

CI-1

CREON[®] (Pancrelipase Delayed-Release Capsules)

NDA 20-725

Solvay Pharmaceuticals, Inc.

CI-2

Introduction

Victor Raczkowski, MD

Vice President

US Regulatory Affairs

Solvay Pharmaceuticals, Inc.

CI-3

CREON Proposed Indication

Treatment of patients with maldigestion
due to exocrine pancreatic insufficiency

CI-4

Agenda

| | |
|--|---|
| Introduction | Victor Raczowski, MD <i>VP, US Regulatory Affairs, Solvay Pharmaceuticals, Inc.</i> |
| Medical Need | Virginia Stallings, MD <i>Director, Nutrition Center Professor of Pediatrics Children's Hospital of Philadelphia</i> |
| Clinical Efficacy & Safety | Earl Sands, MD <i>VP, Research & Development Solvay Pharmaceuticals, Inc.</i> |
| Assessment of Porcine Viruses | X.J. Meng, MD, PhD <i>Professor of Molecular Virology College of Veterinary Medicine VA Polytechnic Institute and State University</i> |
| Viral Risk Identification and Evaluation | Earl Sands, MD <i>VP, Research & Development Solvay Pharmaceuticals, Inc.</i> |

CI-5

Exocrine Pancreatic Insufficiency (EPI)

- ◆ Deficiency of digestive enzymes impairs nutrition
 - Lipases: Digest fats
 - Proteases: Digest proteins
 - Amylases: Digest carbohydrates
- ◆ Comorbidity of serious conditions
 - Cystic fibrosis
 - Chronic pancreatitis
 - Pancreatectomy
- ◆ PERT essential for adequate nutrition

CI-6

Medical Need

- ◆ Exocrine pancreatic insufficiency results from serious medical conditions
- ◆ Good nutrition is a vital component of treatment
- ◆ “No treatment” is not an option
- ◆ No FDA-approved treatments available

CI-7

Solvay Pharmaceuticals and CREON

- ◆ Preceded passage of FD&C Act of 1938
- ◆ Solvay Pharmaceuticals: 100+ years of experience with pancreatic enzyme products
- ◆ CREON (currently marketed product/CMP) available since 1993
- ◆ 5 million patient-years experience
- ◆ To be marketed product (TbMP)
 - Refined and improved version of CMP
 - Active ingredient: in-house pancrelipase
 - Formulation adjusted to meet current regulatory requirements

CI-8

CREON Efficacy

- ◆ Positive efficacy study in patients with cystic fibrosis (S245.3.126)
 - Improvement of Coefficient of Fat Absorption (CFA)
 - Improvement of symptoms
- ◆ Consistent with pooled CREON efficacy data from studies over 20 years

CI-9

Clinical Safety

- ◆ Generally safe and well tolerated
 - Clinical trial experience (> 1500 patients)
 - Postmarketing experience:
 - Abdominal pain, diarrhea, nausea/vomiting, flatulence, constipation, rash, pruritus, urticaria
 - No pattern of viral illness / conditions

CI-10

Solvay's Approach to Viral Safety in Production

- ◆ Robust and validated system for reducing viral loads
 - Careful sourcing of pancreatic glands
 - Viral inactivation in manufacturing steps
 - Release testing
- ◆ Enveloped viruses are effectively inactivated
- ◆ Realistic risks from non-enveloped viruses are low

CI-11

Viral Risk Identification and Evaluation Proposal

- ◆ **Retrospective data analysis**
 - US claims (MarketScan)
 - UK medical records (GPRD)
- ◆ **Prospective observation and evaluation**
 - Active clinical surveillance
 - Sentinel sites to collect biomaterial
- ◆ **Labeling considerations**

CI-12

Key Points Today

- ◆ **EPI serious condition affecting infants through adults**
- ◆ **Established clinical experience with CREON**
 - 25 years, 5 million patient years
- ◆ **Outcomes of manufacturing**
 - Enveloped viruses are effectively inactivated
 - Realistic risks from non-enveloped viruses are low
- ◆ **Viral risk identification and evaluation**
 - Rapid identification of safety signals
 - Prompt reaction to safety signals

CI-13

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CM-1

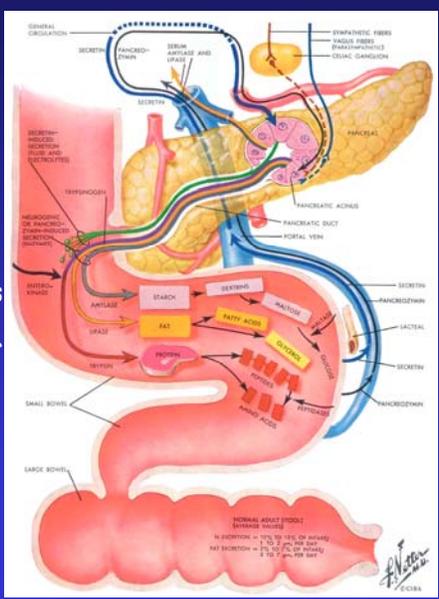
Medical Need

Virginia Stallings, MD
Director, Nutrition Center
Professor of Pediatrics
Children's Hospital of Philadelphia

CM-2

Exocrine Pancreatic Insufficiency

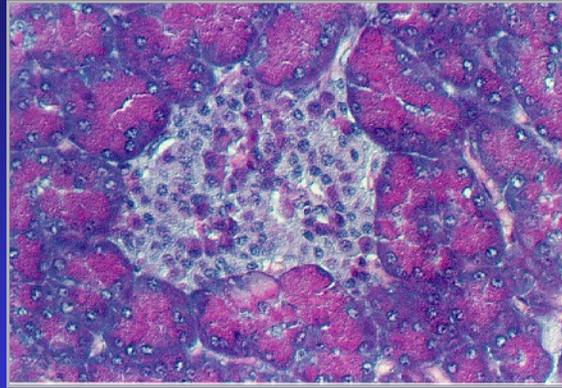
©Netter Atlas of Physiology. The Ciba Collection 1980



- Inability to digest food due to a lack of digestive enzymes secreted by the pancreas
- Goal to optimize digestion and prevent malnutrition

CM-3

Acinar and Ductal Cell Damage → EPI



<http://images.google.com/imgres?imgurl=http://cellbio.utmb.edu/microanatomy/endocrines/pancreas1.jpg&imgrefurl=http://cellbio.utmb.edu/microanatomy/endocrines/endocrines.htm>

CM-4

Exocrine Pancreatic Insufficiency

INHERITED

- Cystic Fibrosis (CF)
- Shwachman-Diamond Syndrome
- Pearson Pancreas / Marrow Syndrome
- Pancreatic Agenesis
- Hereditary Pancreatitis
- Isolated Enzyme Deficiencies

ACQUIRED

- Chronic Pancreatitis (CP)
- Pancreatic Surgery
- Acute Severe Pancreatitis
- Tropical Calcific Pancreatitis

CM-5

Clinical Signs and Symptoms

- Maldigestion, malabsorption, and malnutrition
 - Fat calories (9 kcal/g), fat soluble vitamins A, D, E, K, essential fatty acids, zinc, calcium, selenium
- Abdominal pain, flatulence, steatorrhea
- Growth failure in children (weight, stature, head/brain)
- Weight loss in adults
- Altered body composition (lean, fat, bone mass)
- Morbidity and mortality

Haaber, et al. *Int J Pancreatology*. 2000;27:1-27.
Quilliot, et al. *Pancreas*. 2001;22:299-306.

Mann, et al. *Metabolism*. 2003;52:579-658.
Konstan, et al. *J Pediatr*. 2003;142:624-630.

CM-6





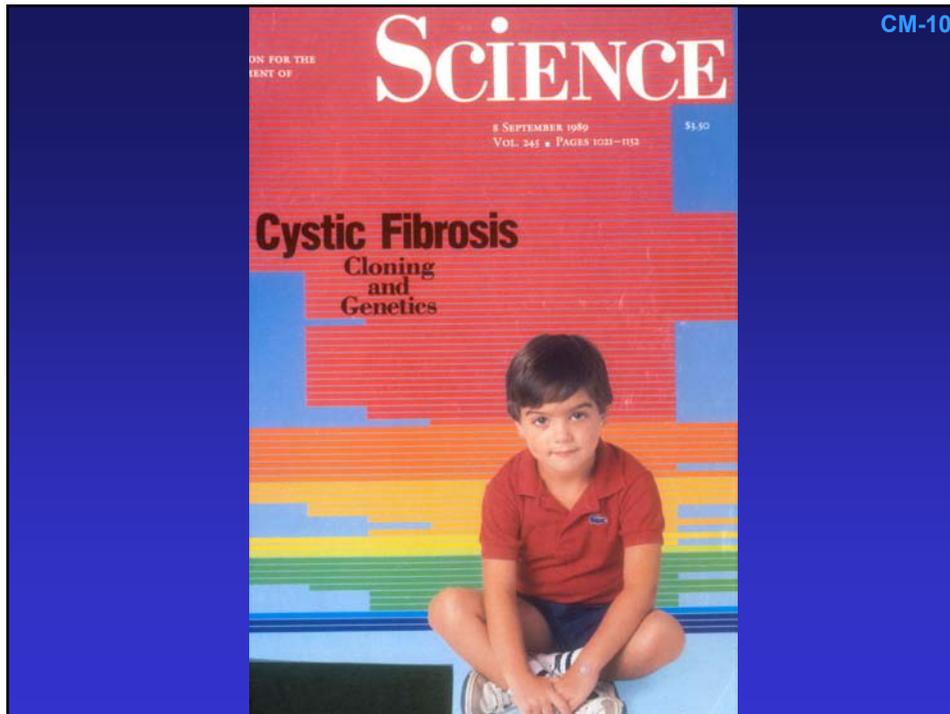
CM-9

Pancreatic Enzyme Replacement Therapy (PERT)

- Enzyme classes lipase, protease and amylase
- Orally during meals and snacks
- Dose determined by severity of EPI and fat intake of meal or snack
- Enzymes and food to duodenal lumen for digestion of fat, protein and carbohydrate

Dominguez-Munoz, et al. *Aliment Pharmacol Ther.* 2005;21:993-1000.
Dominguez-Munoz, et al. *Clin Gastro Hepatol.* 2007;5:484-488.
Ferrone, et al. *Pharmacotherapy.* 2007;27:910-920.

