

ROTHSCHILD FINANCIAL CONSULTING

115 SCARLET OAK DRIVE
WILTON, CONNECTICUT 06897

PHONE (203) 762-3090
FAX (203) 834-2634

2004 MAY 27 9:35

May 18, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

RE Docket No. 2004N0086

Dear Sirs:

This letter is in response to your invitation for the public to submit letters suggesting what can be done to improve diabetes care.

I am a long-term investor in Amylin Pharmaceuticals who is frustrated. After years of regulatory review and two approvable letters, the FDA has yet to approve Symlin. Diabetics are best served if both patients and investors have confidence that the process of introducing new diabetes is handled reliably and efficiently. It is essential that rules of logic prevail. The current delay in the approval of Symlin appears unjustified to patients and their doctors who wait for the benefits of Symlin and investors who must continue to provide funds to make research possible.

Clinical data has proven that Symlin is an important new first-in-class drug badly needed by both Type 1 and Type 2 insulin-dependent diabetics. To make progress in diabetes care, timely and economical approval of safe and effective drugs is essential.

Symlin is safe and effective. Symlin lowers HbA1c, improves weight control, and once the patient's body readjusts to having its amylin receptors reactivated, Symlin reduces severe hypoglycemia. Yet, paradoxically, the only apparent hold-up to Symlin approval is severe hypoglycemia concerns among only Type 1 diabetics and only during the first four weeks of therapy. This temporary increase in the risk of severe hypoglycemia for Type 1 diabetics is real. However, the risk is no higher than the permanently elevated levels of severe hypoglycemia already deemed by experts to be worth the risk in consideration of the benefits associated with intensive insulin therapy.

It would be best if there were no periods of increased severe hypoglycemia either while using intensive insulin therapy or when initiating Symlin therapy. However, in contrast to what happens with intensive insulin therapy, with Symlin, the increase in risk of severe hypoglycemia is brief. With Symlin, in a matter of a few weeks the increased

2004N-0086

EMCH

risk is offset by a permanent reduced risk of severe hypoglycemia. When viewed in this broader context, Symlin improves patient safety.

Symlin's success in phase 3 trials was predictable because Symlin is the analog of natural amylin. Natural amylin is co-secreted along with insulin from the beta cells in healthy humans. That secretion occurs concurrently with insulin for a good reason.

Based upon generally accepted inference from the results of the primary end-point of HbA1c reduction, Symlin has proven in pivotal clinical trials its ability to reduce the incidents of blindness, kidney failure, heart disease, and circulatory problems that lead to required limb amputations by approximately 15% to 35%, with numbers towards the lower end of this range applicable to:

- a) the overall Type 1 population;
- b) the overall Type 2 population;

and the numbers towards or above the higher end of this range applicable to:

- c) the sub-set of the Symlin target group who both takes Symlin and are sufficiently motivated or otherwise capable of keeping insulin usage stable;
- d) the approximately 40% to 50% of patients in the Symlin phase 3 trials who were shown to be "responders" after 30 days of the initiation of Symlin therapy.

In addition to proving statistically significant efficacy for its primary end-point of HbA1c reduction, the phase 3 trials of Symlin have proven the following:

- a) Symlin causes weight loss in overweight diabetics in contrast to the weight gain associated with most diabetes drugs. Improvement in weight is a method to reduce the high blood pressure and heart disease that is especially prevalent in diabetics.
- b) Symlin has an ability to smooth the post-prandial glucose curve for insulin-dependent diabetics. Medical theory and recent clinical studies show that reducing glucose peaks is a highly significant factor independent of HbA1c that will reduce the long-term damage caused by diabetes.
- c) Many patients feel materially better while on Symlin. Feeling better improves the quality of life and further reduces the complications of diabetes by permitting patients to exercise more. The feel better effect is so strong in many patients that some have testified before the FDA during Symlin's Advisory Panel meeting that Symlin has "...given me my life back" and that they live in fear that absent FDA approval the day would come when they could no longer be able to get Symlin.
- d) As previously stated, after the initial adjustment period, patients on Symlin have less hypoglycemia than those not on Symlin.

