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Marlene E. Haffner, MD, MPH, Director  
Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
Parklawn Building, Room 6A-55  
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Rockville, Maryland 20857

RE: Comparison of results from Insmed's clinical study of rhIGF-I/rh IGFBP-3 with the results from research conducted under my rhIGF-I investigator IND #34,914

Dear Dr. Haffner:

After communication with your Deputy Director, Dr. John McCormick, I have been informed that information about my experience with rhIGF-I and rhIGF-I/rhIGFBP-3 in the treatment of GHIS would be of interest to your group. I have been involved in the development of both of these products for this indication. To the best of my knowledge, the majority of the primary data submitted for the rhIGF-I NDA (Tercica's) comes from my clinical research, and I have served on the steering committee for the clinical trial for the rhIGF-I/rhIGFBP-3 NDA (Insmed's) since its beginning. I believe there are differences between the conduct, monitoring and oversight of the clinical research I have conducted with rhIGF-I, and that of the clinical study with rhIGF-I/rhIGFBP-3. For this reason, I think it would be difficult to accurately compare these two sets of data for the purpose of determining whether there is a difference in the safety profiles of rhIGF-I/rhIGFBP-3 and rhIGF-I.

I will begin by giving you the **history of my involvement with rhIGF-I:**

- (1) I have been on the faculty of the University of North Carolina (UNC) as a pediatric endocrinologist since I completed my fellowship at UNC in 1970.
- (2) My research focus has been on the hormonal control of growth, mainly growth hormone & IGF-I.
- (3) In 1989-90, Genentech started producing rhIGF-I. Since I had been working with them in previous years as a primary investigator on the trial to get rhGH approved for use in GH deficient children and had been involved with laboratory studies of IGF-I (including development of the first RIA for IGF-I), I proposed that I acquire an IND for research use of IGF-I in children with growth hormone insensitivity syndrome (GHIS). Genentech

- agreed, the FDA granted approval, and I obtained an IND (# 34,914) in 1990. Under this IND, I began treating children with GHIS.
- (4) The first group of approximately 8 children was treated here at UNC through our General Clinical Research Center (GCRC) protocol. As most of these children were living outside the United States, Genentech sponsored their trips to UNC every 6 months for the first few years, and my fellow (or I) would travel to the office of their pediatric endocrinologist every 6 mo to examine the children. This would allow us to have contact with these patients every 3 months.
  - (5) About 2-3 years after we started this clinical research, Genentech asked a former trainee of our unit (Steven Chernausek, at Cincinnati Children's Hospital) to begin a similar study under another IND acquired by Genentech. Dr. Chernausek was then able, with my help, to recruit approximately 12-14 more patients, all but 1 from outside the United States.
  - (6) At about the same time, Genentech began a trial for the use of IGF-I in adults with diabetes. Subsequently, Genentech discontinued the trial because of some retinal problems in the subjects with diabetes.
  - (7) Because the trial on diabetes was intended to be quite large, Genentech had a large amount of rhIGF-I in their refrigerator(s). They obtained permission from the FDA to keep checking the preparation for stability & to send it to me, so that I could continue treating our children with GHIS.
  - (8) Subsequently, Genentech discontinued their IND for use of IGF-I in children with GHIS, and Dr. Chernausek's patients were transferred to my IND.
  - (9) I then began what I refer to as a compassionate use protocol. Whereas the worldwide community of pediatric endocrinologists is not terribly large, and is close-knit, the word got out that we had rhIGF-I for treatment of children with GHIS. When colleagues had a child they thought had GHIS, they would get in touch with me. I would require sufficient information on each patient so that I could be sure that the child had GHIS and would qualify for the IND that the FDA had given me. We would then require that the investigator obtain permission from his local IRB to participate in the research and sign-on as a sub-investigator (FDA form 1572).
  - (10) The sub-investigators were required to follow our protocol, and to keep us informed about the progress of the child under treatment. We did not develop detailed case report forms for them to record information on the efficacy/safety of the IGF-I treatment. We simply allowed the sub-investigators to provide the information in the form of a periodic written progress report. We would generally ship IGF-I to the sub-investigator to treat the child for 6 months. The sub-investigators would contact us when their supply of IGF-I was running low, and I would require that they send us a progress report (if they had not already sent one) before we would send more IGF-I. The number of children who have received/are receiving IGF-I in the compassionate use section of the protocol is 45-50 vs approximately 20 in the first phase (from our first 8 and Dr. Chernausek's 12 subjects). Most of the children in the compassionate use group are living in the middle east – Saudia Arabia, Kuwait & Egypt. A few live in South America, Europe, 3 in Taiwan and 1 in Australia.
  - (11) Following the first approximately two years of the trial, Genentech would send monitors to examine our data at UNC and Cincinnati (March 1992

through October 1998). However, to my knowledge, Genentech did not send monitors to examine patient data at the sub-investigator's sites. Beginning in 1999, the compassionate use protocol continued with funding from the Genentech Center for Clinical Research and Education. Annual progress reports were filed with the Center and our GCRC, but Genentech did not send monitors to examine our data.