CM-10



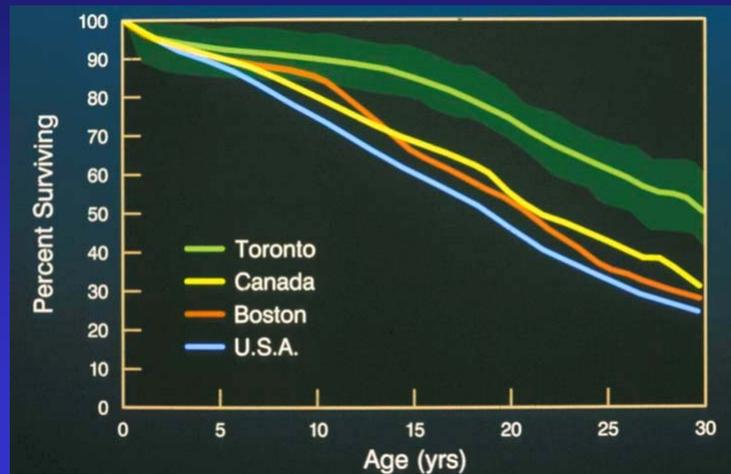
CM-11

Cystic Fibrosis

- ~30,000 patients in USA
 - Chronic lung disease (FEV₁)
 - ~90% EPI with maldigestion and malabsorption
 - ↓ Bicarbonate, fluid secretion, bile acid pool
-
- Newborn screening in future
 - Survival: 25 yrs in 1985 to > 37 yrs today

CM-12

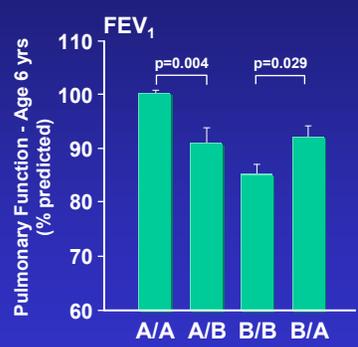
1972 - 1981 CF Survival Curves Canada and USA



Corey, et al. *J Clin Epidemiol.* 1988;41:583-91.

CM-13

FEV₁ % Predicted and Pattern of Change in Wt-for-Age %tile Between Age 3 and 6

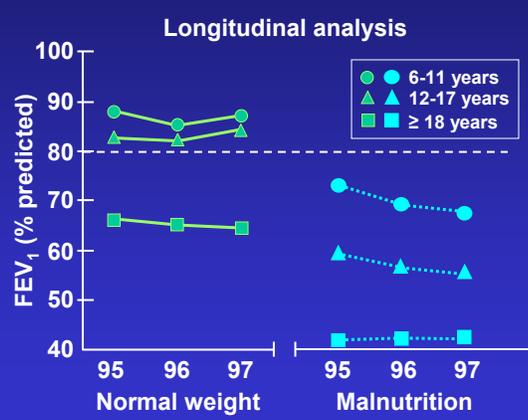


- Patients with malnutrition at age 3 → lower lung function at age 6 yr

Konstan, et al. *J Pediatr.* 2003;142:624-630.
 Values are mean ± SEM, adjusted for weight at age 3 yrs. A/A = Above/Above (>10th to >10th), N = 688 (74%); A/B = Above/Below (>10th to <10th), N = 55 (6%); B/B = Below/Below (<10th to <10th), N = 104 (11%); B/A = Below/ Above (<10th to >10th), N = 84 (9%).

CM-14

FEV₁ % Predicted in Children with/without Malnutrition German Quality Assurance Project



- Patients with malnutrition had lower FEV₁ in all age groups

Steinkamp & Wiedemann. *Thorax.* 2003;57:596-601.

CM-15

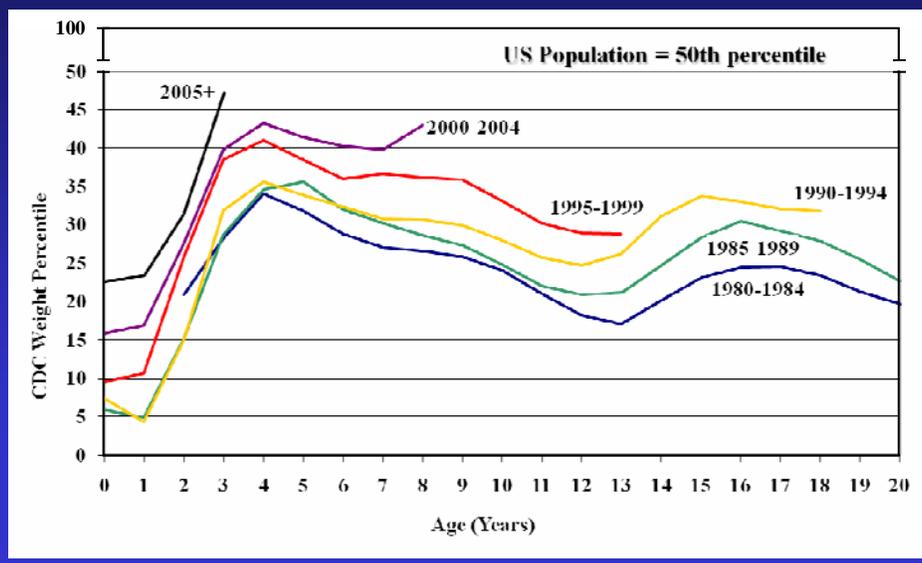
CF Guidelines Support Enzyme Replacement Therapy

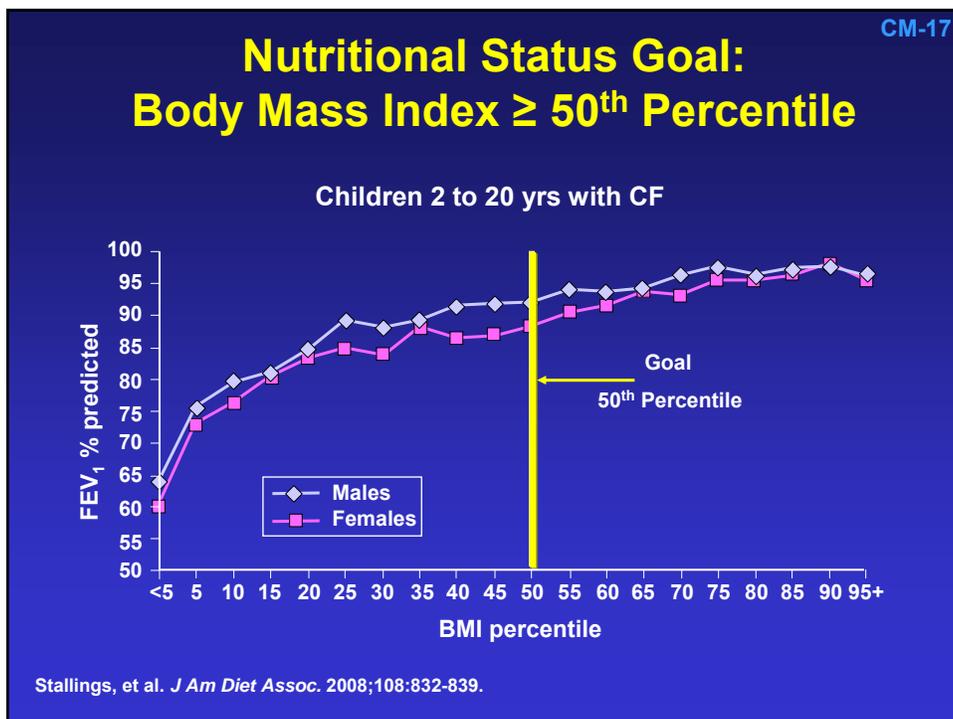
- 2008 CF evidence-based practice guidelines
- ↑ energy intake → ↑ weight gain
- ↑ height- and weight-for-age, weight-for-height percentiles associated with better pulmonary function and survival
- Comprehensive nutrition management
- Higher fat intake and PERT

Stallings, et al. *J Am Diet Assoc.* 2008;108:832-839.

