SOLLPPURA™
(liprotamase)

Alnara Pharmaceuticals, Inc
A wholly-owned subsidiary of Eli Lilly and Company

Gastrointestinal Drugs
Advisory Committee
# Presentation Agenda

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</table>
Attending Experts and Consultants

- **Peter Durie, MD, FRCP(C)**
  - Professor, Department of Paediatrics, and Member of the Institute of Medical Sciences, Faculty of Medicine, University of Toronto

- **Paul B. Watkins, MD**
  - Verne S. Caviness Professor of Medicine
  - Director, Hamner-UNC Institute for Drug Safety Sciences, University of North Carolina-Chapel Hill

- **John Balser, PhD**
  - President, Veristat

- **Marilyn Campion, MS**
  - Consultant Statistician
Proposed Indication

Sollpura™ (liprotamase) is indicated for the treatment of patients with Exocrine Pancreatic Insufficiency (EPI) due to cystic fibrosis (CF), chronic pancreatitis (CP), pancreatectomy, or other conditions.
Mechanism of Action

- Liprotamase enzymes digest ingested food within the GI tract to enable nutrient absorption and maintenance of nutrition
  - Triglycerides into free fatty acids
  - Proteins into small peptides and amino acids
  - Complex carbohydrates into simple sugars

- Enzymes are not systemically absorbed
Recommended Dose

• **Starting Dose**
  - Adults and Children ≥7 years of age
    - Initiate with 1 capsule (32,500 U) per meal or snack
  - Dose: Children 2 - 6 years of age
    - Suspended in water or apple juice
    - Initiate dosing with 1,625 U/g fat

• **Individualize dose as necessary**

• **Maximum daily dose should not exceed CFF guidelines**
  - ≤2,500 U/kg BW/meal (or ≤10,000 U/kg BW/day), or <4,000 U/g fat ingested/day
Abbreviated Product History

- 2001: Initial Cystic Fibrosis Foundation (CFF) grant
- 2002: IND Filed by Altus Pharmaceuticals
- 2003: Fast Track Designation by FDA due to un-met medical need
- 2004: Accepted into FDA CMA Pilot 2 program
- 2007: Phase III efficacy protocol developed under a Special Protocol Assessment (SPA)
- 2009: Product transferred to the CFF and subsequently licensed to Alnara Pharmaceuticals
- 2010: NDA filed
- 2010: Lilly acquired Alnara, CFF’s Liprotamase interests
Product Development

• Microbial enzymes
  – Similar activity profile to mammalian pancreatic enzymes

• *In vitro* screening
  – Non-specific digestion of a broad range of substrates
  – Stability at low pH
    • No need for enteric coating
  – No requirement for co-factors

• Canine model of EPI
  – Final enzyme selection
  – Selection of enzyme ratios
Liprotamase Enzymes

- **Lipase (32,500 U USP)**
  - Crystallized and crosslinked to increase low pH stability (Lipase-CLEC [crossed-linked enzyme crystal])

- **Protease (25,000 U USP)**
  - Crystallized to prevent proteolysis in the capsule over product shelf life

- **Amylase (3,750 U USP)**
  - Amorphous
Phase I/II & Phase III Product Comparability

- Phase III manufacturing process has been refined over time
- Comparability established through biochemical analyses
- Capsules filled based on activity
- Phase II and Phase III clinical data are similar
  - FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (April 1996)
Summary

- Liprotamase is a novel Pancreatic Enzyme Replacement Therapy (PERT)
  - New Molecular Entity
- Microbial lipase, protease, amylase
  - Highly active, stable, purified enzymes with broad substrate specificity
- Stable and convenient capsule Drug Product formulation
- Same enzymes and Drug Product formulation used throughout clinical program
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Normal Pancreatic Function

• Critical in digestion
• 90% reserve
• Enzymes are active in proximal small bowel
• Optimal function is dependent on bile, pH, co-lipase and other factors
  – These factors are altered in CF and post-surgical patients
Diseases Commonly Associated with EPI

- Cystic fibrosis
- Chronic pancreatitis
- Pancreatectomy
- Malignancy
Clinical Symptoms and Signs of Pancreatic Insufficiency

- **Nutritional deficits**
  - Weight loss, delayed growth
    - Macronutrient deficiencies
    - Micronutrient deficiencies

- **Gastrointestinal Symptoms**
  - Abdominal pain
  - Steatorrhea
  - Bloating, flatulence

- **Same symptoms and signs regardless of the cause of EPI**
Maturation of the Pancreas

• Lack of lipase is the major contributor to nutritional deficiencies and symptoms

• Lipase activity is at adult levels by 2 years of age
  – 210 ± 20 Units/mg in healthy infants age 2*
  – 245 ± 22 Units/mg in healthy adults (age 23-30)**

** Borovicka et al; Am J Physiol (1997) 273:G374-380
Factors Altering the Effectiveness of Porcine PERTs in EPI

- Fat digestion
  - Low pH
  - Precipitation of bile salts
  - Late release due to enteric coating

- Fat absorption
  - Gut mucosal factors
  - Bacterial overgrowth
  - Poor micelle formation
Requirements for Optimal Exocrine Pancreatic Enzyme Replacement Therapy

- Active at wide pH range
- Unaffected by presence or absence of bile salts
- Lipase does not require complex interactions with co-factors
Principles of Therapies with PERT

- Problem is lack of pancreatic enzymes
- Treatment is effective replacement of enzymes
- Treatment is the same regardless of underlying cause or age
- Dosing in clinical practice dependent upon:
  - Lipase activity of the pancreatic enzyme formulation
  - Quantity and type of foods and fats ingested more so than weight or age
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Manifestations of CF

Pulmonary & Sinus
- Chronic infections,
- Obstructive lung disease

Pancreatic
- Exocrine pancreatic insufficiency,
- Pancreatitis

Other
- Skin salt loss,
- Digital clubbing

Gastrointestinal
- Meconium ileus,
- Distal intestinal obstruction syndrome

Hepatic
- Cirrhosis,
- Elevated transaminases

Endocrinologic
- CF-related diabetes

Reproductive
- CBAVD, reduced fertility

Elevated transaminases

21
EPI in CF: Clinical Symptoms and Signs

- **Nutritional**
  - PCM, growth failure
  - Vitamin and essential fatty acid deficiencies

- **Gastrointestinal**
  - Abdominal pain
  - Steatorrhea
  - Bloating, flatulence

- **Early intervention for EPI is life-sustaining**
  - Pancreatic Enzyme Replacement Therapy
  - $\geq 120\%$ of daily recommended caloric intake (40% as fat)
Pancreatic Enzyme Replacement Therapy

- **1940’s →**
  - Porcine extracts used to treat EPI

- **Early 1990’s – Dose creep**
  - “No upper limit” → Fibrosing colonopathy

- **1995 CFF/FDA Guidelines**
  - Weight-based dosing because of need to establish dose exposure

