Placebo

Study 22
N=250
0%
13%
p < 0.001

Study 23
N=258
3%
19%
p < 0.001

N=258

N=256
1-Grade Composite Responder Rate Achieved

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>ATX-101</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 22</td>
<td>19%</td>
<td>70%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Study 23</td>
<td>22%</td>
<td>66%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

N=250, N=256, N=258, N=258
Most ATX-101 Subjects Experienced a $\geq 1$-Grade Improvement in 2 – 4 Treatments

Evaluations occurred 4 weeks after each treatment
Efficacy Agenda

Primary Efficacy Endpoints:
• Composite (CR- and PR-SMFRS) 2-grade Responders
• Composite (CR- and PR-SMFRS) 1-grade Responders

Secondary Endpoints:
• MRI Assessment
• Improvement in Visual and Emotional Impact (PR-SMFIS)

Examples of Patient Photographs of 2-grade and 1-grade Responders
Blinded MRI Assessment Supports Primary Endpoint Results (Secondary Endpoint)

Patients Achieving $\geq 10\%$ Reduction in MRI Volume (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>ATX-101</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 22</td>
<td>46%</td>
<td>5%</td>
</tr>
<tr>
<td>Study 23</td>
<td>40%</td>
<td>5%</td>
</tr>
</tbody>
</table>

$p < 0.001$
**PR-SMFIS: Subjects Report Improvement in Visual and Emotional Impact (Secondary Endpoint)**

*Mean PR-SMFIS Total Scale Score*

**Study 22**
- Baseline: Placebo $= 6.2$, ATX-101 $= 3.6$
- 12 Wks after Last Tx: Placebo $= 5.8$, ATX-101 $= 3.9$

**Study 23**
- Baseline: Placebo $= 8.0$
- 12 Wks after Last Tx: Placebo $= 5.8$

$p < 0.001$, change from baseline, placebo vs. ATX-101 in both studies
Efficacy Agenda

Primary Efficacy Endpoints:
• Composite (CR- and PR-SMFRS) 2-grade Responders
• Composite (CR- and PR-SMFRS) 1-grade Responders

Secondary Endpoints:
• MRI Assessment
• Improvement in Visual and Emotional Impact (PR-SMFIS)

Examples of Patient Photographs of 2-grade and 1-grade Responders
2-Grade Improvement by Both Clinician & Patient Assessment

<table>
<thead>
<tr>
<th>Age 26</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td>CR-SMFRS</td>
</tr>
<tr>
<td></td>
<td>PR-SMFRS</td>
</tr>
<tr>
<td></td>
<td>Satisfaction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks After Last Treatment</th>
<th>6 Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI</td>
<td>26.4 kg/m²</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>134 lbs</td>
</tr>
<tr>
<td></td>
<td>CR-SMFRS</td>
<td>Absent (0)</td>
</tr>
<tr>
<td></td>
<td>PR-SMFRS</td>
<td>Slight (1)</td>
</tr>
<tr>
<td></td>
<td>Satisfaction</td>
<td>Extremely Satisfied (6)</td>
</tr>
</tbody>
</table>
1-Grade Improvement by Both Clinician & Patient Assessment

<table>
<thead>
<tr>
<th>Age 55</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>21.8 kg/m²</td>
</tr>
<tr>
<td>Weight</td>
<td>150 lbs</td>
</tr>
<tr>
<td>CR-SMFRS</td>
<td>Moderate (2)</td>
</tr>
<tr>
<td>PR-SMFRS</td>
<td>Moderate (2)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>Dissatisfied (1)</td>
</tr>
<tr>
<td>12 Weeks After Last Treatment</td>
<td></td>
</tr>
<tr>
<td><strong>5 Treatments</strong></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>21.8 kg/m²</td>
</tr>
<tr>
<td>Weight</td>
<td>150 lbs</td>
</tr>
<tr>
<td>CR-SMFRS</td>
<td>Mild (1)</td>
</tr>
<tr>
<td>PR-SMFRS</td>
<td>Slight (1)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>Slightly Satisfied (4)</td>
</tr>
</tbody>
</table>
Non-Responder

**Baseline**
- **Age**: 44
- **BMI**: 27.7 kg/m²
- **Weight**: 179 lbs
- **CR-SMFRS**: Moderate (2)
- **PR-SMFRS**: Moderate (2)
- **Satisfaction**: Dissatisfied (1)

**12 Weeks After Last Treatment**
- **BMI**: 27.3 kg/m²
- **Weight**: 175 lbs
- **CR-SMFRS**: Moderate (2)
- **PR-SMFRS**: Moderate (2)
- **Satisfaction**: Slightly Dissatisfied (2)
Conclusions