CM-16

Median Weight Percentiles by Age by Birth Cohort





CM-18

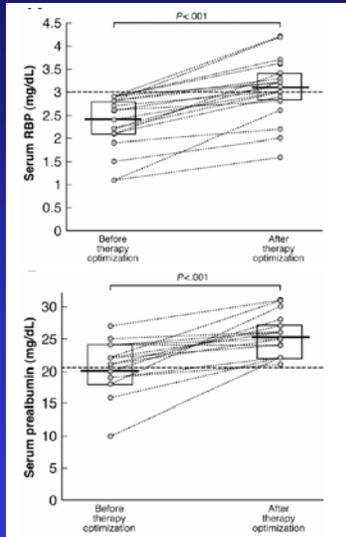
Chronic Pancreatitis

- Inflammatory condition → permanent structural changes
- Most frequent cause of EPI
 - 8.2 per 100,000 in US (2004)
- Steatorrhea, weight loss and malnutrition
- Post-pancreatic resection → 35 to 74% EPI (CP, cancer)

Gupta and Toskes. *Postgrad Med J.* 2005;81:491-497.

CM-19

CP and EPI with PERT



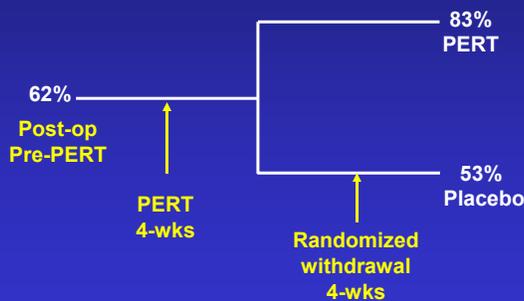
- Benefit of 1 yr of optimized PERT
- Body weight (kg): 68 ± 12 vs 72 ± 13
- RBP (mg/dl): 2.4 ± 0.6 vs 3.1 ± 0.6
- Pre-albumin (mg/dl): 20.7 ± 4.1 vs 25.2 ± 3.1

Dominguez-Munoz, et al. *Clin Gastro Hepatol.* 2007;5:484-488.

CM-20

Benefit of PERT in Partial Pancreatectomy

CFA and enzyme supplementation in CP after surgery⁵



- PERT benefits some patients post-op
- PERT prevents fat maldigestion and improves post-op nutritional status

1. Han, et al. *Hepatogastroenterology.* 2007;54:1831. 2. Armstrong, et al. *Pancreatology.* 2002;2:528.
 3. Ghaneh. *Digestion.* 1999;60(S1):104-110. 4. Braga. *Int J Pancreatol.* 1989;5(S):37-44.
 5. van Hozen, et al. *Pancreas.* 1997;13:174-180.

CM-21

Conclusions

- **Cystic Fibrosis with EPI**
 - Lifelong PERT is essential for digestion and maintenance of optimal nutritional status, and supports lung health (FEV_1)
- **Chronic Pancreatitis and Pancreatic Surgery**
 - Lifelong PERT is essential for most patients with CP and for a subset of patients with pancreatic surgery to support nutritional status and health
- **Evidence and Consensus Conference-based guidance (US and European) include PERT as the cornerstone of EPI treatment**

1. Borowitz, et al. *J Pediatr Gastroenterol Nutr.* 2002;35:246-259. 2. Sinaasappel, et al. *J Cyst Fibros.* 2002;1:51-75. 3. Nutrition For Your Infant With Cystic Fibrosis. Bethesda, MD: Cystic Fibrosis Foundation 2002. 4. Nutrition For Your Child With Cystic Fibrosis (Four to Seven Years). Bethesda, MD: Cystic Fibrosis Foundation 2002. 5. Nutrition For Your Toddler With Cystic Fibrosis (One to Three Years). Bethesda, MD: Cystic Fibrosis Foundation 2002. 6. Nutrition For Teens With Cystic Fibrosis. Bethesda, MD: Cystic Fibrosis Foundation 2002. 7. AWMF Guideline Register 021/003 – Z Gastroenterol 1998, 36, 359-367. Stallings, et al. *J Am Diet Assoc.* 2008;108:832-839.

CM-22



CM-23

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CE-1

Clinical Efficacy and Safety

Earl Sands, MD
Vice President
Research & Development
Solvay Pharmaceuticals, Inc.

CE-2

Agenda

- ◆ Cystic Fibrosis (CF)
 - S245.3.126
 - Additional efficacy and safety data
- ◆ Chronic Pancreatitis (CP) and Pancreatectomy (PY)
 - Additional efficacy and safety data
- ◆ Conclusions

CE-3

Study Design

Study S245.3.126

- ◆ Double-blind, placebo-controlled, two-period crossover study
- ◆ Main inclusion criteria
 - CF subjects aged ≥ 12 yrs
 - Fecal elastase $< 50 \mu\text{g} / \text{g}$ stool
- ◆ Target dose: 4,000 U lipase / g fat / day
- ◆ Individualized diet
 - Containing over 40% calories from fat
 - Identical daily diet in both crossover periods

CE-4

CFF Consensus Dosing Guidelines

- ◆ Recommended starting doses for infants and children in lipase units:
 - < 12 mo: 2,000 - 4,000 U per 120 mL formula or per breast-feed
 - < 4 yrs: 1,000 U / kg / meal
 - > 4 yrs: 500 U / kg / meal
- ◆ Doses $> 2,500$ U / kg / meal should be used with caution and only if documented to be effective by 3-day fecal fat measures indicating a significantly improved CFA
- ◆ Total dose should not usually be $> 10,000$ U / kg / day or $> 4,000$ U / g fat / day
- ◆ CREON dosing was consistent with these dosing guidelines

Borowitz, et al. *J Pediatr Gastroenterol Nutr.* 2002;35:246-259.
Stallings, et al. *J Am Diet Assoc.* 2008;108:832-839.

CE-5

Endpoints

Study S245.3.126

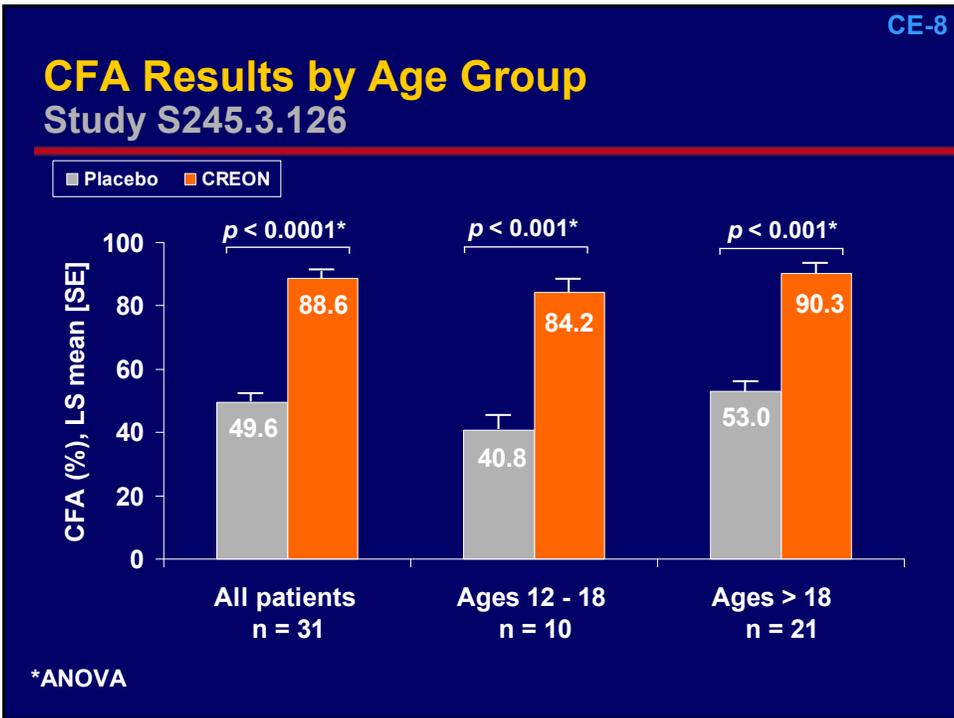
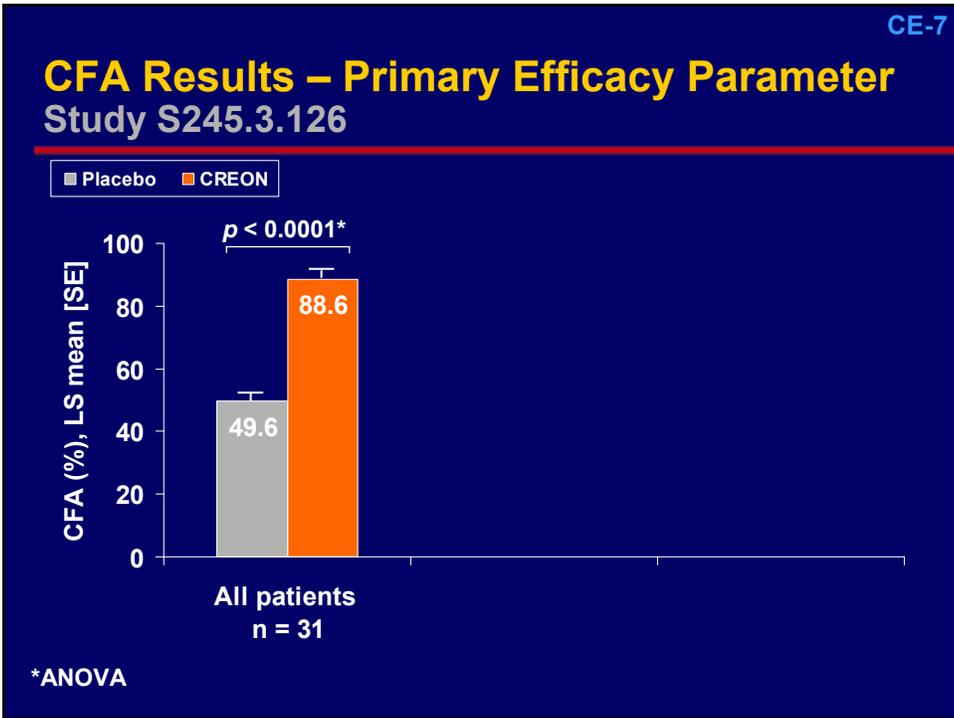
- ◆ **Primary endpoint**
 - Coefficient of Fat Absorption (CFA)
 $100 \times (\text{fat intake} - \text{fat excretion}) / (\text{fat intake})$
- ◆ **Secondary endpoints**
 - Coefficient of Nitrogen Absorption (CNA)
 - Clinical symptomatology (abdominal pain, flatulence, stool consistency, stool frequency)
 - Safety and tolerability