Symlin is badly needed because it produces multiple clinically relevant benefits to the patients in Symlin's intent to treat group. This insulin-dependent group needs to have Symlin available.

While Type 2 diabetics have various oral medications available, eventually these oral medications fail. They desperately need something else to improve therapy. Currently, after oral meds fail, the next step for Type 2 diabetics is insulin. However, as proven by the progressive nature of the disease, insulin alone provides essential but

inadequate protection from diabetes. Since natural amylin is the partner hormone to insulin, the best way to maximize the value of insulin therapy is to administer it in conjunction with natural amylin's analog, Symlin.

For Type 1 diabetics, Symlin and insulin are the only two drugs that have ever been proven to lower HbA1c. For Type 1 diabetics, the only currently approved drug is insulin. When insulin therapy alone is inadequate, they currently have nowhere to turn.

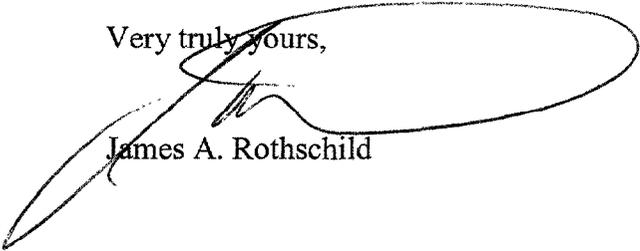
In the approvable letter issued in December 2003, the FDA is currently asking if the benefits of Symlin therapy worth the risk. After clinical trials on over 5,000 patients, the only identified risk is the increase in severe hypoglycemia during the first four weeks of therapy and then only among Type 1 diabetics. Therefore, for Type 2 diabetics, the answer is that there are no risks, but the benefits are many. For Type 1 diabetics, the temporary increase in severe hypoglycemia is easily worth the risk:

- a) The elevation in incidents of severe hypoglycemia during the first few weeks of Symlin therapy were the same as the increased incidents of severe hypoglycemia when following the DCCT trial recommendations for insulin usage. However, for Symlin the elevated risk is transitory. Other Phase 3 trials of Symlin have shown that the incidents of severe hypoglycemia are less for people on Symlin than those on placebo once the first four week adjustment period has passed. **While there is room for a difference of opinion on how much of a lowering of HbA1c is necessary to justify an increased risk of severe hypoglycemia, all should agree that the price of a few weeks of exposure to an increased risk of severe hypoglycemia is more than justified if cumulatively there is less severe hypoglycemia over the entire time a patient is on Symlin.**
- b) The DCCT trials led to the recommendation that intensive insulin therapy be used to lower HbA1c. This was done in spite of higher incidents of severe hypoglycemia and significant weight gain leading to a high percentage of patients becoming obese. Symlin accomplishes a lowering of HbA1c beyond the level obtainable with insulin alone and does so with weight loss instead of weight gain.
- c) The positive effects of Symlin are so important that even over the first year of Symlin therapy, double-blind placebo controlled studies showed that there was a **statically significant lower death rate among Type 2 patients on Symlin than those on placebo**
- d) Diabetes is a progressive disease. This and other normal variations in lives causes a patient's insulin needs to be ever changing. Because of these changes, severe hypoglycemia risk is always present. As a result, endocrinologists routinely deal with the threat of severe hypoglycemia and are trained in its management.

As an investor, I neither expect nor want any drug to be approved unless such approval is in the best interests of patients. Symlin has been proven to be in the best interests of patients. Therefore, both patients and investors are best served with timely approval.

Thank you for providing this opportunity for me to express what has been very much on my mind since Symlin received its second approvable letter from the FDA in December 2003. Hopefully, approval will occur soon.

Very truly yours,



James A. Rothschild