- **2008 CFF Evidence-based Review**
  - No data upon which to base dosing recommendations
Coefficient of Fat Absorption (CFA) in PERT Studies

- Short-term measure (snapshot)
- Surrogate endpoint accepted by the FDA
- No correlation between a specific CFA cut point and clinically meaningful endpoints
- Multiple factors affect digestion and absorption
“Optimized” CFA (>80%) Not Achieved in Many Patients with CF on PERT
Growth: Despite Standard of Care, Nutritional Status Gets Worse with Age

Source: CF Foundation Patient Registry; cross-sectional data
Growth is a Clinically Relevant Outcome: Strong Association of Lung Function (FEV₁) and Growth (BMI) in Patients with CF (Age 2 - 20 Years)

CFF Patient Registry, 2008 data
CF Population Spans All Age Ranges with Different Rates of Growth

- **BMI (kg/m\(^2\))** – one of the two national clinical outcomes
  - Assesses nutritional status
  - Z-score is SD relative to mean
    - Flat line = normal rate of growth
Mean US Population: BMI Z-score

Normal Rate of Growth
Development of an NME PERT

• Short-term measure (CFA)
  – Dose ranging
  – Identification of appropriate starting dose
    • Demonstration of short-term efficacy

• Long-term clinically meaningful measures
  – BMI (Z-scores)
  – Weight (Z-scores)
  – Height (Z-scores)
Why Is it Important to Develop a New PERT Formulation?

• Sourcing and supply concerns
  – Pig herd
  – Transmission of pathogens from porcine source
  – Consistency of manufacturing

• Pill burden contributes to poor adherence
  (27-46%; Modi et al, J Cyst Fibr 2006)
  – Likely a major factor in ongoing symptoms and malnutrition
  – Daily dose = 16.7 to 25.7 capsules/day*

• Lack of stability in acid environment

* CF Services Pharmacy (n=3,250)
Development Goals for Liprotamase

• Demonstrate safety and efficacy with:
  – Reliable source with reproducible and precise manufacturing process
  – No excess protease, no purines
  – Lower daily pill burden
  – Acid stable / does not need enteric coating
  – A data-driven approach to dose
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Overview

• Short-term efficacy
• Long-term clinical activity
• Dosing guidelines
• CFA
Liprotamase Efficacy Summary

• Efficacious starting dose identified and confirmed (TC-2A and 726)
  – Consistently met primary and secondary study objectives

• Met clinically meaningful long term goals of replacement therapy (767 and 810)
  – Nutritional status maintained
  – Age appropriate growth and weight gain in children
  – Maintenance of pulmonary function (FEV₁)

• Dosing established (TC-2A, 726, 767, 810)
  – Initiate one capsule (32,500 U) per meal/snack
  – Individualize dose if necessary
# Liprotamase Clinical Development

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Patient Population</th>
<th>No. of Subjects</th>
</tr>
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<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td></td>
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<tr>
<td>TC-1A</td>
<td>Healthy volunteers</td>
<td>20</td>
</tr>
<tr>
<td>TC-1B, TC-1C</td>
<td>Cystic fibrosis</td>
<td>31</td>
</tr>
<tr>
<td><strong>Short-term Efficacy Studies</strong></td>
<td></td>
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<tr>
<td>TC-2A</td>
<td>Cystic fibrosis</td>
<td>125</td>
</tr>
<tr>
<td>726 (International)</td>
<td>Cystic fibrosis</td>
<td>163</td>
</tr>
<tr>
<td><strong>Supportive Long-term Studies</strong></td>
<td></td>
<td></td>
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<tr>
<td>767 (International)</td>
<td>Cystic fibrosis</td>
<td>214</td>
</tr>
<tr>
<td>810</td>
<td>Chronic pancreatitis/pancreatectomy</td>
<td>39</td>
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<tr>
<td><strong>Total Unique Subjects</strong></td>
<td></td>
<td>492</td>
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Short Term Efficacy Studies

TC-2A and 726
## TC-2A and 726: Key Entrance Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>TC-2A</th>
<th>726</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>CF-related EPI</td>
<td>CF-related EPI</td>
</tr>
<tr>
<td>Age</td>
<td>≥7 years</td>
<td>≥7 years</td>
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<tr>
<td>Fecal elastase</td>
<td>&lt;100 µg/g stool</td>
<td>&lt;100 µg/g stool</td>
</tr>
<tr>
<td>Weight</td>
<td>≥40 kg</td>
<td>no restriction</td>
</tr>
<tr>
<td>Baseline CFA</td>
<td>no restriction</td>
<td>≤80%</td>
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</tbody>
</table>
TC-2A and 726: Common Study Features

- Large, parallel group, controlled, randomized trials
- Nutritionally and functionally compromised patients included
- CFA primary endpoint measurement
  - Target 100g of fat/day diet
  - Fixed dose (No dose optimization allowed)
TC-2A and 726: Primary Endpoint Measurement

- Coefficient of Fat Absorption (CFA)
  - ~72 hr (marker to marker) stool collection
  - Short term measure of drug effect
- 100 g of fat per day diet

\[
\text{CFA (\%) = } \frac{\text{Fat ingested} - \text{Fat in stool}}{\text{Fat ingested}} \times 100
\]
TC-2A and 726: Secondary Endpoint Measurements

- Coefficient of Nitrogen Absorption (CNA)

- Supportive Secondary Endpoints
  - Stool Weight
  - Stool Frequency
  - Starch Challenge (exploratory)
TC-2A: Dose Selection

- Phase 1 (TC-1B) Dose Ranging (U/kg/meal)

<table>
<thead>
<tr>
<th></th>
<th>100 U</th>
<th>500 U</th>
<th>1,000 U</th>
<th>2,500 U</th>
<th>5,000 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in CFA (%)</td>
<td>1.2</td>
<td>22.7</td>
<td>17.7</td>
<td>18.9</td>
<td>17.2</td>
</tr>
</tbody>
</table>

- TC-2A – Dose range selected (per meal or snack)
  - 6,500 U (100 U/kg)
  - 32,500 U (500 U/kg)
  - 130,000 U (2000 U/kg)
TC-2A: Study Schematic (N=125)

- **Randomized DB Period**
  - 72 hr 100g/day high-fat diet
  - Marker-marker stool collection

- **Baseline**
  - 72 hr 100g/day high-fat diet
  - Marker-marker stool collection

- **CFA CNA**

- **Off-Enzyme 3 Days**
  - 130,000 U
  - 32,500 U
  - 6,500 U

- **28 Days**
## TC-2A: Subject Disposition and Demographics

<table>
<thead>
<tr>
<th>Liprotamase</th>
<th>6,500 U</th>
<th>32,500 U</th>
<th>130,000 U</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>129</td>
</tr>
<tr>
<td>Treated (ITT)</td>
<td>41</td>
<td>43</td>
<td>41</td>
<td>125</td>
</tr>
</tbody>
</table>

