

**Testimony to the FDA Gastrointestinal  
Drug Advisory Committee Regarding  
Liprotamase – Risk : Benefit Assessment  
Ethics of Further Clinical Trials**

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**(We have no financial conflict of interest)**

## Benefits of Liprotamase – FDA Medical Officer Comments

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“In multiple pre-submission meetings, the Division has stated that in the subgroup of patients with baseline coefficient of fat absorption (CFA)  $<40\%$ , *a  $\geq 30\%$  difference between the liprotamase and placebo groups would be considered clinically meaningful.*”

[emphasis added]

# Benefits of Liprotamase – Results of Study 726

## Change in CFA – Subgroup Analysis

|  | Liprotamase                | Placebo                     | Liprotamase - Placebo | p-value  |
|--|----------------------------|-----------------------------|-----------------------|----------|
| All Subjects                               | 11% ( $\pm 17$ )<br>(n=70) | 0.2% ( $\pm 16$ )<br>(n=68) | 11%                   | p<0.001  |
| Baseline CFA<40%<br>(1° Efficacy Analysis) | 20% ( $\pm 16$ )<br>(n=24) | 5% ( $\pm 15$ )<br>(n=20)   | 15%                   | p=0.001* |
| Baseline CFA $\geq$ 40%                    | 7% ( $\pm 15$ )<br>(n=46)  | -2% ( $\pm 16$ )<br>(n=48)  | 9%                    | p=0.006  |

\* Although this difference was statistically significant, it fell far short of FDA's pre-specified 30% difference for clinical significance.

## Benefits of Liprotamase – Improvements in CFA: Porcine-Derived PEPs versus Liprotamase

| Baseline CFA Category | Porcine-derived PEPs |               |           | Study 726     |
|-----------------------|----------------------|---------------|-----------|---------------|
|                       | Creon                | Zenpep        | Pancreaze | Liprotam.     |
| Overall               | 41%                  | 26%           | 33%       | 11%           |
| Baseline CFA < 40%    | 61%<br>(n=8)         | 47%<br>(n=5)  | —         | 15%<br>(n=44) |
| Baseline CFA ≥ 40%    | 31%<br>(n=23)        | 20%<br>(n=27) | —         | 9%<br>(n=94)  |

# CFA Advantage of Porcine-Derived PEPs

## FDA Medical Officer Comments

“Study 726 demonstrated efficacy of liprotamase by achieving a statistically significant increase in CFA compared to the placebo group. *However, the differences observed in this trial do not appear as large in magnitude as have been observed in studies of porcine derived PEPs;* we note that there are limitations of cross-study comparisons.... Although the more severely affected patients had numerically larger increases in CFA [with liprotamase:15%] than less severely affected patients, *the changes in this subgroup were not numerically as large as observed with porcine derived PEPs [47% and 61%].*” [emphasis added]

# Possible Advantage of Porcine-Derived PEPs

## FDA Medical Officer Comments

“While the porcine derived PEPs contain multiple enzyme classes, including lipases, amylases and proteases, each of which may contain multiple enzymes with the same catalytic activity, lipotamase only contains one enzyme for each class.... The complex nature of pancreatic enzymes is due to the fact that the crude extracts represent the typical enzyme output provided by the pancreas. As such, multiple enzymes in each major class (i.e., phospholipases for the lipase class and chymotrypsin, trypsin and carboxypeptidases for the protease class) function in digesting the components present in food. ***Therefore, it is biologically plausible that porcine derived PEPs might allow for a more efficient digestion of food in the intestine.***” [emphasis added]

## Risks of Liprotamase

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The sponsor asserts that “No unexpected safety signals were identified.”

However, based on its analysis of the data, the FDA medical officer identified the following safety concerns:

- Potential for inadequate growth and malnutrition in children
- Hepatic transaminase elevations (ALT and/or AST)
- Distal intestinal obstruction syndrome (DIOS)
- Risk of fibrosing colonopathy.

## Risks of Liprotamase – Inadequate Growth/Malnutrition FDA Medical Officer Comments

“If this observation [small CFA difference] is a true reflection of a smaller therapeutic effect on CFA associated with liprotamase relative to porcine derived PEPs, *administration of this product to children could result in impaired growth relative to treatment with porcine derived PEPs. For young children where adequate nutrition is a necessity for continued growth, less efficacy is a safety concern, since it could result in growth retardation and failure to gain appropriate weight.*” [emphasis added]

## **Risks of Liprotamase – Transaminase Elevations FDA Medical Officer Comments**

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**“.... In Study 726 a numerically higher number of patients had transaminase elevations  $\geq 5x$  ULN in the liprotamase group than the placebo group. During the long-term studies 767 and 810...the proportion of patients in each of the elevation categories (i.e.,  $>1$  to  $<2.5x$  ULN,  $\geq 2.5$  to  $<5x$  ULN, and  $\geq 5x$  ULN to  $<10x$  ULN) was numerically higher on treatment compared to at baseline or screening.”**