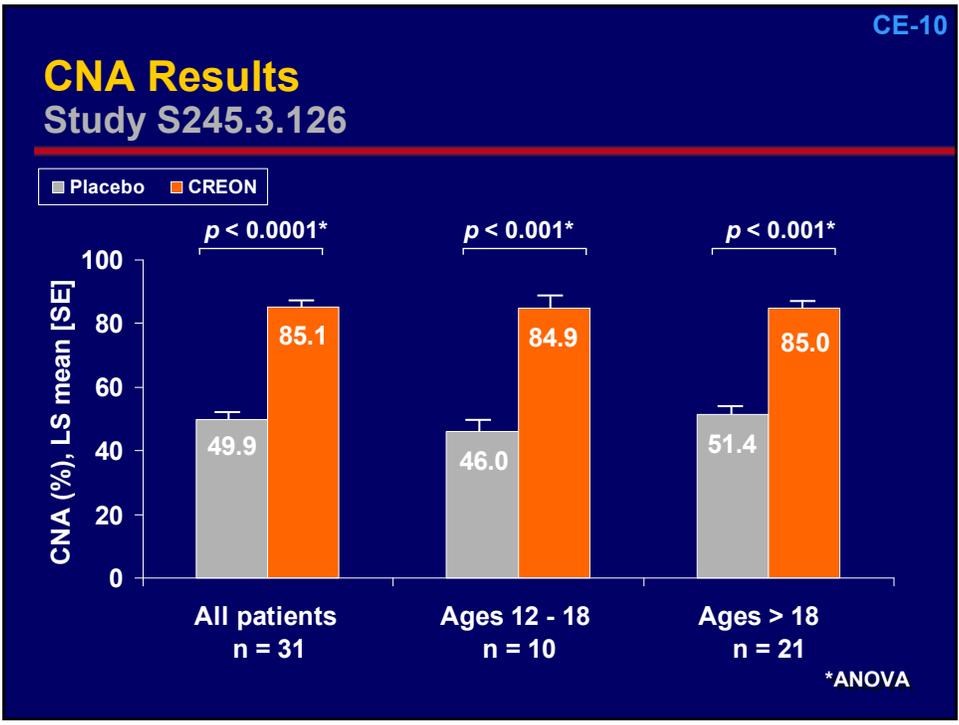
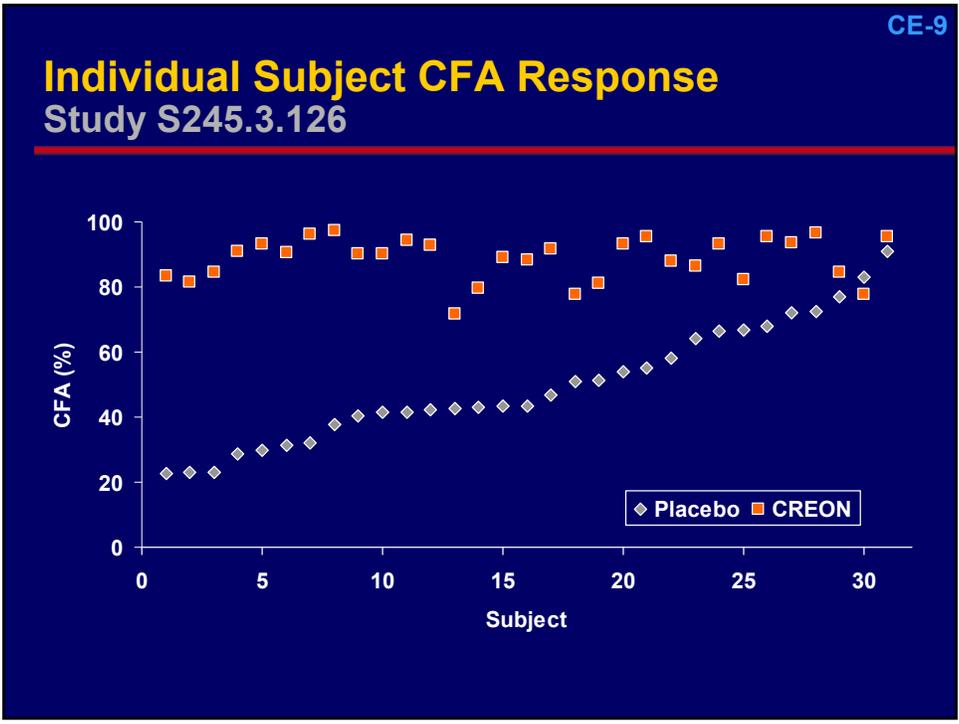
CE-6

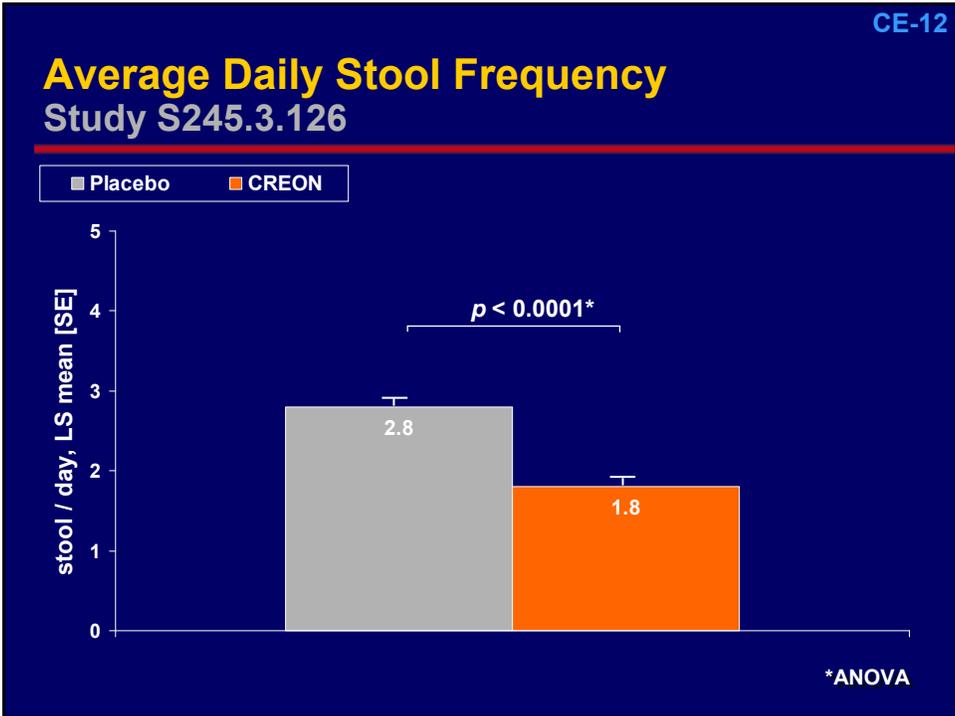
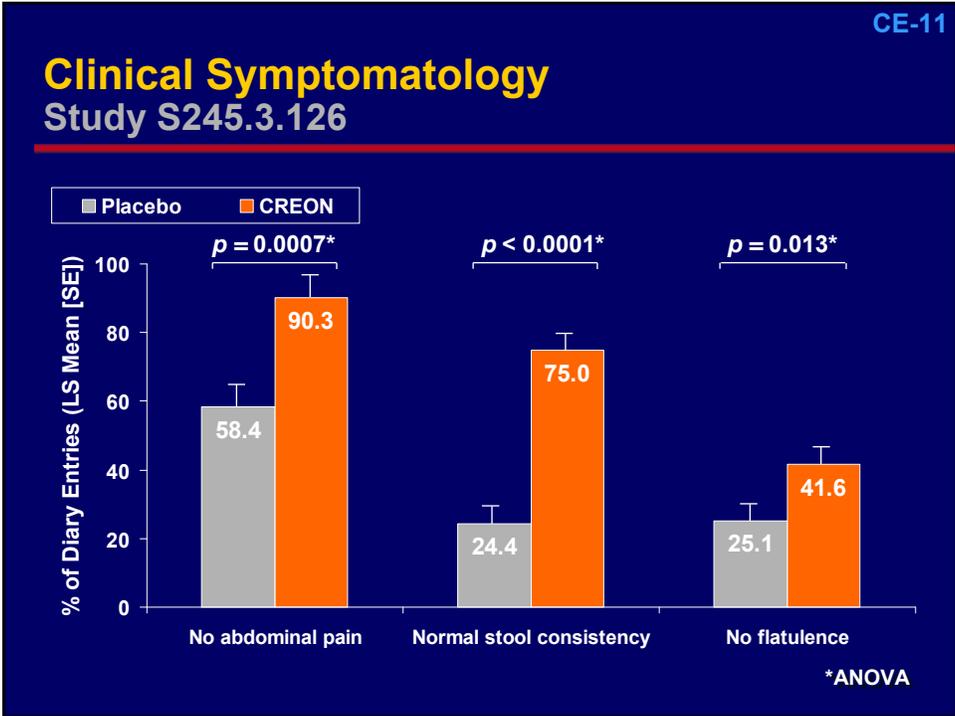
Demographics and Disposition