- (12) About 2-3 years ago, Genentech reached an agreement with Tercica, and Tercica began the process of manufacturing more rhIGF-I. We have been working with Tercica since then – giving them our data on the children we have been treating, and they have been supplying the newly-manufactured rhIGF-I since October 2004. It is my impression that the newly-manufactured rhIGF-I is safe and effective, although the period of time that we have been distributing their rhIGF-I is minimal.

For the last two years, I have been **servicing on the steering committee for the trial of rhIGF-I/IGFBP-3 (SomatoKine)** with Professor Martin Savage and Dr. Cecilia Camacho-Hubner. I was invited to serve as an advisor for Tercica, but I declined to do so, because I had already agreed to advise Insmmed. I felt that providing advice on these two drugs, which were intended for the same purpose, would create some problems for me. Approximately 29 children with GHIS have been treated with rhIGF-I/IGFBP-3 to date. The steering committee has overseen the design and conduct for the trial, selected the patients to be included in the trial and reviewed the data at meetings every 4 to 6 months. We also have periodic conference calls. We have held 2 investigators' meetings in the past two years to ensure that all investigators understand the requirements of the study and are consistent in the collection of data for each patient. In addition, each study site has been monitored regularly since the beginning of the study. As a steering committee member, I have become familiar with this study and the degree to which it has been prospectively conducted and monitored. I have observed that the participating investigators were properly trained for the protocol, and that the study is being conducted in compliance with good clinical practices as is expected in industry sponsored prospective clinical trials. I think you will now understand the difference in the data collected under my investigator IND and the data being submitted by Insmmed.

Although I am quite confident that the accuracy of the growth data and the occurrence of serious adverse events being submitted by Tercica from my work accurately reflect the data provided by us, I have the impression that the non-serious AEs could have been under-reported to me. I draw this conclusion because the 8 patients we treated in the first group had many more minor side-effects than reported by the sub-investigators participating in the compassionate use group. The side-effects we have observed first-hand in the first patients we treated rhIGF-I include enlargement of tonsils and adenoids, snoring, and thickening of the soft tissues of the face. These have occurred in nearly all of our 8 patients.

I understand now that Insmmed has more thoroughly conducted their protocol and collected data across the sites that have participated in their study, than we were able to do with our research under my IND.

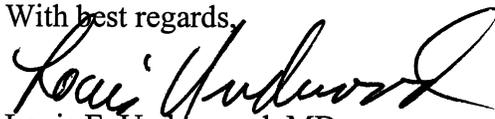
It is my opinion and the opinion of the other physicians on the steering committee, (Professor Savage and Dr. Camacho-Hubner), who coordinated a similar patient treatment program with rhIGF-I in Europe, that rhIGF-I/rhIGFBP-3 has a superior safety profile (particularly for the risk of hypoglycemia) when compared to rhIGF-I. This is based on our personal experience with rhIGF-I (my experience with Genentech's rhIGF-I and Drs. Savage and Camacho-Hubner's with Pharmacia's rhIGF-I) and our knowledge of the rhIGF-I/rhIGFBP-3 study. It is also my opinion that a comparison of the safety profiles of both products to determine whether rhIGF-I/rhIGFBP-3 is superior to rhIGF-I using the results from my research could be complicated by the bias introduced as result of the differences in the conduct, monitoring and oversight between my research and the Insmed study.

I would like to close this lengthy communication by providing you with **my opinions about the differences between rhIGF-I and rhIGF-I/rhIGFBP-3.**

- (1) The production of IGF-I, IGFBP-3 and the acid-labile subunit (ALS) are each dependent on the secretion and action of GH. These 3 peptides combine to form the 150K ternary complex in the circulation, and this may have consequences for delivery of IGF-I in the tissues.
- (2) In normal individuals, the ALS is present in an approximately two-fold molar excess of the IGF-I/IGFBP-3. In children with GHIS, all 3 are reduced.
- (3) When rhIGF-I is injected, the levels of IGF-I (and free IGF-I) shoot-up and the secretion of GH is suppressed. This results in a further decrease of IGFBP-3 and ALS. With sequential injections of rhIGF-I, there is more free IGF-I in the circulation, because the IGFBP-3 and ALS are further reduced.
- (4) I believe that these very high levels of free IGF-I are responsible for the imbalance of growth we see in these children, i.e., overgrowth of lymphoid tissues and thickening of soft tissues of the face.
- (5) Whereas the injection of the rhIGF-I/rhIGFBP-3 preparation is also likely to suppress GH secretion, I hope that enough ALS will remain in the circulation to provide for the ternary complex to be sufficient, thus reducing the free IGF-I concentrations.
- (6) Also, it is my experience over the past 15 years that IGF-I is not very effective when given once daily (instead of twice daily). The Insmed trial has shown that IGF-I/IGFBP-3 can be effective when given once daily.

Please feel free to contact me should you have any questions.

With best regards,



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