### Mean Age (range)
- 21.3 (11, 55)

### Mean BMI Z-score (percentile)
- -0.495 (31st)
TC-2A: Mean Change from Baseline CFA (ITT)

Mean Change in CFA (%)

- 6,500 U (n=41) 1.1
- 32,500 U (n=43) 10.9
- 130,000 U (n=39) 16.0

P-values:
- P = 0.001
- P = 0.029
- P = NS
TC-2A: Mean Change from Baseline CNA (ITT)

Mean Change in CNA (%)

- 6,500 U (n=41) 1.0
- 32,500 U (n=43) 11.9
- 130,000 U (n=39) 16.2

P-values:
- P = <0.001
- P = 0.011
- P = NS
TC-2A: Conclusions

• Met primary endpoint
  – Significant improvement of fat absorption (CFA)

• Met key secondary endpoints
  – Significant improvement of protein absorption (CNA)
  – Significant decrease in stool weight

• Selected liprotamase 32,500 U as an appropriate efficacious starting dose
726: Key SPA Agreements

- Randomized, double-blind, parallel group
- Liprotamase 32,500 U vs placebo
- Primary Analysis Population: Subjects with baseline off-enzyme CFA <40%
  - Least Squares Mean (LSM) difference in CFA compared to placebo
- Secondary endpoints (supportive)
- Subjects with off-enzyme CFA >80% excluded
726: Study Schematic

Baseline
- 72 hr 100g/day high-fat diet
- Marker-marker stool collection

Randomized DB Period
- 72 hr 100g/day high-fat diet
- Marker-marker stool collection

CFA CNA

Off-Enzyme
6 Days Inpatient

Liprotamase
21-31 Days

Placebo
6 Days Inpatient
## 726: Subject Disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Liprotamase 32,500 U</th>
<th>Total</th>
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<tbody>
<tr>
<td>Treated (open-label)</td>
<td>NA</td>
<td>163</td>
<td>163</td>
</tr>
<tr>
<td>Randomized (ITT)</td>
<td>68</td>
<td>70</td>
<td>138</td>
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**726: Demographics**

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<thead>
<tr>
<th></th>
<th>Total</th>
<th>US</th>
<th>Eastern Europe</th>
<th>Other non-US</th>
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<tr>
<td>N</td>
<td>138</td>
<td>68</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
<td>Mean age</td>
<td>18.1</td>
<td>20.2</td>
<td>13.5</td>
<td>20.9</td>
</tr>
<tr>
<td>Mean BMI Z-score (percentile)</td>
<td>-0.517 (30\textsuperscript{th})</td>
<td>-0.354 (36\textsuperscript{th})</td>
<td>-0.869 (19\textsuperscript{th})</td>
<td>-0.328 (37\textsuperscript{th})</td>
</tr>
<tr>
<td>Nutritionally compromised*</td>
<td>52 (38%)</td>
<td>21 (31%)</td>
<td>26 (58%)</td>
<td>5 (20%)</td>
</tr>
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*BMI <20kg/m\(^2\) (≥18 years) or <25\textsuperscript{th} percentile (<18 years)*
726: Primary Efficacy Results in Primary Analysis Population

* * ANCOVA adjusting for acid suppression use

**LSM change from baseline CFA (ITT)**

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<tr>
<th></th>
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<th>Placebo</th>
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<td>LSM difference</td>
<td>15.1*</td>
<td>6.0</td>
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<tr>
<td>* ANCOVA adjusting for acid suppression use</td>
<td>P = 0.0011</td>
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**726: Primary Efficacy Results**

*LSM change from baseline CFA (ITT)*

![Graph showing change in CFA (%)](image)

- **Liprotamase**
  - LSM difference 15.1*  
  - P = 0.0011
  - LSM difference 10.6**  
  - P <0.0001
  - LSM difference 10.6**  
  - P <0.0001

- **Placebo**
  - LSM difference 6.0  
  - P = 0.0064
  - LSM difference 3.2
  - LSM difference 7.7

CFA <40% (n=44)  
Overall (n=138)  
CFA ≥40% (n=94)

* ANCOVA adjusting for acid suppression use
** ANCOVA adjusting for acid suppression use and baseline CFA category
726: Secondary Efficacy Results

**LSM change from baseline CNA (ITT)**

**LSM difference 12.7***
- P = 0.001

**LSM difference 9.2***
- P < 0.001

**LSM difference 6.6***
- P = 0.012

* ANCOVA adjusting for acid suppression use

**ANCOVA adjusting for acid suppression use and baseline CFA category

† Including treatment group by acid suppression use interaction
726: Secondary Efficacy Results

**LSM change from baseline stool weight (ITT)**

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<td><strong>LSM difference</strong></td>
<td>-255.3*</td>
<td>255.3*</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>LSM difference</strong></td>
<td>-217.0**</td>
<td>217.0**</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>LSM difference</strong></td>
<td>-149.8* †</td>
<td>149.8*†</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.055</td>
<td>0.055</td>
</tr>
</tbody>
</table>

* ANCOVA adjusting for acid suppression use

** CFA <40% (n=42)

- CFA Baseline CFA
- Overall (n=134)
- CFA ≥40% (n=92)

** ANCOVA adjusting for acid suppression use and baseline CFA category

† Including treatment group by acid suppression use interaction
726: Subgroup Analyses (CFA)

**LSM difference liprotamase vs placebo**

**Geographic Region**
- US Sites
- Non-US Sites

**Age**
- 7 to <20 yrs
- ≥20 yrs

**Gender**
- Male
- Female

**Acid Suppression**
- On
- Off

**LS Mean Difference in Change in CFA Between Liprotamase and Placebo (95% CI)**
726: Subgroup Analyses (CFA)

*Intra-treatment difference*

**Geographic Region**
- US Sites
- Non-US Sites

**Age**
- 7 to <20 yrs
- ≥20 yrs

**Gender**
- Male
- Female

**Acid Suppression**
- On
- Off

**LS Mean Change in CFA for Liprotamase (95% CI)**

---

58
TC-2A and 726: Significant Improvement in CFA Across Studies (<40% Baseline CFA)

LSM difference and mean change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>LSM Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study TC-2A</td>
<td>32,500 U</td>
<td>36.0%</td>
<td>0.007</td>
</tr>
<tr>
<td>(US) (n=16)</td>
<td>6,500 U</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>Study 726</td>
<td>32,500 U</td>
<td>21.2%</td>
<td>0.0011</td>
</tr>
<tr>
<td>(Overall) (n=44)</td>
<td>Placebo</td>
<td>6.0%</td>
<td></td>
</tr>
</tbody>
</table>

* ANCOVA adjusting for acid suppression use
TC-2A and 726: Significant Improvement in CFA in US Subjects (<40% Baseline CFA)