Study S245.3.126

- ◆ **Safety sample (n = 32)**
 - Gender: 21 male; 11 female
 - Age
 - Mean age: 23 yrs
 - Age range: 12 - 43 yrs
 - 11 subjects \leq 18 yrs
- ◆ **Evaluable for efficacy (n = 31)**
 - One drop-out after 1st crossover period







CE-13

TEAEs (> 1 Patient in Any Group)

Study S245.3.126

| | Patients, n (%) | | |
|----------------------|-----------------|----------|-------------------|
| | CREON | Placebo | CREON and placebo |
| Patients | 32 | 31 | 31 |
| Abdominal pain | 2 (6.3) | 7 (22.6) | 1 (3.2) |
| Abdominal pain upper | 0 | 3 (9.7) | 0 |
| Abnormal feces | 0 | 5 (16.1) | 1 (3.2) |
| Flatulence | 0 | 5 (16.1) | 3 (9.7) |
| Weight decrease | 1 (3.1) | 2 (6.5) | 0 |
| Dizziness | 2 (6.3) | 0 | 0 |
| Headache | 1 (3.1) | 7 (22.6) | 1 (3.2) |

TEAE = Treatment-emergent adverse event.

CE-14

Efficacy and Safety Summary

Study S245.3.126

- ◆ CREON treatment significantly improves CFA
- ◆ CREON treatment significantly improves CNA and maldigestion symptomatology
- ◆ The overall incidence of adverse events is higher in the placebo period and driven by GI disorders

CE-15

Additional Efficacy and Safety Data in Cystic Fibrosis

CE-16

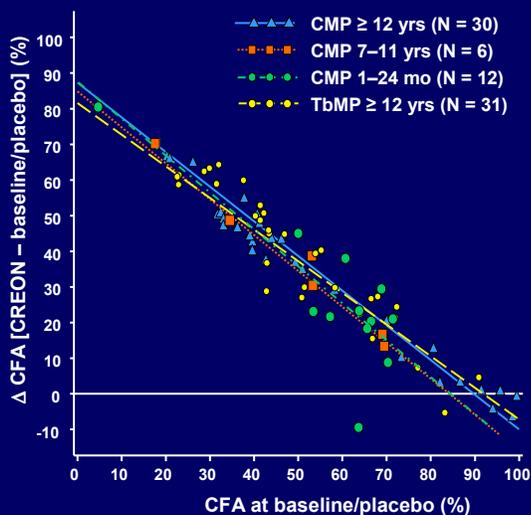
Mean CFA (%) Controlled Studies in Cystic Fibrosis

| Study | n | Ages CREON | Baseline/ Placebo | Δ CFA | CREON |
|-------|----|---------------|----------------------|--------------|-------|
| 3126 | 31 | 12 - 43 yr | 49.8 | 38.8 | 88.6 |
| 3003 | 12 | 1 - 24 mo | 58.0 | 26.7 | 84.7 |
| 3101* | 19 | 8 - 17 yr | 52.2 | 34.9 | 87.1 |
| 3102* | 18 | 18 - 53 yr | 50.9 | 36.9 | 87.8 |

* Values for placebo-treated patients only

CE-17

Pooled CFA Data from Controlled Studies



◆ Regardless of age, formulation, or study design, subjects with the same baseline CFA experience the same improvement in CFA

CE-18

Summary of Adverse Events Multiple Dose Studies in Cystic Fibrosis

| | Patients, n (%) | | | | |
|--------------------------------|-----------------|-----------|------------|------------|-----------|
| | Age, yr | | | | |
| | 0 to < 4 | 4 to 12 | > 12 to 18 | > 18 to 30 | > 30 |
| Patients | 55 | 143 | 102 | 73 | 15 |
| Deaths | 0 | 0 | 0 | 1 (1.4) | 0 |
| ≥ 1 TESAE | 2 (3.6) | 5 (3.5) | 8 (7.8) | 2 (2.7) | 0 |
| ≥ 1 TEAE leading to withdrawal | 1 (1.8) | 1 (0.70) | 2 (2.0) | 2 (2.7) | 1 (6.7) |
| ≥ 1 TEAE | 39 (70.9) | 75 (52.5) | 57 (55.9) | 37 (50.7) | 11 (73.3) |

TEAE = Treatment-emergent adverse event.
TESAE = Treatment-emergent serious adverse event.

CE-19

TEAEs Across Age Groups

Multiple Dose Studies in Cystic Fibrosis

| n (%) | Patients, n (%) | | | | |
|-----------------------------|-----------------|-----------|-----------|-----------|-----------|
| | Age, yr | | | | |
| | 0 to <4 | 4 to 12 | >12 to 18 | >18 to 30 | >30 |
| Patients | 55 | 143 | 102 | 73 | 15 |
| Any TEAE* | 39 (70.9) | 75 (52.5) | 57 (55.9) | 37 (50.7) | 11 (73.3) |
| Conjunctivitis | 3 (5.5) | 0 | 1 (1.0) | 1 (1.4) | 0 |
| Flatulence | 0 | 2 (1.4) | 2 (2.0) | 4 (5.5) | 3 (20.0) |
| Toothache | 4 (7.3) | 0 | 0 | 0 | 0 |
| Constipation | 4 (7.3) | 4 (2.8) | 2 (2.0) | 2 (2.7) | 0 |
| Hyperthermia | 2 (3.6) | 0 | 0 | 0 | 0 |
| Bronchitis | 5 (9.1) | 2 (1.4) | 1 (1.0) | 3 (4.1) | 0 |
| Nasopharyngitis | 5 (9.1) | 3 (2.1) | 2 (2.0) | 0 | 0 |
| Rhinitis | 3 (5.5) | 3 (2.1) | 1 (1.0) | 0 | 0 |
| Respiratory tract infection | 2 (3.6) | 0 | 1 (1.0) | 0 | 0 |
| Cough | 9 (16.4) | 17 (11.9) | 11 (10.8) | 7 (9.6) | 0 |
| Bronchial obstruction | 3 (5.5) | 2 (1.4) | 1 (1.0) | 0 | 0 |

* > 2% difference of youngest or oldest age group as compared to the other age groups.

CE-20

Conclusions

Cystic Fibrosis

- ◆ Efficacy and safety results for CREON are not different across formulations and age groups
- ◆ CREON is safe and effective for the treatment of maldigestion due to CF

CE-21

Mean CFA (%)

Controlled Studies in CP and PY

| Study | n | Disease | Baseline | Δ CFA | CREON |
|----------|----|---------|----------|-------|-------|
| 223.2.01 | 12 | CP | 49.9 | 36.7 | 86.6 |
| 3115* | 12 | CP | 77.9 | 11.4 | 84.9 |
| 3115* | 21 | PY | 62.2 | 21.3 | 82.6 |

* 3 g CREON / Day.
 CP - Chronic Pancreatitis.
 PY - Pancreatic Surgery.

CE-22

Summary of TEAEs in CP and PY

| Disease | Patients, n (%) | | | | All Multiple Dose Studies | |
|--------------------------------|--------------------|-----------|-----------|-----------|---------------------------|-----------|
| | Placebo-Controlled | | | | CP | PY |
| | CP | PY | CP | PY | CP | PY |
| Treatment | CREON | Placebo | CREON | Placebo | CREON | |
| Patients | 55 | 45 | 44 | 22 | 132 | 137 |
| ≥ 1 TEAE | 24 (43.6) | 14 (31.1) | 29 (65.9) | 13 (59.1) | 70 (53.0) | 91 (66.4) |
| ≥ 1 TESAE | 1 (1.8) | 2 (4.4) | 0 | 1 (4.5) | 4 (3.0) | 16 (11.7) |
| ≥ 1 TEAE leading to withdrawal | 0 | 0 | 0 | 0 | 2 (1.5) | 3 (2.2) |
| TE deaths | 0 | 0 | 0 | 0 | 0 | 0 |

TEAE = Treatment emergent adverse event.
 TESAE = Treatment emergent serious adverse event.

