Summary Minutes of the
Gastrointestinal Drugs Advisory Committee (GIDAC)
FDA White Oak Campus, the Great Room, White Oak Conference Center
Silver Spring, Maryland

January 12, 2011

All external requests for the meeting transcript should be submitted to the CDER, Freedom of Information office.

These summary minutes for the Gastrointestinal Drugs Advisory Committee meeting of the Food and Drug Administration were approved on 2/2/11.

I certify that I attended the January 12, 2011 meeting of Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kristine Khuc, Pharm.D.
Designated Federal Officer,
GIDAC

_____/s/_____
Jean-Pierre Raufman, M.D.
Committee Chair, GIDAC

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)
Gastrointestinal Drugs Advisory Committee (GIDAC)
FDA White Oak Campus, the Great Room, White Oak Conference Center
Silver Spring, Maryland
January 12, 2011
Summary Minutes

The Gastrointestinal Drugs Advisory Committee (GIDAC) met on January 12, 2011 at the FDA White Oak Campus, the Great Room, White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and Sponsor. The meeting was called to order by Jean-Pierre Raufman, M.D., (Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Officer). There were approximately 100 persons in attendance. There were five speakers for the Open Public Hearing session.

Attendance:
Gastrointestinal Drugs Advisory Committee Members Present (Voting):
Ronal Fogel, M.D., William Hasler, M.D., Jean-Pierre Raufman, M.D. (Chair), Jill Sklar (Consumer Representative)

Temporary Member (Non-Voting):
Richard Hubbard, M.D. (Acting Industry Representative)

Special Government Employee Consultants Present (Temporary Voting Members):
Christopher Forsmark, M.D., Charles Hawkins (Patient Representative), Jesse Joad, M.D., M.S., Alexander Krist, M.D., M.P.H., Jenifer Lightdale, M.D., Mark Lowe, M.D., Ph.D., Weichung Shih, Ph.D.

Regular Government Employee Present (Temporary Voting Member):
Van Hubbard, M.D., Ph.D.

FDA Participants Present (Non-Voting):
Julie Beitz, M.D., Gilbert Burckart, Pharm.D., Marjorie Dannis, M.D., Andrew Mulberg, M.D., FAAP, Anil Rajpal, M.D.

Designated Federal Officer:
Kristine Khuc, Pharm.D.

Open Public Hearing Speakers:
Preston Campbell, M.D., Cystis Fibrosis Foundation; Joan Finnegan Brooks, Cystic Fibrosis Foundation; Patrick Marshall, Cystic Fibrosis Foundation; Francine Healey, Cystic Fibrosis Foundation; Joan Finnegan Brooks on behalf of The National Pancreas Foundation; Michael Carome, M.D., Health Research Group of Public Citizen

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 022486, for Sollpura (liprotamase) Capsules, by Alnara Pharmaceuticals, for the proposed indication (use) in the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy (surgical removal of all or part of the pancreas), or other conditions that may impair or limit function of the pancreas. The pancreas is an organ involved, in part, in the digestion of food through the use of specialized proteins

called enzymes. Exocrine pancreatic insufficiency is a decreased ability to digest food due to deficient enzyme production by the pancreas.

The Agenda was as follows:

Call to Order at 8:00 a.m. Introduction of Committee	Jean-Pierre Raufman, M.D. Chair, GIDAC
Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Officer, GIDAC
FDA Opening Remarks	Andrew Mulberg, M.D., FAAP Deputy Director Division of Gastroenterology Products CDER, FDA
Sponsor Presentations	Alnara Pharmaceuticals
Introduction	Don Burstyn, Ph.D. Senior Vice President, Regulatory Affairs Alnara Pharmaceuticals, Inc.
Exocrine Pancreatic Physiology And Insufficiency	Steven Freedman, M.D., Ph.D. Director, The Pancreas Center Beth Israel Deaconess Medical Center Professor of Medicine, Harvard Medical School
Disease State Overview and Management of Patients	Drucy Borowitz, M.D. Director, Cystic Fibrosis (CF) Center Professor of Clinical Pediatrics Women and Children's Hospital of Buffalo
Summary of Efficacy	Lee Brettman, M.D., FACP Chief Medical Officer Alnara Pharmaceuticals, Inc.
Summary of Safety	Christopher Stevens, M.D. Senior Vice President, Clinical Development Alnara Pharmaceuticals, Inc.
Benefit/Risk Profile	Drucy Borowitz, M.D.