## Risks of Liprotamase – DIOS FDA Medical Officer Comments

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“Seven DIOS events occurred in six patients during the liprotamase clinical trials (in the patient that had two events of DIOS, the events were separated by more than two years). It should be noted that no DIOS cases were observed in the clinical trials of the approved porcine-derived PEPs. *There is the concern that the DIOS cases occurred with liprotamase because of lower efficacy than PEPs.*” [emphasis added]

# Risks of Liprotamase – Fibrosing Colonopathy

## FDA Review Executive Summary Comment

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“Fibrosing colonopathy, a rare but serious condition that may result in colonic stricture, has been associated with prolonged high-dose PEP administration. *The risk of FC with liprotamase could be higher than with PEPs if the dose is excessively increased in response to lower efficacy.* (PEP products are routinely titrated to optimize treatment effect.) *In addition, theoretically, liprotamase might be associated with a higher potential risk for FC because its chemical features may render it more resistant to proteolytic activity, causing it to be persistently active in the colon.*” [emphasis added]

## **Concerns About Porcine-Derived PEPs Supply Interruptions**

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**Concern:** The supply could be interrupted due to disease or other threats to pig herds that are the sole source of these enzymes.

**Response:** We are not aware of any interruptions in the supply of porcine-derived PEPs. Such problems are unlikely and do not justify marketing of the drug for routine use in the absence of such supply problems.

**Furthermore,** supplies of liprotamase could be disrupted for different reasons, as has occurred with many other drugs.

## **Concerns About Porcine-Derived PEPs Potential Risk of Porcine Viral Infection**

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**Concern:** The FDA-approved porcine-derived PEPs have the potential risk of zoonotic viral contamination and transmission to patients.

**Response:** This is a theoretical risk, but the FDA-approved labels for all three porcine-derived PEPs state: “However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.”

**Furthermore,** eliminating this extremely unlikely risk by using a less effective product with greater safety risks would not be a rational approach.

## **Concerns About Porcine-Derived PEPs High Daily Burden of Porcine Enzymes**

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**Concern: Patients daily need to ingest large numbers of capsules for the porcine-derived PEPs.**

**Response: Given the data demonstrating that liprotamase is less effective than the porcine-derived PEPs, consuming a smaller number of less effective capsules would not represent an improvement in care of patients with pancreatic insufficiency.**

## Concerns About Porcine-Derived PEPs

### Lack of Pediatric or Gastrostomy Tube Formulation

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**Concern:** The FDA-approved porcine-derived PEPs lack a pediatric or gastrostomy tube formulation due largely to the requirement for an enteric coating to prevent the degradation of the porcine enzymes in the stomach.

**Response:** Per the FDA-approved labels for the three porcine-derived PEPs, capsules of these PEPs may be opened and contents given to infants or young children in water, directly into the mouth, or sprinkled in applesauce or other acidic food.

More importantly, as noted the FDA Medical Officer, *“liprotamase might be associated with a higher potential risk for FC [fibrosing colonopathy] because its chemical features may render it more resistant to proteolytic activity, causing it to be persistently active in the colon.”*

## **Would it be Ethical to Conduct Another Clinical Trial Comparing Liprotamase to an Active Comparator ?**

- **Based on the available data regarding the FDA-approved porcine-derived PEPs and liprotamase, there is substantial evidence that liprotamase is less efficacious than the porcine-derived PEPs and appears to expose subjects to greater risk. Therefore, a randomized trial comparing liprotamase to an FDA-approved active comparator would not be ethical because equipoise would not exist.**
- **Properly informed parents, aware of the above information, would likely not consent to enroll their children in such a study. Furthermore, given the data presented, such a randomized study would not satisfy the criteria for approval under FDA regulations concerning the additional safeguards for children in clinical investigations.**

## Questions to the Committee

**Question 1(a):** In the overall Study 726 population, is the observed difference in change in CFA between the liprotamase group (11%) and the placebo group (0.2%) of sufficient magnitude to be clinically meaningful?

**Response:** No, especially because of the greater benefit with FDA-approved porcine-derived PEPs.

**Question 1(b):** In the subgroup of patients with a baseline CFA <40% in Study 726, is the observed difference in change in CFA between the liprotamase group (20%) and the placebo group (5%) of sufficient magnitude to be clinically meaningful?

**Response:** In the context of the data on FDA-approved porcine-derived PEPs and FDA's pre-specified 30% CFA difference, clearly not.

## Questions to the Committee

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**Question 4: Are there additional efficacy studies that should be obtained prior to approving liprotamase for EPI?**

**Response: No; as we discussed, further studies would be unethical.**

**Question 5(a): Are there safety concerns associated with the use of liprotamase in EPI that preclude approval?**

**Response: Yes, there are significant safety concerns raised by the data presented regarding inadequate growth and malnutrition, hepatic toxicity, and DIOS.**

## Questions to the Committee

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**Question 6(a): Based on the currently available data, do the benefits outweigh the potential risks of liprotamase for treatment of patients wit EPI?**

**Response: No**