* LSM difference and mean change from baseline

**Study TC-2A (US) (n=16)**
- 32,500 U: 36.0% change in CFA
- 6,500 U: 10.8% change in CFA
- LSM difference: 25.1%*, $P = 0.007$

**Study 726 (US only) (n=23)**
- 32,500 U: 22.7% change in CFA
- Placebo: -1.1% change in CFA
- LSM difference: 23.8%*, $P = 0.001$

* ANCOVA adjusting for acid suppression use
Liprotamase: Efficacy Summary

Studies TC-2A and 726

- Consistently met its primary and key secondary endpoints
- Consistently superior to control in TC-2A, 726 and in sub-group analyses
- Liprotamase 32,500U (1,625 U/g of fat) is an appropriate and efficacious starting dose for chronic therapy
Clinical Activity
Long-term Studies

767 and 810
## Studies 767 and 810

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age Range</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>767</td>
<td>214</td>
<td>7-62</td>
<td>CF</td>
</tr>
<tr>
<td>810</td>
<td>39</td>
<td>27-82</td>
<td>Chronic Pancreatitis and S/P pancreatectomy</td>
</tr>
<tr>
<td>Total</td>
<td>253</td>
<td>7-82</td>
<td>–</td>
</tr>
</tbody>
</table>
767: Study Overview

• Primary objective
  – Evaluate the long-term safety and tolerability of liprotamase treatment

• Target enrollment was up to 200 subjects with CF-related EPI
  – Including at least 20 children 7 to 11 years of age
  – 100 subjects completing one year
767: Prospectively Defined Clinical Activity Measurements

• Serial measurement of BMI and weight
  – Z-scores
  – Determine the effect of liprotamase treatment on maintenance of nutritional status
767: Long-Term Study Schematic

726 Rollover (n=88)
- Fixed Dose

Open-Label

Liprotamase Naïve (n=126)
- Flexible Dosing
  - 48-52 weeks

- Starting dose: One capsule (32,500 U) per meal or snack
- Individualize dose, if necessary
  - 2 capsules per meal
  - Occurrence of EPI related GI symptoms
  - Involuntary weight loss
  - Diet
Post-Hoc US CFF Registry Group Match

• Contemporaneous data (2007-2008)
  – ~ 27,000 US patients in database

• Matched to 767 entry criteria (n=5660)
  – Subjects ≥7 years of age
  – Porcine-PERT users
  – Serial height, weight, and BMI

• Hospitalization information
# 767 vs. US CFF Registry: Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>767</th>
<th>CFF Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>214</td>
<td>5660</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>18.6</td>
<td>19.2</td>
</tr>
<tr>
<td>Mean BMI Z-score</td>
<td>-0.494</td>
<td>-0.243</td>
</tr>
<tr>
<td>On Acid Suppression</td>
<td>51%</td>
<td>54%</td>
</tr>
</tbody>
</table>
## 767: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>US</th>
<th>Eastern Europe</th>
<th>Other non-US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>214</td>
<td>112</td>
<td>56</td>
<td>46</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>18.6</td>
<td>20.3</td>
<td>13.2</td>
<td>20.9</td>
</tr>
<tr>
<td><strong>Mean BMI Z-score (percentile)</strong></td>
<td>-0.494  (31st)</td>
<td>-0.214 (42nd)</td>
<td>-1.004 (16th)</td>
<td>-0.553 (29th)</td>
</tr>
<tr>
<td><strong>Nutritionally compromised</strong>*</td>
<td>80 (38%)</td>
<td>27 (24%)</td>
<td>35 (63%)</td>
<td>18 (39%)</td>
</tr>
</tbody>
</table>

*BMI <20kg/m² (≥18 years) or <25th percentile (<18 years)
767 vs. CFF Registry: BMI Z-score (LOCF) Long-term Maintenance of Nutritional Status by Region

- CFF Registry (n=5660)
- 767: US (n=112)
- 767: Other non-US (n=46)
- 767: Eastern Europe (n=56)

• Consistent results in subgroups:
  - Acid suppression status (on or off)
  - Completer or non-completer status
767: Mean LOCF Weight Z-scores by Weight Loss of at Least 5% by Month 3 (All subjects)

- 19/23 were non-US subjects
- 13/23 completed study
- Weight-loss was not progressive
767: Stable Pulmonary Function (FEV₁) Mean (SE)

Baseline (n=213) - 76.4
6 months (n=149) - 75.9
12 months (n=141) - 76.5
810: Key Entrance Criteria

- Subjects ≥18 years of age
- Chronic Pancreatitis or Pancreatectomy
- EPI
  - Fecal elastase <100 µg/g stool and/or
  - Steatorrhea, weight loss, diarrhea and on enzyme replacement therapy for ≥3 months
810: Long-term Study Schematic

Open-Label

Liprotamase
Flexible Dosing
48-52 weeks

- Starting dose: One capsule (32,500 U) per meal or snack
- Individualize dose, if necessary
  - 2 capsules per meal
  - Occurrence of EPI related GI symptoms
  - Involuntary weight loss
  - Diet
### 810: Subject Disposition

<table>
<thead>
<tr>
<th>Liprotamase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrolled</strong></td>
</tr>
<tr>
<td><strong>ITT Population</strong></td>
</tr>
<tr>
<td>Chronic Pancreatitis</td>
</tr>
<tr>
<td>Pancreatectomy</td>
</tr>
<tr>
<td>Completed 3 months</td>
</tr>
<tr>
<td>Median Time on Study (weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Liprotamase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>41</td>
</tr>
<tr>
<td>ITT Population</td>
<td>39</td>
</tr>
<tr>
<td>Chronic Pancreatitis</td>
<td>77%</td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td>23%</td>
</tr>
<tr>
<td>Completed 3 months</td>
<td>74%</td>
</tr>
<tr>
<td>Median Time on Study (weeks)</td>
<td>25</td>
</tr>
</tbody>
</table>
810: Mean Weight Over Time
Mean (SE)
Dosing Guidelines

- Children ≥7 years and adults
- Children 2 - <7 years
### 767 and 810: Summary of Dosing

<table>
<thead>
<tr>
<th></th>
<th>767</th>
<th>810</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average capsules per day</strong></td>
<td>5.5</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Maximum average capsules per day</strong></td>
<td>10.6*</td>
<td>10.5</td>
</tr>
</tbody>
</table>

* Did not exceed CFF guidelines
Liprotamase Dosing in Children 7 Years and Older and Adults

- **Starting dose**: One capsule (32,500) U per meal or snack (1,625 U/g of fat)

- **Individualize dose, if necessary**
  - Increase to 2 capsules per meal (one per snack)
    - Occurrence of EPI related GI symptoms
    - Involuntary weight loss
    - Diet

- **Maximum dose of ≤10,000 U/kg or <4,000 U/g of fat per day** *(CFF Guidelines)*
Liprotamase Dosing in Children 2 to <7 Years

- Physiology and pathophysiology
- Extrapolation of large safety and efficacy database in children and adults