- Co-Primary Endpoints were achieved
  - 1-grade and 2-grade composite CR-SMFRS and PR-SMFRS
- Secondary Endpoints were also achieved
  - MRI Assessment
  - Patient-Reported Submental Fat Impact Scale (PR-SMFIS)
Safety

Paul F. Lizzul, MD, PhD, FAAD
Senior Medical Director
KYTHERA Biopharmaceuticals, Inc.
Private Practice, Westlake Village, CA
Safety Agenda

Collection of AEs and Definition of Safety Population

Overview of Vital Signs, Lab Results, AEs

Overview of SAEs

Adverse Events of Special Interest

Long-term Safety Data
Collection of Adverse Events

- Spontaneous AE reports observed or elicited at each study visit
- Clinical evaluations:
  - Submental area
  - Physical examinations
- Evaluation of laboratory test results
Pivotal Studies Safety Population Analyzed for Common Adverse Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>ATX-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 22</td>
<td>248</td>
<td>257</td>
</tr>
<tr>
<td>Study 23</td>
<td>256</td>
<td>258</td>
</tr>
<tr>
<td>Total</td>
<td>504</td>
<td>515</td>
</tr>
</tbody>
</table>
Safety Agenda

Collection of AEs and Definition of Safety Population

Overview of Vital Signs, Lab Results, AEs

Overview of SAEs

Adverse Events of Special Interest

Long-term Safety Data
Safety: Vital Signs & Laboratory Results

- Treatment with ATX-101 not associated with any clinically meaningful changes in:
  - Vital signs
  - Clinical chemistry
    - Serum lipid concentrations
    - Liver function tests
    - Renal function tests
  - Hematology results
# Adverse Event Severity

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=504</th>
<th>ATX-101 N=515</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Reporting Any Adverse Event</td>
<td>452 90%</td>
<td>501 97%</td>
</tr>
<tr>
<td><strong>Severity of Reported Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2807 89%</td>
<td>4479 81%</td>
</tr>
<tr>
<td>Moderate</td>
<td>328 10%</td>
<td>969 18%</td>
</tr>
<tr>
<td>Severe</td>
<td>21 1%</td>
<td>90 2%</td>
</tr>
</tbody>
</table>

Patients who experienced 1 or more adverse events are counted for the worst, or maximum, severity.
# Most Common Treatment-Emergent AEs Associated with Injection-site Reactions

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA Preferred Term)</th>
<th>Patients (%) with Injection-site Events (≥10% of patients)</th>
<th>Placebo N=504</th>
<th>ATX-101 N=515</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma (Bruising)</td>
<td></td>
<td>70%</td>
<td>72%</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>31%</td>
<td>70%</td>
</tr>
<tr>
<td>Anesthesia (Numbness)</td>
<td></td>
<td>6%</td>
<td>66%</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td>18%</td>
<td>27%</td>
</tr>
<tr>
<td>Induration</td>
<td></td>
<td>3%</td>
<td>23%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td></td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Nodule</td>
<td></td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>6%</td>
<td>12%</td>
</tr>
</tbody>
</table>

MedDRA=Medical Dictionary for Regulatory Activities
Incidence and Severity of Most Common Treatment-Emergent AEs Associated with Injection-site Reactions

P = Placebo; N = 504
A = ATX-101; N = 515
## Adverse Event Severity

<table>
<thead>
<tr>
<th>Patients Reporting Any Adverse Event</th>
<th>Placebo N=504</th>
<th>ATX-101 N=515</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Patients Reporting Any Adverse Event</td>
<td>452</td>
<td>90%</td>
</tr>
</tbody>
</table>

### Severity of Events

<table>
<thead>
<tr>
<th>Severity of Events</th>
<th>Placebo N=504</th>
<th>ATX-101 N=515</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2807</td>
<td>89%</td>
</tr>
<tr>
<td>Moderate</td>
<td>328</td>
<td>10%</td>
</tr>
<tr>
<td>Severe</td>
<td>21</td>
<td>1%</td>
</tr>
</tbody>
</table>

*N=55 patients

Patients who experienced 1 or more adverse events are counted for the worst, or maximum, severity.
Characterization of Severe AEs

**Bruising; Pain; Numbness; Edema; Swelling**
- 52 events in 37 patients
  - Onset at 1st treatment (n=36)
  - Median duration = 4 days
  - 100% resolved without sequelae