Questions to the Sponsor

Break

FDA Presentations

Marjorie Dannis, M.D.
Medical Officer
Division of Gastroenterology Products
CDER, FDA

Emanuela Lacana, Ph.D.
Associate Lab Chief
Division of Therapeutic Proteins
Office of Biotechnology Products
CDER, FDA

Lin Zhou, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology III
Office of Translational Sciences
CDER, FDA

Questions to the FDA

Lunch

Open Public Hearing

Continue Clarification Questions to FDA and Sponsor

Committee Discussion and Questions

Adjournment

Questions to Committee:

The body of evidence submitted to establish the effectiveness of liprotamase for the proposed indication [treatment of patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF), chronic pancreatitis (CP), pancreatectomy, or other conditions] consists of clinical trials that primarily studied patients with cystic fibrosis. No children less than 7 years of age were entered in these clinical trials and the single randomized, placebo-controlled trial enrolled 64 pediatric patients ≥7 years (Study 726) and was only six weeks in duration. The long-term open label study (Study 767) did not have a prospectively defined control arm. The dose studied in the randomized, placebo-controlled trial was a fixed dose (not individually titrated).

Clinical outcome trials have not been required to support approval of porcine-derived pancreatic enzyme products (PEPs). Coefficient of fat absorption (CFA) has been accepted as a surrogate endpoint for PEPs based on the long history of use of these products and the existence of a body of literature that has linked the increase of fat absorption associated with PEPs with improvement in clinical outcome. However, the magnitude of change in CFA required to achieve improvement of clinical outcome has not been established. The magnitude of change in CFA associated with PEP products has ranged 26-41% in CF studies, and 47-61% in those studies in the subgroup of CF patients whose baseline CFA was <40%. If a threshold exists for CFA to serve as a surrogate, approval of a product associated with a treatment effect that does not reach that threshold could result in weight loss, impaired growth in children, and detrimental effects on lung function (in the setting of CF).

In light of the limitations of the studies and the absence of definitive information to establish the minimum magnitude of change in CFA that is necessary to achieve clinical benefit, we have the following questions to the Committee:

1. (a) **VOTE:** 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? (please explain your vote)

YES= 1 **NO= 10** **ABSTAIN= 0**

The majority of the committee voted "NO" and based their vote on limited efficacy data for the drug. The committee also recognized that there is a need for alternative therapies and new approaches are needed to treat patients with EPI. There was also discussion of whether CFA is an established and appropriate surrogate endpoint to be used.

The member who voted "YES" was uneasy about CFA as a surrogate, but believed that there was modest improvement in efficacy shown by weight maintenance.

(b) **VOTE:** 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? (please explain your vote)

YES= 1 **NO= 10** **ABSTAIN= 1**

The majority of the committee who voted "NO" agreed that there is lack of sufficient efficacy data. Again, the committee emphasized the unmet need for a new approach to treat patients with EPI. The minority of the committee felt that there was only a modest demonstration of efficacy or that there was not sufficient efficacy data.

(Please see official transcript for details)

2. Do the results of Study 726 and the exploratory analyses of data from Study 767 (including comparisons to CFF Registry data) constitute substantial evidence of the efficacy of liprotamase for the treatment of patients with:

   (a) **VOTE:** EPI due to CF?

YES= 3 **NO= 9** **ABSTAIN= 0**

The majority of the members who voted "NO" had concerns about interpretation of the study (767) due to a lack of a comparator control.

The other members who voted "YES" commented that there is modest evidence of efficacy.

   (b) **VOTE:** EPI due to CF in children less than age 7 years?

YES= 0 **NO= 12** **ABSTAIN= 0**

The committee unanimously voted "NO" for this question based on the lack of substantial evidence of efficacy. They also commented on the concerns of how the preparations will be used in this certain patient population.

   (c) **VOTE:** EPI due to CF in children ≥7 years of age?

YES= 1 **NO= 11** **ABSTAIN= 0**

The overall majority of the members who voted "NO" on this question remarked that there was insufficient substantial evidence of efficacy.

The member who voted "YES" noted that there is data to support the ≥7 age group.