767: BMI Z-scores by Age

7 - <12 (n=55)  12 - <17 (n=57)  ≥17 (n=102)

Mean US Population

Mean BMI Z-score vs. Month

0 1 2 3 4 5 6 7 8 9 10 11 12

0 1 2 3 4 5 6 7 8 9 10 11 12

-2.50 -2.00 -1.50 -1.00 -0.50 0.00 0.50 1.00 1.50 2.00 2.50
Liprotamase Dosing in Children 2 to <7 Years

• Physiology and pathophysiology

• Extrapolation of large safety and efficacy database in children and adults
  – 112 children 7 to <17 years of age in Study 767

• Enzymes digest food in the gut and are not systemically absorbed

• Regulatory precedent for extrapolation with porcine PERTs
Dosing Guidelines for Children 2 to <7 Years

- Starting dose based upon average fat intake
- Open capsule and mix contents in 5 mL of water

<table>
<thead>
<tr>
<th>Dose</th>
<th>2 to 3 years</th>
<th>3 to &lt;7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose/meal or snack</td>
<td>2.5 mL</td>
<td>3.5 mL</td>
</tr>
<tr>
<td>Maximum dose/day</td>
<td>25 mL (5 capsules)</td>
<td>35 mL (7 capsules)</td>
</tr>
<tr>
<td>Maximum lipase dose/day</td>
<td>&lt;4,000 U/gram of fat or ≤10,000 U/kg/day, unless otherwise directed by a physician</td>
<td></td>
</tr>
</tbody>
</table>
CFA Overview

• Valuable short term surrogate measure
  – Can demonstrate difference between effective treatment and placebo or ineffective control

• The degree of improvement in CFA that is required for clinical benefit is unknown
  – No studies correlating the magnitude of change in CFA with long-term clinically meaningful outcomes have been done
Study Design and Patient Selection in Porcine Studies have Dramatic Impact on CFA Results

• Design
  – Small cross-over studies (30-40 subjects)
  – “Responder” studies
  – Maximal doses studied (CFF guidelines)

• Subject selection
  – Stable patients only
  – Exclusion of nutritionally compromised patients
  – Exclusion of symptomatic patients
  – US only

• It is inappropriate and misleading to compare results from these studies to liprotamase
TC-2A and 726: Significant Improvement in CFA in US (<40% Baseline CFA)

**LSM difference and mean change from baseline**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage (U)</th>
<th>LS Mean (SE)</th>
<th>Change in CFA (%)</th>
<th>LSM Difference*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study TC-2A</td>
<td>32,500</td>
<td>36.0%</td>
<td>10.8%</td>
<td>25.1%</td>
<td>0.007</td>
</tr>
<tr>
<td>(US) (n=16)</td>
<td>6,500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 726</td>
<td>32,500</td>
<td></td>
<td>22.7%</td>
<td>23.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>(US only) (n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ANCOVA adjusting for acid suppression use
726: Significant Improvement in CFA in US (Overall and <40% Baseline CFA)

LSM difference and mean change from baseline

**LSM difference 16.6%***
P < 0.001

**LSM difference 23.8%**
P = 0.001

* ANCOVA adjusting for acid suppression use and baseline CFA category
**ANCOVA adjusting for acid suppression use
767: Mean LOCF BMI Z-scores for 726 Rollover Subjects

- BMI Z-scores maintained regardless of:
  - Baseline CFA
  - On-treatment CFA
  - Change from baseline CFA

Borowitz et al. Pediatr Pulmonol 2010; Suppl 33:424
767 vs. CFF Registry: BMI Z-Score (LOCF) Long-term Maintenance of Nutritional Status (US Only)

- Consistent results in subgroups:
  - Acid suppression status (on or off)
  - Completer or non-completer status
767: Stable Pulmonary Function (FEV$_1$) Mean (SE)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Predicted</td>
<td>76.4 (n=213)</td>
<td>75.9 (n=149)</td>
<td>76.5 (n=141)</td>
</tr>
</tbody>
</table>
Liprotamase Efficacy Summary

• Efficacious starting dose identified and confirmed (TC-2A and 726)
  – Consistently met primary and secondary study objectives

• Met clinically meaningful long term goals of replacement therapy (767 and 810)
  – Nutritional status maintained
  – Age appropriate growth and weight gain in children
  – Maintenance of pulmonary function (FEV$_1$)

• Dosing established (TC-2A, 726, 767, 810)
  – Initiate one capsule (32,500 U) per meal/snack
  – Individualize dose if necessary
<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td><strong>Don G. Burstyn, PhD</strong></td>
</tr>
<tr>
<td></td>
<td>Senior Vice President, Regulatory Affairs</td>
</tr>
<tr>
<td></td>
<td>Alnara Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>Exocrine Pancreatic Physiology and Insufficiency</td>
<td><strong>Steven D. Freedman, MD, PhD</strong></td>
</tr>
<tr>
<td></td>
<td>Director, The Pancreas Center</td>
</tr>
<tr>
<td></td>
<td>Beth Israel Deaconess Medical Center</td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine, Harvard Medical School</td>
</tr>
<tr>
<td>Disease State Overview and Management of Patients</td>
<td><strong>Drucy Borowitz, MD</strong></td>
</tr>
<tr>
<td></td>
<td>Director, CF Center</td>
</tr>
<tr>
<td></td>
<td>Professor of Clinical Pediatrics</td>
</tr>
<tr>
<td></td>
<td>Women and Children’s Hospital of Buffalo</td>
</tr>
<tr>
<td>Summary of Efficacy</td>
<td><strong>Lee R. Brettman, MD, FACP</strong></td>
</tr>
<tr>
<td></td>
<td>Chief Medical Officer</td>
</tr>
<tr>
<td></td>
<td>Alnara Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>Summary of Safety</td>
<td><strong>Christopher Stevens, MD</strong></td>
</tr>
<tr>
<td></td>
<td>Senior Vice President, Clinical Development</td>
</tr>
<tr>
<td></td>
<td>Alnara Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>Benefit/Risk Profile</td>
<td><strong>Drucy Borowitz, MD</strong></td>
</tr>
</tbody>
</table>
Outline of Clinical Safety Review

• Exposure
  – Short-term and Long-term studies

• General safety
  – Deaths/Serious adverse events
  – Common adverse events
  – Discontinuations

• Safety topics of interest
  – Distal Intestinal Obstruction Syndrome (DIOS)
  – Transaminase Elevations

• Risk management
# Safety Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposure</th>
<th>Overall N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>3-14 days</td>
<td>51</td>
</tr>
<tr>
<td>Short-term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC-2A</td>
<td>28 day</td>
<td>288</td>
</tr>
<tr>
<td>726</td>
<td>Up to 44 days</td>
<td>288</td>
</tr>
<tr>
<td>Long-term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>767</td>
<td>Up to 1 year</td>
<td>253*</td>
</tr>
<tr>
<td>810</td>
<td>Up to 1 year</td>
<td>253*</td>
</tr>
</tbody>
</table>