**Induration; Tingling; Dysphagia; Hypersensitivity**
- 7 events in 6 patients
  - Median duration = 8 days
  - 100% resolved without sequelae
## Other Severe AEs
(31 Events in 18 Patients)

- Abdominal abscess
- Abdominal distension
- Abdominal pain
- Abdominal pain upper
- Back pain
- Breast cancer recurrent
- Chest pain
- Colitis microscopic
- Concussion and related AEs
- Coronary artery disease
- Dental caries (cavity)
- Endometriosis
- Gastroenteritis viral
- GE reflux disease
- Norovirus test positive
- Osteoarthritis
- Ovarian cancer
- Retinal tear
- Road traffic accident
- Spinal column stenosis
- Spinal fusion surgery
- Syncope
- Type 2 diabetes mellitus
- Upper respiratory tract infection
- Uterine cancer
- Vertigo
Safety Agenda

Collection of AEs and Definition of Safety Population

Overview of Vital Signs, Lab Results, AEs

Overview of SAEs

Adverse Events of Special Interest

Long-term Safety Data
# Safety Population of All SMF Studies Using 2 mg/cm² Dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>ATX-101 2 mg/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 22</td>
<td>248</td>
<td>257</td>
</tr>
<tr>
<td>Study 23</td>
<td>256</td>
<td>258</td>
</tr>
<tr>
<td>Other Phase 3/3b</td>
<td>236</td>
<td>408</td>
</tr>
<tr>
<td>Phase 2</td>
<td>81</td>
<td>76</td>
</tr>
<tr>
<td>Phase 1</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>875</td>
<td>1050</td>
</tr>
</tbody>
</table>
## Serious Adverse Events by SOC

<table>
<thead>
<tr>
<th>Adverse Event by SOC</th>
<th>Placebo N=875</th>
<th>ATX-101 N=1050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With Any SAE</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Infections and Infestation</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Injury, Poisoning, Procedural Complications</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorder</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System Disorder</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Surgical and Medical Procedures</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac Disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy, Puerperium, Perinatal Conditions</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorder</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary Disorder</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Safety Agenda

Collection of AEs and Definition of Safety Population

Overview of Vital Signs, Lab Results, AEs

Overview of SAEs

Adverse Events of Special Interest

Long-term Safety Data
# Injection Site Motor Nerve Injury

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=875</th>
<th>ATX-101 N=1050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting event</td>
<td>3 0.3%</td>
<td>30 2.9%</td>
</tr>
<tr>
<td>Resolution:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved</td>
<td>3 100%</td>
<td>29 96.7%</td>
</tr>
<tr>
<td>Resolving</td>
<td>0 0%</td>
<td>1* 3.3%</td>
</tr>
<tr>
<td>Ongoing</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Median duration (range)</td>
<td>54 days (4-115)</td>
<td>45 days (1-298)</td>
</tr>
</tbody>
</table>

* Case resolved after study completion
Example of Moderate Injection Site Nerve Injury and Resolution (Study 26)

2 days after treatment

95 days after treatment
Safety Agenda

Collection of AEs and Definition of Safety Population

Overview of Vital Signs, Lab Results, AEs

Overview of SAEs

Adverse Events of Special Interest

Long-term Safety Data
No Unexpected Findings in Long-Term Post-Treatment Safety

- 2 of 4 long-term follow up studies completed
  - Up to 4 year data
  - N=374 patients*
  - 36 patients reported AEs during follow-up
  - AEs were not severe
  - No drug-related SAEs
- No unexpected findings

* 2 mg/cm²
Summary: ATX-101 Safety Profile is Well-characterized

- AEs were typical for facial injectables
- AEs common but generally:
  - Transient in nature
  - Mild
  - Resolved without intervention or sequelae
  - Less frequent with successive treatment
- Consistent with expectation of clinicians and patients
Education/Training and Summary

Frederick C. Beddingfield III, MD, PhD, FAAD
Chief Medical Officer
KYTHERA Biopharmaceuticals, Inc.
Clinical Associate Professor of Medicine,
Division of Dermatology
University of California at Los Angeles
Comprehensive Training for Healthcare Providers

- Training made available in multiple formats
- Training topics
  - Anatomy of submental region
  - Injection techniques
  - Patient evaluation and selection
  - Patient experience
ATX-101 Anatomy and Injection Training to Mitigate Motor Nerve Injury

- Key internal anatomic structures
- Platysma and SMF compartment
- Marginal mandibular nerve
  - Do not inject above inferior mandible
  - Do not inject below inferior border of mandible in the area of the marginal mandibular nerve
## ATX-101 Provides Clinically Meaningful Efficacy