(Please see official transcript for details)

3. **VOTE:** For each of the approved porcine-derived PEPs, a short-term trial in patients with EPI due to CF supported an approved indication of EPI due to CF "…or other conditions," based on a large body of evidence in the literature. However, liprotamase is a new drug that differs from the porcine-derived PEPs and the majority of the patients studied in this application were CF patients; if you voted "yes" in response to Question 2 (a) above, do the data in this application support an indication for EPI due to conditions other than CF (e.g., chronic pancreatitis or pancreatectomy)?

The committee members did not vote on this question. The three previous members who voted "YES" on question 2a were asked to make comments. The overall consensus is that there is support for an indication for EPI due to conditions other than CF. The pathophysiology of pancreatic insufficiency is not significantly different among these conditions.

(Please see official transcript for details)

4. **VOTE:** Are there additional efficacy studies that should be obtained prior to approving liprotamase for EPI? If yes, please describe the design of the studies (e.g., placebo-controlled, active-control, or dose-ranging), including selection of endpoints [e.g., change in CFA or clinical outcome such as growth parameters – height, weight, and body mass index (BMI)].

YES= 11 **NO= 1** **ABSTAIN= 0**

There was a nearly unanimous vote for additional studies to be obtained. The committee member who voted "NO" felt that for the adult population, there is not a need for additional studies, but for younger patients there should be more long term studies. The committee members recommended the following:

- Long term study with at least a year in duration;
- Look at CFA on customary diet;
- Head to head comparisons with current porcine therapies to validate change in CFA as a surrogate;
- Active control study using clinical parameters (i.e. height, weight, BMI, FEV1, change in CFA) with stratification by age;
- Primary endpoints include height, weight, BMI, blood tests (i.e. prealbumin, nutritional status);
- Secondary endpoints include symptoms (flatulence, steatorrhea), general quality of life assays;
- Further look at effects of drug on microbiome;
- Additional need for gastrostomy tube studies.

(Please see official transcript for details)

5. (a) **VOTE:** Are there safety concerns associated with the use of liprotamase in EPI (e.g., distal intestinal obstruction syndrome, fibrosing colonopathy, other) that preclude approval? If yes, please describe.

YES= 6* **NO= 4** **ABSTAIN= 2**

***A panel member placed a vote in the electronic voting system as "YES"; however, the panel member verbally stated his vote as "NO". The chair stated for the record that the vote is 5 "YES", 5 "NO", and 2 abstentions.**

The committee members who voted "YES" expressed that there is a safety concern for growth retardation and patient dose manipulations could result in adverse events (i.e. fibrosing colonopathy).

The members who voted "NO" commented that the safety data does not show significant signal for concern. However, a few members also noted that extensive post-marketing studies would be needed.

The committee members who abstained felt that the data presented had limitations in sample size, exposure, and dosing. In addition, further exploration of the location of the enzyme activity is needed.

(b) **VOTE:** Are there additional safety data or studies that should be obtained prior to approving liprotamase for EPI? If yes, please describe.

YES= 7 **NO= 5** **ABSTAIN= 0**

Those committee members who voted "YES" had safety concerns regarding higher doses of the drug and concerns related to the failure of the drug to hydrolyze other important vitamins and nutrients in the body.

Committee members who voted "NO" opined that there is a need for post-marketing studies to look at rare adverse events.

(Please see official transcript for details)

6. (a) **VOTE:** Based on currently available data, do the benefits outweigh the potential risks of liprotamase for the treatment of patients with EPI? If yes, specify whether your answer is limited to particular subpopulation(s) defined by age or etiology of EPI.

YES= 4 **NO= 7** **ABSTAIN= 1**

The overall majority who voted "NO" agreed that there is lack of substantial evidence of efficacy. The minority who voted "YES" felt that the limitation is in the age subpopulation. The member who abstained felt that there is not sufficient data to demonstrate benefits.

(b) **Discussion:** If you believe this product should be approved, are there any additional studies you would recommend post-approval?

The committee members suggested the following:

- Further surveillance of rare adverse events;
- Further dosing studies are needed;
- Weight gain and growth observations over an extended time period;

- Studies in adult chronic pancreatitis and quality of life;
- Evaluation of titration of doses and adverse events reported;
- Appropriate and wide dissemination of patient and provider education.

(Please see official transcript for details)

Meeting adjourned at approximately 4:00 p.m.