492 Unique Subjects

* Includes 88 patients rolled over from 726
Short-term Exposure Safety Profile

Studies TC-2A and 726
## Safety Population

*Short-term studies*

<table>
<thead>
<tr>
<th></th>
<th>TC-2A</th>
<th>726</th>
<th></th>
<th></th>
<th>Placebo</th>
<th>32,500 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)</td>
<td>41</td>
<td>43</td>
<td>41</td>
<td>163</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>6,500 U</td>
<td>32,500 U</td>
<td>130,000 U</td>
<td>All</td>
<td>Placebo</td>
<td>32,500 U</td>
<td></td>
</tr>
</tbody>
</table>

- **Off-Enzyme**:
  - 3 Days
  - 6,500 U

- **Liprotamase**:
  - 6 Days
  - 21-31 Days
  - Placebo

- **Day 28**:
  - 32,500 U
### Serious Adverse Events (%)

*Short-term studies*

<table>
<thead>
<tr>
<th>Body System</th>
<th>TC-2A (28 days)</th>
<th>726 (44 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6,500 U (n=41)</td>
<td>32,500 U (n=43)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>14.6%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Infections</td>
<td>2.4%</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7.3%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.4%</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>2.4%</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune System</td>
<td>0</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
## Discontinuation Due to AEs (%)

*Short-term studies*

<table>
<thead>
<tr>
<th>Body System</th>
<th>TEAE Leading to Discontinuation</th>
<th>TC-2A (28 days)</th>
<th>726 (44 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6,500 U (n=41)</td>
<td>32,500 U (n=43)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.4%</td>
<td>4.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Blood Disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism/Nutrition</td>
<td>2.4%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### 726: Serious Adverse Events (%)
#### 6-day placebo-controlled period

<table>
<thead>
<tr>
<th>Body System</th>
<th>726 (6 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n=65)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>1.4%</td>
</tr>
<tr>
<td>Infections</td>
<td>1.4%</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>0</td>
</tr>
<tr>
<td>Body System</td>
<td>Placebo (n=65)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Any AE</td>
<td>49.2%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>29.2%</td>
</tr>
<tr>
<td>Investigations</td>
<td>10.8%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>10.8%</td>
</tr>
<tr>
<td>Infections</td>
<td>7.7%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>3.1%</td>
</tr>
<tr>
<td>General disorders</td>
<td>6.2%</td>
</tr>
<tr>
<td>Injury/procedural complications</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

AEs reported in >5% of subjects in either group
# 726: Discontinuation Due to AEs (%)

6-day placebo-controlled period

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo (n=65)</th>
<th>32,500 U (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE Leading to Discontinuation</td>
<td>1.5%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Blood Disorders</td>
<td>0</td>
<td>1.4%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.5%</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System</td>
<td>0</td>
<td>1.4%</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td>0</td>
<td>1.4%</td>
</tr>
<tr>
<td>Metabolism/Nutrition</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Long-term Exposure Safety Profile

Studies 767 and 810
Safety Population and Exposure

*Long-term, open-label, flexible-dose studies*

<table>
<thead>
<tr>
<th>Population</th>
<th>767 (N=214)</th>
<th>810 (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median exposure (weeks)</td>
<td>49</td>
<td>25</td>
</tr>
<tr>
<td>≥3 months treatment (n)</td>
<td>171</td>
<td>28</td>
</tr>
<tr>
<td>≥6 months treatment (n)</td>
<td>157</td>
<td>15*</td>
</tr>
<tr>
<td>Completed Study (n)</td>
<td>145</td>
<td>4*</td>
</tr>
</tbody>
</table>

*Chronic Pancreatitis / Pancreatectomy*

*Study terminated for corporate reasons by former Sponsor*
Deaths

Long-term, open-label, flexible-dose studies

• Two unrelated deaths reported in long-term studies
  – 25-year-old male, died of CF-related respiratory failure and sepsis after 11 months on Study 767
  – 62-year-old male; accidental death due to a house fire 6 weeks after the last dose of study medication. The subject received 8 months of liprotamase treatment in Study 810
### Serious Adverse Events (%)
*Long-term, open-label, flexible-dose studies*

<table>
<thead>
<tr>
<th>Body System</th>
<th>767 (N=214)</th>
<th>810 (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>28.5%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Infections</td>
<td>24.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3.3%</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>General Disorder</td>
<td>0.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Injury/Procedural Complications</td>
<td>0.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

767 SAEs shown for ≥22% of subjects; 810 all SAEs
Hospitalizations: CFF Registry and Study 767

- CFF Registry (n=5,660)
- 767 Annualized (n=214)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent (95% CI) of Subjects Hospitalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized for Any Cause</td>
<td>~45 (±5)</td>
</tr>
<tr>
<td>Hospitalized for Pulmonary Exacerbation</td>
<td>~35 (±5)</td>
</tr>
<tr>
<td>Hospitalized for GI Complication</td>
<td>~3 (±1)</td>
</tr>
</tbody>
</table>
## Common AEs (%)

*Long-term, open-label, flexible-dose studies*

<table>
<thead>
<tr>
<th>Body System</th>
<th>767 (N=214)</th>
<th>810 (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>98.6%</td>
<td>97.4%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>87.9%</td>
<td>89.7%</td>
</tr>
<tr>
<td>Infections</td>
<td>71.5%</td>
<td>48.7%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>59.3%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Investigations</td>
<td>45.8%</td>
<td>51.3%</td>
</tr>
<tr>
<td>General Disorders</td>
<td>29.9%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>26.6%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>18.2%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td>18.2%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Injury/Procedural Complications</td>
<td>17.8%</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

AEs reported in ≥15% of subjects
767: Incidence of GI AEs Decrease Over Time

All subjects, by severity, weekly

Percent of Subjects with Events

Onset Week
767: Incidence of EPI Related GI AEs
All subjects, first 4 weeks of treatment

Percent of Subjects with Events

- Abdominal Pain
- Steatorrhea
- Diarrhea
- Flatulence

- Week 1 (n=214)
- Week 2 (n=207)
- Week 3 (n=207)
- Week 4 (n=205)
### 767: Reasons for Discontinuation from the Study (By age subgroup and overall)

<table>
<thead>
<tr>
<th>Disposition</th>
<th>7 to &lt;12 (n=55)</th>
<th>12 to &lt;17 (n=57)</th>
<th>≥17 (n=102)</th>
<th>Total (N=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Withdrawal</td>
<td>27%</td>
<td>25%</td>
<td>39%</td>
<td>32%</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>15%</td>
<td>12%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Consent Withdrawn</td>
<td>2%</td>
<td>12%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Protocol Non-compliance</td>
<td>6%</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
<td>0%</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>
767: Time to Discontinuation of Treatment due to AE