<table>
<thead>
<tr>
<th>Pre-specified Endpoint</th>
<th>ATX-101 Result Range</th>
<th>p-value vs. Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-grade composite SMFRS response (CR-SMFRS and PR-SMFRS)</td>
<td>13-19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-grade composite SMFRS response (CR-SMFRS and PR-SMFRS)</td>
<td>66-70%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRI Assessment (≥ 10% reduction)</td>
<td>40-46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Improvement in Visual and Emotional Impact (PR-SMFIS)</td>
<td>-3.4 to -3.6 reduction</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Most Patients Remain on Treatment Until Desired Results Achieved

- Patients can expect to experience treatment area AEs
- Most AEs were mild or moderate in severity and rarely resulted in discontinuation from the study
- Transient in nature
ATX-101 Benefit-risk

- Unlicensed or compounded lipolytic drugs
- ATX-101 provides patients with a less-invasive alternative to surgical options
- Efficacy has been conclusively demonstrated
  - Statistically significant and clinically relevant improvements in all pre-specified endpoints
- Safety and tolerability have been well characterized
ATX-101 Deoxycholic Acid (DCA) Injection Submental Contouring Injectable Drug for the Reduction of Submental Fat

March 9, 2015
FDA Dermatologic and Ophthalmic Drugs Advisory Committee
KYTHERA Biopharmaceuticals, Inc.
Backup Slides Shown
SAE: Neoplasms
(All SMF Studies – 2 mg/cm² dose)

- Comparable numbers in both ATX and PBO
- No event was considered related to study drug

- ATX-101: 7 subjects (0.5%) ; 8 events
  - 1 gastric, ovarian, uterine, breast, bile duct, thyroid, and colon cancer
  - 1 uterine leiomyoma

- PBO: 4 subjects (0.5%); 4 events
  - 2 breast cancer
  - 1 each non-Hodgkin’s lymphoma, multiple myeloma
## Analysis of Potential Unblinding Adverse Events (Composite 1-Grade)

| Injection Site Adverse Event | ATX-101 | | | Placebo | | |
|-----------------------------|---------|---------|---------|---------|---------|
|                             | Patients With AE | Patients Without AE | Patients With AE | Patients Without AE |
|                             | n | % | n | % | n | % | n | % |
| Induration                  | 83 | 76% | 246 | 71% | 2 | 14% | 92 | 21% |
| Numbness                    | 239 | 72% | 90 | 73% | 12 | 28% | 82 | 20% |
| Nodule                      | 56 | 81% | 273 | 71% | 2 | 15% | 92 | 21% |
| Swelling                    | 295 | 73% | 34 | 69% | 46 | 23% | 48 | 19% |
| Pain                        | 234 | 72% | 95 | 72% | 38 | 26% | 56 | 18% |

Chi square p-value = <0.001
# Total Number of Treatments Received

<table>
<thead>
<tr>
<th>Treatment Session</th>
<th>Placebo N = 504</th>
<th>ATX-101 N = 515</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>3.4%</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>4.2%</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>3.8%</td>
</tr>
<tr>
<td>6</td>
<td>411</td>
<td>81.5%</td>
</tr>
</tbody>
</table>

41%
Triglyceride Profile Before (Stage A) and Following ATX-101 Administration (Stage B)

![Graph showing mean triglycerides plasma concentration over time.]

- **Normal range**: 50 - 200 mg/dL
- **Stage A**: Baseline
- **Stage B**: ATX-101
Patient with Grade 2* Bruising

*Spreading beyond four or more individual needle insertion points but contained within the treatment area.
Reason for Receiving < 6 Treatments

SMF resolved / Patient satisfaction
Lost to follow up / Withdrew consent
AE / Discomfort

Patients at Each Treatment Visit (%)

P = Placebo
A = ATX-101

Treatment 1
P (N=504) A (N=515)

Treatment 2
P (N=487) A (N=456)

Treatment 3
P (N=466) A (N=427)

Treatment 4
P (N=450) A (N=394)

Treatment 5
P (N=430) A (N=345)
# Medical History ≥ 2% (Slide 1 of 3)