CE-23

TEAEs > 5% in Any Group, GI Disorders Only Chronic Pancreatitis

| | Patients, n (%) | | |
|----------------------|--------------------|-----------|---------------------------|
| | Placebo-Controlled | | All multiple dose studies |
| | CREON | Placebo | CREON |
| Patients | 55 | 45 | 132 |
| Any TEAE | 24 (43.6) | 14 (31.1) | 70 (53.0) |
| Abdominal distension | 3 (5.5) | 0 | 9 (6.8) |
| Abdominal pain | 1 (1.8) | 2 (4.4) | 9 (6.8) |
| Constipation | 5 (9.1) | 1 (2.2) | 9 (6.8) |
| Nausea | 2 (3.6) | 0 | 9 (6.8) |
| Diarrhea | 1 (1.8) | 1 (2.2) | 7 (5.3) |

TEAE = Treatment emergent adverse event

CE-24

TEAEs > 5% in Any Group in Placebo-Controlled Studies Pancreatectomy

| | Patients, n (%) | | |
|----------------------|--------------------|-----------|---------------------------|
| | Placebo-Controlled | | All multiple dose studies |
| | CREON | Placebo | CREON |
| Patients | 44 | 22 | 137 |
| Any TEAE | 29 (65.9) | 13 (59.1) | 91 (66.4) |
| Abdominal pain | 5 (11.4) | 2 (9.1) | 20 (14.6) |
| Diarrhea | 7 (15.9) | 3 (13.6) | 19 (13.9) |
| Abdominal distension | 2 (4.5) | 3 (13.6) | 14 (10.2) |
| Vomiting | 3 (6.8) | 0 | 14 (10.2) |
| Hyperglycemia | 5 (11.4) | 0 | 13 (9.5) |
| Back pain | 3 (6.8) | 0 | 13 (9.5) |
| Headache | 4 (9.1) | 0 | 12 (8.8) |

TEAE = Treatment emergent adverse event

CE-25

Conclusions

Chronic Pancreatitis and Pancreatectomy

- ◆ CREON is effective and safe in patients with maldigestion due to CP and PY
- ◆ Most frequently reported TEAEs were gastrointestinal symptoms representative of underlying disease

CE-26

Overall Clinical Efficacy and Safety Conclusions

- ◆ CREON improves maldigestion
 - CFA, CNA and symptomatology
 - Efficacy regardless of age and etiology
- ◆ CREON is safe
 - Favorable safety profile in all age groups
 - Adverse event rates less or similar to placebo
 - Most adverse events are related to the underlying disease

CE-27

Agenda

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| Introduction | Victor Raczkowski, MD <i>VP, US Regulatory Affairs</i> <i>Solvay Pharmaceuticals, Inc.</i> |
| Medical Need | Virginia Stallings, MD <i>Director, Nutrition Center</i> <i>Professor of Pediatrics</i> <i>Children's Hospital of Philadelphia</i> |
| Clinical Efficacy & Safety | Earl Sands, MD <i>VP, Research & Development</i> <i>Solvay Pharmaceuticals, Inc.</i> |
| Assessment of Porcine Viruses | X.J. Meng, MD, PhD <i>Professor of Molecular Virology</i> <i>College of Veterinary Medicine</i> <i>VA Polytechnic Institute and State University</i> |
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DMC- 1

Risk Assessment of Viruses Potentially Present in Porcine-derived Products Intended for Human Use

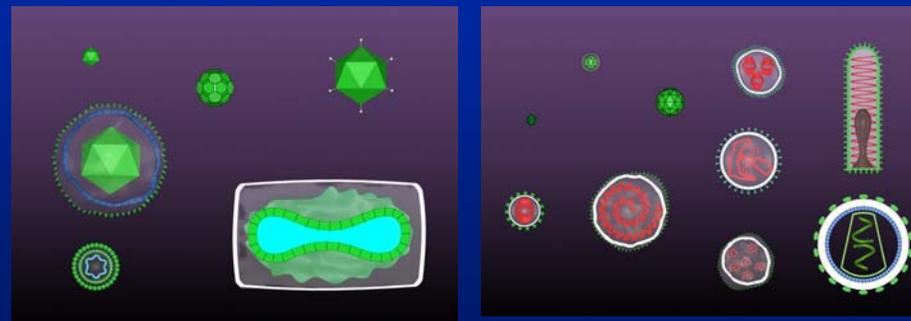
XJ Meng, MD, PhD
Professor of Molecular Virology

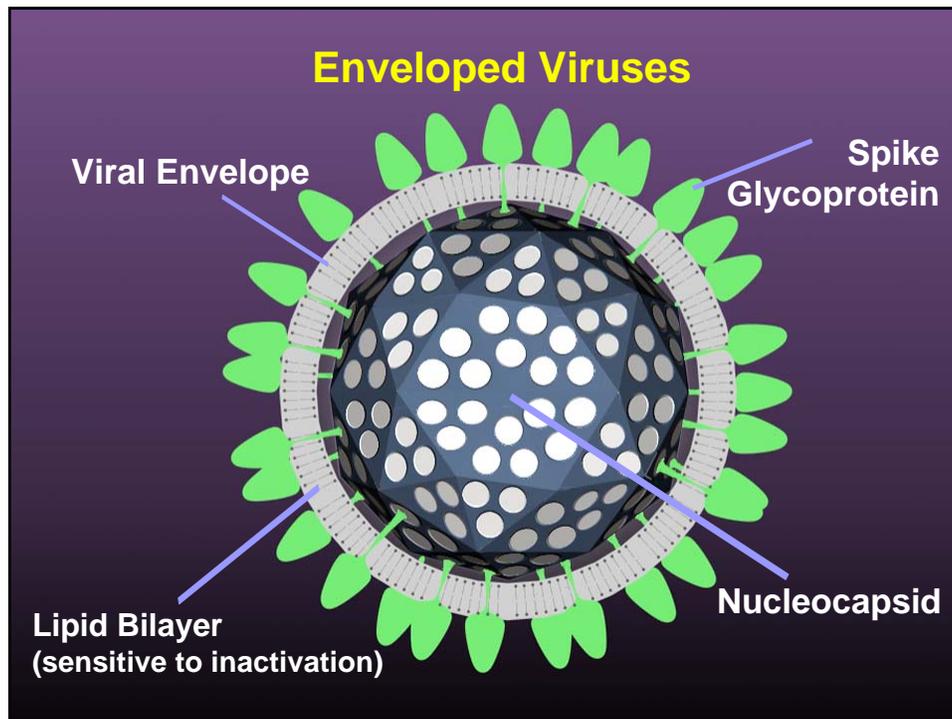
Center for Molecular Medicine and Infectious Diseases
College of Veterinary Medicine
Virginia Polytechnic Institute and State University
Blacksburg, Virginia

DMC- 2

Viruses of Swine

- **Exogenous and indigenous swine viruses:** More than 30 different viruses
- **Detection:** tremendous challenges in detection and control
- **General classification:** Enveloped viruses, and non-enveloped viruses





Biological Characteristics of Enveloped Viruses

DMC- 4

- **Inactivation:** Very sensitive to inactivation by chemical, physical and environmental forces including temperature and lipid solvent
- **Epidemiology:** short period of survival, relatively easier to eliminate, generally causing seasonal diseases

The electron micrograph shows two distinct components of a herpesvirus: a spherical **nucleo-capsid** on the left and a larger, more complex **envelope** on the right. A scale bar indicates 0.1 μm. The caption below the image reads: "Porcine alphaherpesvirus nucleo-capsid and envelope separated."