![Graph showing the percentage of discontinued patients over weeks of treatment.](image-url)
Safety Topics of Interest

- Fibrosing colonopathy
- Hyperuricosemia and hyperuricosuria
- Distal Intestinal Obstruction Syndrome (DIOS)
- Transaminase elevations
Distal Intestinal Obstruction Syndrome (DIOS)

Summary of findings

- 7 DIOS episodes in 6 subjects in all CF studies (433 CF subjects)
  - Three of the 6 subjects continued on treatment with no recurrence of DIOS
  - No surgeries; no deaths

Annualized incidences of DIOS

- All studies: 3.4%
- 767: 1.9%
- Literature: 3.8%* to 22%**

*Cystic Fibrosis Foundation Annual Report 2008
Distal Intestinal Obstruction Syndrome (DIOS)

*Short-term studies*

- 4 (1.4%) of 281 CF subjects
- All events occurred within 5 days of off-enzyme period

<table>
<thead>
<tr>
<th>Study</th>
<th>Age/ Sex</th>
<th>Dose</th>
<th>Onset of DIOS Symptoms during Off-Enzyme Period</th>
<th>Liprotamase Exposure at Time of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC-2A</td>
<td>24/M*</td>
<td>6,500 U</td>
<td>No</td>
<td>20 doses/5 days</td>
</tr>
<tr>
<td></td>
<td>21/M*</td>
<td>130,000 U</td>
<td>Yes</td>
<td>1 dose/1 day</td>
</tr>
<tr>
<td></td>
<td>15/M*</td>
<td>130,000 U</td>
<td>Yes</td>
<td>3 doses/2 days</td>
</tr>
<tr>
<td></td>
<td>726</td>
<td>25/M</td>
<td>32,500 U</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Hx of DIOS or meconium ileus
**Completed the study without recurrence
Distal Intestinal Obstruction Syndrome (DIOS)

Long-term CF Study 767

- 3 (1.4%) of 214 CF subjects

<table>
<thead>
<tr>
<th>Age/ Sex</th>
<th>Day of DIOS</th>
<th>Comments</th>
<th>Hospitalized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/M</td>
<td>Day 7</td>
<td>Hx of meconium ileus; DIOS in TC-2A; Discontinued from treatment</td>
<td>Yes, 1 Day</td>
</tr>
<tr>
<td>21/M</td>
<td>Day 31</td>
<td>Continued on study without recurrence</td>
<td>No</td>
</tr>
<tr>
<td>13/M</td>
<td>Day 85</td>
<td>Continued on study without recurrence</td>
<td>No</td>
</tr>
</tbody>
</table>
CF Liver Disease

• Transaminase elevations frequent and sporadic
  – Present in 16% to 40% of patients with CF*
  – Not predictive of disease severity
  – Not predictive of progression to severe liver disease/cirrhosis

• Severe liver disease/cirrhosis occurs in 5-7% of patients with CF**
  – Diagnosis of severe liver disease/cirrhosis: median age 10 yrs

• Ursodeoxycholic acid used as treatment

*Goss CH. J Cyst Fibros 2007; Columbo C. Hepatology 2002
**CFF Patient Registry Report, 2008
Hy’s Law

- Hy’s law of drug induced hepatotoxicity:
  - No other cause of liver disease
  - ALT/AST >3X ULN AND total bilirubin >2X ULN
Peak ALT and Total Bilirubin on Study

Short-term studies

Peak ALT/ULN vs Peak Total Bilirubin/ULN scatter plot:
- Study 726
- Study TC-2A

Hy’s Law

- 2X ULN
- 3X ULN
Summary of Transaminase Elevations

Short-term studies

• Study TC-2A
  – 6 subjects ALT/AST >5X ULN
    • 2 in mid dose (32,500 U)
      – Both had ALT >2X ULN at BL
    • 4 in high dose (130,000 U)
      – 2 had ALT >2X ULN at BL (1 was >5X ULN); both were on ursodeoxycholic acid
  – None associated with increase in bilirubin
  – No withdrawals due to LFT elevations
Summary of Transaminase Elevations

Short-term studies

• Study 726
  – 4 subjects ALT/AST >5X ULN
    • 2 had ALT >2X ULN at BL; 1 additional on ursodeoxycholic acid
  – None associated with increase in bilirubin
  – No withdrawals due to LFT elevations
Peak ALT and Total Bilirubin on Study

*Long-term, open-label, flexible-dose studies*

- Study 767
- Study 810

Hy’s Law

- 2X ULN
- 3X ULN
Summary of Transaminase Elevations

*Long-term, open-label, flexible-dose studies*

- **Study 767 (N=214)**
  - 48 (22%) subjects had ALT and/or AST >ULN at baseline
  - 21% of subjects taking ursodeoxycholic acid
  - 6 subjects >5X ULN on study
    - 1 was rollover from 726
    - 4/6 completed study
    - 4/6 resolved while continuing liprotamase
  - 3 other subjects withdrew due to transaminase elevations; all <5X ULN
Summary of Transaminase Elevations

Long-term, open-label, flexible-dose studies

• Study 810 (N=39)
  – 5 (12.8%) subjects had ALT and/or AST >ULN at Baseline
  – 2 subjects >5X ULN; 1 occurred in follow-up
  – 1 subject withdrew; elevation <5X ULN
Shifts in ALT from Baseline in Long-term Clinical Trials of Subjects with CF

- **767 (52 Weeks, N=210)**
  - 146 (70%) had no shift
  - 40 (19%) shifted to a worse Grade
    - 16% shifted from Grade 0 to Grade 1
    - 3% shifted to Grade 2; <1% shifted to Grade 3
  - 24 (11%) shifted to a better Grade

- **Inhaled tobramycin study (24 weeks, placebo arm, N=243)**
  - 15% shifted to a worse Grade
    - 12% shifted from Grade 0 to Grade 1
    - 3% shifted from Grade 0 to Grade 2

*Goss CH. J Cyst Fibros 2007*
Safety Summary and Conclusions

- Largest prospective safety experience for a PERT (n=492)
- No major organ safety signals
  - No evidence of dose relationship
  - DIOS: low incidence, temporally associated with off enzyme period
  - No evidence of drug-related hepatotoxicity
- No risk of hyperuricosemia or hyperuricosuria
Key Elements of Risk Management

- **Risk Evaluation**
  - Regular pharmacovigilance of all safety reporting
  - Follow-up Observational Study for DIOS and fibrosing colonopathy using the CFF Patient Registry

- **Risk Mitigation**
  - Prescribing information to physicians
  - MedGuide for patients and care-givers