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Placebo N = 508</th>
<th>ATX-101 2 mg/cm² N = 514</th>
<th>Total N = 1022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause</td>
<td>20.5 %</td>
<td>24.7 %</td>
<td>22.6 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24.2 %</td>
<td>20.4 %</td>
<td>22.3 %</td>
</tr>
<tr>
<td>Depression</td>
<td>16.1 %</td>
<td>16.9 %</td>
<td>16.5 %</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>17.7 %</td>
<td>15.6 %</td>
<td>16.6 %</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>14.2 %</td>
<td>12.5 %</td>
<td>13.3 %</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.4 %</td>
<td>11.5 %</td>
<td>11.4 %</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>15.6 %</td>
<td>11.1 %</td>
<td>13.3 %</td>
</tr>
<tr>
<td>Female sterilization</td>
<td>10.4 %</td>
<td>11.1 %</td>
<td>10.8 %</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>9.8 %</td>
<td>10.7 %</td>
<td>10.3 %</td>
</tr>
</tbody>
</table>
# Medical History ≥ 2% (Slide 2 of 3)

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Placebo N = 508</th>
<th>ATX-101 2 mg/cm² N = 514</th>
<th>Total N = 1022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>11.2 %</td>
<td>8.9 %</td>
<td>10.1 %</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.9 %</td>
<td>8.6 %</td>
<td>7.2 %</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>9.1 %</td>
<td>8.6 %</td>
<td>8.8 %</td>
</tr>
<tr>
<td>Migraine</td>
<td>7.9 %</td>
<td>8 %</td>
<td>7.9 %</td>
</tr>
<tr>
<td>Headache</td>
<td>6.5 %</td>
<td>7.2 %</td>
<td>6.8 %</td>
</tr>
<tr>
<td>Blood cholesterol increased</td>
<td>3.7 %</td>
<td>6.4 %</td>
<td>5.1 %</td>
</tr>
<tr>
<td>Acne</td>
<td>5.1 %</td>
<td>5.4 %</td>
<td>5.3 %</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.3 %</td>
<td>5.1 %</td>
<td>5.2 %</td>
</tr>
</tbody>
</table>
**Medical History ≥ 2% (Slide 3 of 3)**

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Placebo N = 508</th>
<th>ATX-101 2 mg/cm² N = 514</th>
<th>Total N = 1022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>4.1</td>
<td>4.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.1</td>
<td>4.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>4.9</td>
<td>3.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2.8</td>
<td>3.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Oral Herpes</td>
<td>3</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Rosacea</td>
<td>3</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Attention deficit/Hyperactivity disorder</td>
<td>4.3</td>
<td>2.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>2.6</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Prespecified ≥1-Grade Change from Baseline on CR-SMFRS, PR-SMFRS, and Composite Endpoint (Study 22)

- Clinician Rating (CR-SMFRS): 36.2% for Placebo, 79.1% for ATX-101
  - p < 0.001

- Patient Rating (PR-SMFRS): 38.5% for Placebo, 82.3% for ATX-101
  - p < 0.001

- Composite Primary Endpoint: 18.6% for Placebo, 70.0% for ATX-101
  - p < 0.001

Sample sizes:
- Placebo: N=250
- ATX-101: N=256
Relationship Between MRI and Composite Response (Pivotal Studies)

MRI % Change from Baseline

Composite Nonresponders 1-Grade Composite Responders 2-Grade Composite Responders

PBO N=161 ATX N=46 PBO N=38 ATX N=142 PBO N=4 ATX N=33

% MRI Responders 5% 34.8% 2.9% 44% 25% 66.7%
## Satisfaction in Studies 22 and 23

<table>
<thead>
<tr>
<th></th>
<th>Study 22 Placebo N=250</th>
<th>Study 22 ATX-101 N=256</th>
<th>Study 23 Placebo N=256</th>
<th>Study 23 ATX-101 N=256</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRS</strong></td>
<td>31.0%</td>
<td>82.8%</td>
<td>36.2%</td>
<td>75.1%</td>
</tr>
<tr>
<td><strong>SGQ-1 ≥ moderately better</strong></td>
<td>16.6%</td>
<td>74.7%</td>
<td>24.7%</td>
<td>70.7%</td>
</tr>
<tr>
<td><strong>SGQ-2 ≥ moderately better</strong></td>
<td>16.2%</td>
<td>68.9%</td>
<td>21.6%</td>
<td>67.4%</td>
</tr>
<tr>
<td><strong>SGQ-3 ≥ moderately better</strong></td>
<td>30.3%</td>
<td>77.8%</td>
<td>33.9%</td>
<td>75.3%</td>
</tr>
</tbody>
</table>
Responder Analysis by Pain

- Subjects with Pain
  - Composite 1-grade – 72.2%
  - Composite 2-grade – 17.9%

- Subjects without Pain
  - Composite 1-grade – 72.0%
  - Composite 2-grade – 15.9%