A herpesvirus

Enveloped Swine Viruses with Known or Potential Zoonotic Risk

DMC- 5

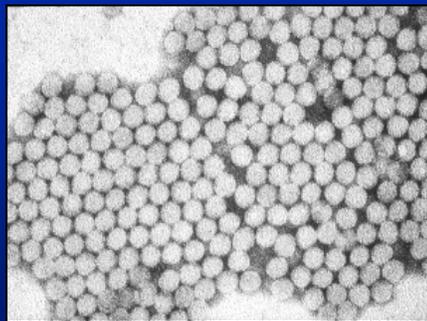
All are effectively inactivated by heat at 56 - 60°C for 30 - 60 min

| Enveloped Viruses | Heat Inactivation |
|---|--|
| Swine influenza virus | Inactivated for 30 - 60 min at 56 - 60°C (De Flora and Badolati, 1973; Swayne and Beck, 2004; Swayne, 2006) |
| Japanese B encephalitis virus | Inactivated at 56°C for 30 min (Joo and Chu, 1999) |
| West Nile virus | Inactivated in whole blood after 30 min at 56°C (Burke and Monath, 2001); Loss of infectivity over 6 orders of magnitude after 30 min at 60°C (Remington, et al. 2004) |
| Vesicular stomatitis virus | 6 log titer reduction at 60°C for 1 hr (Abe H, et al. 2001) |
| Eastern equine encephalomyelitis virus | 6 log titer reduction at 60°C for 30 hr (Espindola, et al. 2006); Inactivated at 65°C for 15 min (Lelie PN, et al. 1987) |
| Hantavirus | All 4 hantaviruse completely inactivated after heating for 1 hr at 60°C (Saluzzo JF, et al. 1998) |
| Rabies virus | Total loss of infectivity within 96 hrs at 37°C (Matouch, et al. 1987); Inactivated at 56°C for 30 min (White, 1982) |
| Porcine paramyxoviruses (Menangle and Nipah viruses) | Inactivated at 56°C for 30 min (Cernik K, et al. 1985), and at 56°C for 4 hrs (Stephano, 1999) |

Non-Enveloped Viruses

DMC- 6

- **“Naked” virus:** Only nucleocapsid
- **Inactivation:** more resistant to inactivation by chemical, physical and environmental forces
- **Epidemiology:** longer period of survival, more difficult to eliminate, causing non-seasonal diseases



A picornavirus

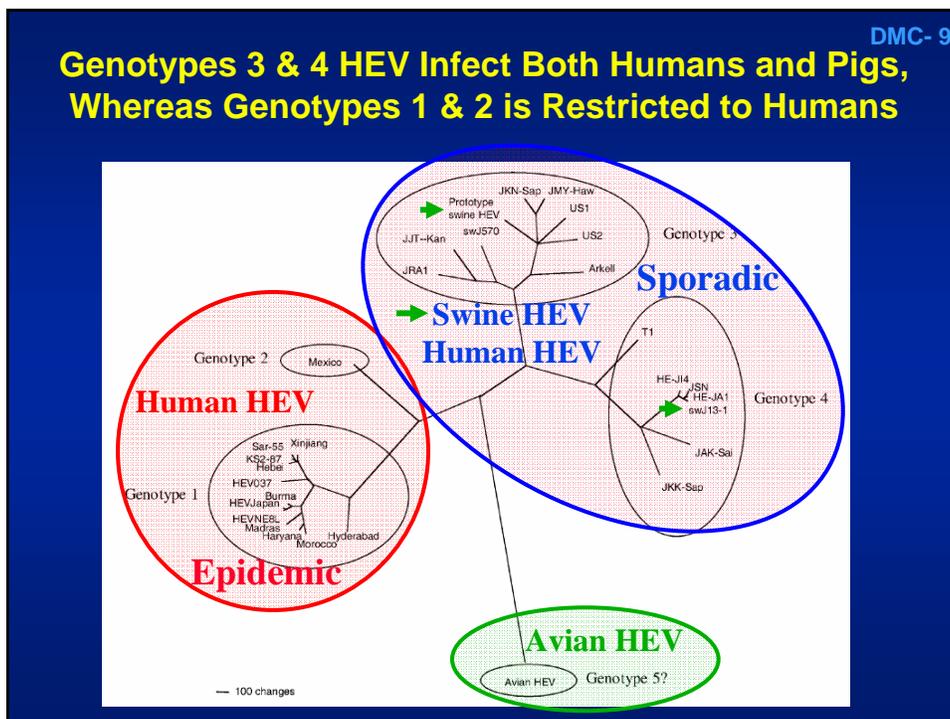
Non-Enveloped Viruses with Known or Potential Zoonotic Risk DMC- 7

Partial to complete inactivation by heat or lipid solvent

| Non-enveloped Viruses | Thermo-stability and Inactivation |
|---|--|
| Swine Hepatitis E Virus | Isopropanol/ethanol (not known); 50% inactivated at 56°C and 96% at 60°C for 1 hr (Emerson, et al. 2005). Stable when exposed to trifluorotrchloroethane |
| Swine Vesicular Disease Virus | Isopropanol/ethanol (not known); Inactivated at pH 7.5-8 at 50-55°C for 5 min, at pH 6.4 at 55-60°C for 5 min |
| Foot and Mouth Diseases Virus | Isopropanol/ethanol (not known); Inactivated in slurry within 3 min at 67°C, 3 min at 62°C and in medium within 5 min at 67°C (Turner C, et al. 2000) |
| Encephalomyocarditis Virus | Isopropanol and ethanol: inefficient with only 2 log reduction; Inactivated at 65°C for 15 min (Lelie, et al. 1987) |
| Porcine Reoviruses Porcine Rotavirus | Isopropanol and ethanol: 3-4 log reduction; Lipid solvent-, pH- and relatively heat-stable. Inactivated at 60°C to 61°C (Spillmann, et al. 1987) |

Swine Hepatitis E Virus (Swine HEV) DMC- 8

- **Agent:** Discovered in 1997 (Meng, et al. 1997); widespread but only subclinical infection in pigs
- **Target organ:** liver
- **Zoonotic risk:** a known zoonotic virus
- **Infectious dose:** highest known infectious dose of swine HEV produced from infected pigs is $5 \times 10^{4.5}$ MID₅₀ per ml of 10% fecal suspension; disease in humans is dose-dependent
- **Route of transmission:** fecal-oral route. Under experimental conditions, it is difficult to infect pigs or monkeys via the oral route, requiring 10^5 PID₅₀ infectious dose
- **Infectivity assay:** no infectivity cell culture assay, 10^7 Q-PCR "titer" = approx. 10^5 MID₅₀ infectious titer (Meng, et al. 1998)



DMC- 10

Swine Vesicular Disease Virus (SVDV)

- **Agent:** enterovirus, family Picornaviridae, ss+ RNA; sequence homologies to human Coxsackie-B5 virus
- **Distribution:** exotic in the U.S., last reported cases in Europe in 2004 (Portugal, Italy) and in 1994 (Netherlands)
- **Route of transmission:** fecal-oral route, and respiratory route
- **Zoonotic risk??:** earlier reported cases of human infection by SVDV (Brown, 1976; Graves, 1973), although severe illness has not been reported recently
- **Surveillance:** clinical signs not always present, sero-surveillance is needed. Netherlands, Italy and Spain in Europe have large-scale sero-surveillance programs

DMC- 11

Encephalomyocarditis Virus (EMCV)

- **Agent:** cardiovirus, family Picornaviridae, ss+ RNA
- **Distribution:** worldwide, infection is common but clinical disease is infrequent
- **Route of transmission:** oral route, rodent as a reservoir
- **Zoonotic risk?:**
 - No firm association between EMCV infection and diseases in humans (Zimmerman, 1994)
 - EMCV antibodies reportedly detected in selected human populations such as hunters but the few reported human cases have yet to be confirmed
 - EMCV infects human myocardial cells (Brewer LA, 2001)

DMC- 12

Porcine Reovirus and Rotavirus (RV)

- **Agent:** family Reoviridae, ds segmented RNA
- **Distribution:** worldwide
- **Route of transmission:** oral route
- **Zoonotic risk?:**
 - Human rotavirus recovered from diarrhea patients in India contain most of the genes (VP4, VP6, NSP1-5) characteristic of a porcine rotavirus (Varghese, et al. 2004): cross-species infection??
 - Genetic reassortments occur between porcine RV and human RV strains, and some reassortants cause diarrhea in humans (Esona, et al. 2004; Gerna, et al. 1992)

Highly-Resistant Non-enveloped Viruses That Are Not Zoonotic

DMC- 13

Non-enveloped Viruses

Inactivation

Porcine Parvovirus (PPV)

- Extremely resistant, stable to heat and pH. Stable at pH3-9, at 56°C for 60 min
- Parvovirus B19 can survive dry-heat at 80°C for 72 hr
- Inactivated by formalin, Clorox and oxidizing agents

Porcine Circoviruses (PCV1 and PCV2)

- Very stable in environment
- Resist to chloroform, pH3, or heat at 56°C and 70°C; resist to inactivation at 60°C for 30 min

Porcine Parvovirus (PPV)

DMC- 14

- **Agent:** family Parvoviridae, ss DNA
- **Distribution:** worldwide
- **Route of transmission:** oral route
- **Inactivation:** extremely resistant to inactivation
- **Zoonotic risk?:** No evidence of human infection. PPV antibodies not detected in human recipients of PPV-contaminated porcine-derived factor VIII (Giangrande, et al. 2002; Soucie, et al. 2000)
- **Genome mutation/evolution:**
 - Canine PV emerged as a variant of feline panleukopenia (FPV) due to mutations in FPV genome and caused host switch (Parrish CR, et al.)
 - PPV evolution??? Unknown and difficult to monitor

DMC- 15

Porcine Circovirus (PCV)

- **Agent:** family Circoviridae, ss circular DNA
- **Distribution:** worldwide; PCV1 (non-pathogenic), PCV2 (pathogenic)
- **Route of transmission:** oral route
- **Inactivation:** extremely resistant to inactivation
- **Zoonotic risk??:** No evidence of human infection
 - A single report on detection of PCV antibodies in humans (Tischer, et al. 1995) but a later study failed to detect PCV antibodies in pig handlers (Elis J, et al. 2001)
 - PCV DNA detected in porcine-derived pepsin product but the contaminated product was not infectious when inoculated into pigs (Fenaux, et al. 2004)
- **Genome mutation/evolution:** PCV genome is stable: only 3 nt changes after 120 passages in vitro (Fenaux, et al. 2004); no nt change after 3 serial passages in pigs (Gillespie, et al. 2008)