- **Other elements of risk management under discussion with the review division**
<table>
<thead>
<tr>
<th>Presentation Agenda</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
</tr>
<tr>
<td><strong>Don G. Burstyn, PhD</strong></td>
</tr>
<tr>
<td>Senior Vice President, Regulatory Affairs</td>
</tr>
<tr>
<td>Alnara Pharmaceuticals, Inc</td>
</tr>
</tbody>
</table>

| Exocrine Pancreatic Physiology and Insufficiency |
| **Steven D. Freedman, MD, PhD** |
| Director, The Pancreas Center |
| Beth Israel Deaconess Medical Center |
| Professor of Medicine, Harvard Medical School |

| Disease State Overview and Management of Patients |
| **Drucy Borowitz, MD** |
| Director, CF Center |
| Professor of Clinical Pediatrics |
| Women and Children’s Hospital of Buffalo |

| Summary of Efficacy |
| **Lee R. Brettman, MD, FACP** |
| Chief Medical Officer |
| Alnara Pharmaceuticals, Inc |

| Summary of Safety |
| **Christopher Stevens, MD** |
| Senior Vice President, Clinical Development |
| Alnara Pharmaceuticals, Inc |

| Benefit/Risk Profile |
| **Drucy Borowitz, MD** |
Development Goals for Liprotamase

- Demonstrate safety and efficacy with:
  - Reliable source with reproducible and precise manufacturing process
  - No excess protease, no purines
  - Lower daily pill burden
  - Acid stable / does not need enteric coating
  - Developed with a data-driven approach to dose
Liprotamase: Benefits

• Met clinically meaningful long-term goals of PERT
  – Nutritional status maintained over one year
  – Age appropriate growth and weight gain
  – Reduction of EPI related GI symptoms
  – Maintenance of pulmonary function

• Fewer capsules per day

• Statistically significant improvement in CFA, CNA and ↓ stool weight in two large well controlled trials

• Well tolerated with a favorable safety profile
Liprotamase: Risks

- As with existing PEPs
  - Not all patients will respond adequately
    - Change therapy, if necessary
  - Weight and symptoms should be monitored
    - Individualize dose, if necessary

- Number of capsules is less than with porcine PERTS
  - MedGuide provides guidance and education
Benefit/Risk Conclusion

Based on the balance of the safety and efficacy demonstrated from the liprotamase development program, I believe that the Advisory Committee should recommend approval of liprotamase as an option for EPI patients.
SOLLPURA™
(liprotamase)

Back-up slides
Serial AST Values in CF Patients
Toronto Experience
Liver Biochemistry in 532 Canadian CF Patients: Effect of Pancreatic Phenotype

Pancreatic insufficient

- AST
  - Normal: 35%
  - Abnormal: 16%
- ALP
  - Normal: 45%
  - Abnormal: 16%
- AST±ALP
  - Normal: 0%
  - Abnormal: 6%

Pancreatic sufficient

- AST
  - Normal: 100%
  - Abnormal: 20%
- ALP
  - Normal: 100%
  - Abnormal: 6%
- AST±ASP
  - Normal: 125%
  - Abnormal: 20%
## Phase I/II and Phase III Formulations

<table>
<thead>
<tr>
<th>Component</th>
<th>Content per Capsule (Nominal)</th>
<th>Phase I/II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipase-CLEC Drug Substance</td>
<td></td>
<td>6,500 U</td>
<td>26,000 U</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32,500 U</td>
<td></td>
</tr>
<tr>
<td>Protease Drug Substance</td>
<td></td>
<td>5,000 U</td>
<td>20,000 U</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25,000 U</td>
<td></td>
</tr>
<tr>
<td>Amylase Drug Substance</td>
<td></td>
<td>750 U</td>
<td>3,000 U</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3,750 U</td>
<td></td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td>10.0mg</td>
<td>40.1mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.6mg</td>
<td></td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td>40.0mg</td>
<td>60.0mg</td>
</tr>
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<td></td>
<td></td>
<td>66.7mg</td>
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<tr>
<td>Disintegrant</td>
<td></td>
<td>5.0mg</td>
<td>20.0mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.0mg</td>
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</tr>
<tr>
<td>Glidant</td>
<td></td>
<td>0.75mg</td>
<td>3.0mg</td>
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<td></td>
<td></td>
<td>3.0mg</td>
<td></td>
</tr>
<tr>
<td>Lubricant</td>
<td></td>
<td>0.25mg</td>
<td>1.0mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0mg</td>
<td></td>
</tr>
<tr>
<td>Glidant</td>
<td></td>
<td>0.5mg</td>
<td>2.0mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0mg</td>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td>75.0mg</td>
<td>200.0mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200.0mg</td>
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</tr>
<tr>
<td>Capsule Size</td>
<td></td>
<td>Size 5</td>
<td>Size 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Size 2</td>
<td></td>
</tr>
</tbody>
</table>

M-17
Increased Acidity in Proximal Small Bowel in Patients with CF-EPI

Dissolution of enteric coating requires exposure to pH > 5.5 or 6 for > 10 minutes

Gelfond et al, Pediatr Pulmonol 2010
Long-term maintenance of nutritional status (N=211)
Variability in CFA in Placebo Subjects, Performed Under Same Conditions ~ 1 Month Apart
Fecal Fat in CF Patients on Optimized Doses of Porcine PEPs (N=240 patient studies)

Matching Criteria for CFF Registry Analysis

- Subjects ≥7 years of age
- Diagnosis of CF
- Taking a pancreatic enzyme supplementation
- Not on enteral tube feedings
- Clinically stable with no evidence of acute upper or lower respiratory tract infection
- No signs and/or symptoms of liver cirrhosis or portal hypertension or documented liver disease unrelated to CF
- No history of liver or lung transplant or significant surgical resection of bowel
- Not pregnant, breastfeeding
- No participation in an investigational study of a drug
- No history of fibrosing colonopathy
Change in BMI Z-score Over Time
767 and CFF Registry Population – ≥0.25 Change

- BMI Z-score Improved ≥0.25
- BMI Z-score Worsened ≥0.25

Percent of Subjects

7 - <12 Years 12 - <17 Years ≥17 Years
Characteristics of EPI Pigs

• Ligation of the accessory pancreatic ducts at the head of pancreas

• Pigs develop:
  – Steatorrhea
  – Impaired growth
  – Duodenal pH is reduced that provokes bile acid precipitation
  – Significantly reduced protein and fat absorption and fats-soluble vitamins and minerals

• Similar to dogs and humans with EPI
% CFA after One Week of Treatment with Liprotamase RDT

Data present mean of n=7 EPI pigs and n=4 Healthy pigs, mean of 3 days collection
Triglyceride (TG)

Liprotamase

Healthy Pigs

AUC_{CONT} = 3.6±2.2
AUC_{Lip} = 5.11±2.7

AUC_{LFD} = 2.5±0.6
AUC_{HFD} = 4.1±0.7
767: Mean LOCF BMI Z-scores by Change in CFA
Rollover Subjects Previously Randomized to Liprotamase

Mean US Population

Above the median change in CFA (≥13.7) (n=18)
Below the median change in CFA (<13.7) (n=18)

Study Visit (Month)