DMC- 16

Potential Risks of Non-enveloped Porcine Viruses in Humans Recipients of Porcine-derived Products

| | |
|--|---------------------|
| Detection of virus nucleic acids in porcine-derived products | Very likely |
| Presence of infectious virus in porcine-derived products | Likely (PPV, PCV) |
| Causing infection in recipients | Unlikely |
| Transmission to close contacts | Very unlikely |
| Causing epidemic and spreading | Very, very unlikely |

- A theoretical risk to patients receiving porcine-derived products
- Realistic risk: Very small

DMC-17

Agenda

| | |
|---|--|
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CV-1

Viral Risk Identification and Evaluation

Earl Sands, MD

CV-2

Agenda

- ◆ Background on theoretical risk to humans
- ◆ Viral Risk Identification and Evaluation Proposal
 - Retrospective Studies – database related
 - MarketScan
 - UK GPRD
 - Prospective Studies
 - Virological Surveillance
 - Active surveillance
 - Bioassay development
- ◆ Labeling considerations

CV-3

Background

- ◆ Potential risk affects all porcine-derived pancrelipase products
 - Risk of porcine viral contamination
 - Theoretical risk of patient infection
- ◆ CREON has been marketed for more than 20 yrs
 - 5 million patient yrs
 - Clinical trial and post-marketing safety data has not revealed any pattern of viral illness

CV-4

Background

- ◆ Solvay Pharmaceutical's manufacturing process minimizes potential viral load
 - Control of sourcing
 - Inactivation during manufacturing
 - Enveloped viruses – effectively inactivated
 - Non-enveloped viruses
 - Testing prior to release
 - Batches that do not meet specifications are destroyed

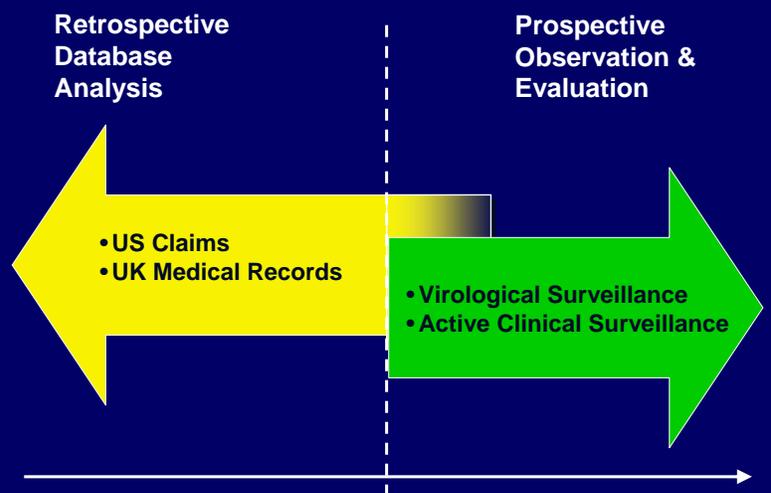
CV-5

Theoretical Nature of Risk to Humans

- ◆ Nonetheless, CREON, like all pancrelipase products, includes low levels of viral genome
- ◆ Viruses must be zoonotic to translate to human infection
- ◆ Potential is very, very small, but does exist
 - Mutation
 - Development of zoonotic infections

CV-6

Potential Viral Risk Identification Program



CV-7

Retrospective Database Analysis

- ◆ More in-depth review of available information
 - Requires feasibility study
- ◆ Database mining to evaluate
 - Incidence of infectious viral diseases
 - Potential relationship to CREON/PERT exposure
- ◆ If feasible, conduct epidemiological study
 - Compare incidences of viral disease between PERT users and controls

CV-8

Retrospective Study 1: MarketScan Database

- ◆ Large US claim databases
 - Covers 33 million patients for up to 12 yrs
 - In- and out-patient encounters
 - Enables linking of prescriptions, diagnoses, and medical events
- ◆ Analysis
 - Incidence/prevalence of infectious diseases, particularly viral GI infections
 - Assess for a potential relationship to drug exposure
- ◆ Status
 - Feasibility needs to be established

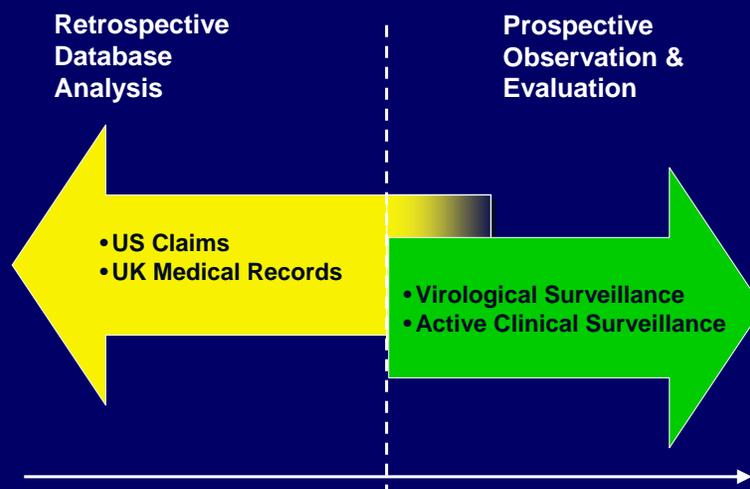
CV-9

Retrospective Study 2: UK General Practice Research Database (GPRD)

- ◆ Epidemiological study using medical records database (GPRD)
 - 6 million lives and 60 million patient-yrs in UK
 - High quality information on drug exposure and medical events (diagnosis)
 - Potential to request detailed clinical information (copies of hospital discharge or referral letters) for medical events
 - Over 5,000 ever users of pancrelipase have been identified
- ◆ Analysis
 - Epidemiologically-adjusted incidence of pre-defined diagnoses and conditions of interest
 - Compare users of pancrelipase and control populations

CV-10

Potential Viral Risk Identification Program



CV-11

Ongoing Virological Surveillance

- ◆ Literature searches
- ◆ Subscription to ProMED-mail*
- ◆ Networking with experts in virology, swine diseases and zoonosis
- ◆ Follow up on trends in the food industry
- ◆ Regular sequence alignments (BLAST**)
- ◆ Surveillance of unknown viruses in Sk-6 cell line (every batch)

Continuous development and update of analytical methods

*<http://www.promedmail.org> **Basic Local Alignment Search Tool

CV-12

Active Clinical Surveillance Program

- ◆ Prospective collection of data via CF Foundation registry
 - CF Foundation sites represent ~90% of all CF patients
 - Augment CRF with questions to identify conditions of interest
 - Specifics to be agreed with stakeholders (CFF, FDA, HCPs)
 - Ongoing effort; regular updates to FDA
- ◆ Sentinel sites to collect biomaterial
 - Blood and stool samples taken at routine intervals and when target symptoms occur
 - Storing of blood samples for future testing could be considered in the future

CV-13

Bioassays Monitoring For Anti-porcine Virus Antibodies

- ◆ Testing for human antibodies to detect potential or known zoonotic viruses
- ◆ Status on availability
 - Some commercial ELISA available for human serology (eg., huRotaV, HEV)
 - Some available only for animal serology (eg., EMCV, SVDV)
 - Positive control sera / human anti-porcine virus antibodies not available to validate assays

CV-14

Risk Identification Program Summary

- ◆ Limitations
 - Influenced by symptomatology of the underlying disease
 - Confounded by symptoms multiple potential sources of contamination, including food
 - Currently no universally available viral bioassay/ screening methods
- ◆ Strengths
 - Multiple sources of data
 - Proactive monitoring
 - Highly reliable population

CV-15

Appropriate Labeling Elements

- ◆ **Balance between informing stakeholders, while avoiding adverse effects on compliance**

- ◆ **Class labeling is appropriate to cover the following areas**
 - **Manufacturing minimizes risk**
 - **Parameters of remaining risk**
 - **HCPs should educate caregivers/patients (supplemented by patient package insert)**

CC-1

Conclusions

Earl Sands, MD
Solvay Pharmaceuticals, Inc.

CC-2

Medical Context

- ◆ Clearly defined medical need
 - Essential therapy
 - Serious, life-threatening conditions
- ◆ Clinical benefit well established
 - Regardless of underlying etiology or age of patients
 - Consistent with CREON data from studies over 20 yrs

CC-3

Viral Risk Considerations

- ◆ Robust, integrated quality controls during manufacturing process
 - Minimize levels
 - Very small risk of human infection
- ◆ Future vigilance provided by comprehensive risk identification and evaluation program
 - Active and ongoing surveillance program
- ◆ Risks can be adequately disclosed in labeling

CC-4

Proposed Indication for CREON

Treatment of patients with maldigestion due to exocrine pancreatic insufficiency

CC-5

External Invited Experts

Karsten Hueffer, DVM, PhD

*Assistant Professor of Microbiology
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