CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761092Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100687

MEETING MINUTES

Sigma-Tau Pharmaceuticals, Inc.
Attention: Raven Jaeger, M.S., RAC
Director, Regulatory Affairs
9841 Washingtonian Boulevard, Suite 500
Gaithersburg, Maryland 20878

Dear Ms. Jaeger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for EZN-2279.

We also refer to the preliminary meeting comments sent on October 12, 2016, the email communications on October 17 and 18, 2016, and the teleconference between representatives of your firm and the FDA on October 19, 2016. The purpose of the meeting was to discuss the nonclinical development plan as well as the content and format of a BLA for this product.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	October 19, 2016 from 1:00 to 2:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 100687
Product Name:	EZN-2279
Indication:	treatment of adenosine deaminase-severe combined immunodeficiency
Sponsor Name:	Sigma-Tau Pharmaceuticals, Inc.
Meeting Chair:	Renata Albrecht, M.D.
Meeting Recorder:	Diana Willard

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Diana Willard	Chief, Project Management Staff/DTOP

SIGMA-TAU PHARMACEUTICALS, INC. ATTENDEES

Gianfranco Fornasini, Ph.D.	Sr. Vice President, Scientific Affairs
Taha Keilani, M.D.	Chief Medical Officer
Raven Jaeger, M.S., RAC	Director, Regulatory Affairs
Joe Testa	Vice President, Product Development and Clinical Affairs
Ed Lemanowicz, Ph.D.	Sr. Consultant, Regulatory Affairs

BACKGROUND

An August 8, 2016, submission from Sigma-Tau Pharmaceuticals, Inc. (Sigma-Tau) requested a meeting to discuss the nonclinical development plan as well as the content and format of a BLA for EZN-2279. The August 17, 2016, Meeting Request Granted letter listed October 19, 2016, as the agreed upon meeting date. Meeting Preliminary Responses to the questions in the Meeting Package dated and received September 21, 2016, were sent to Sigma-Tau via e-mail on October 12, 2016.

An October 17, 2016, e-mail from Sigma-Tau requested clarification to the Agency's response to Question 3 from the September 21, 2016, Meeting Package under Nonclinical. The Agency responded, via e-mail, on October 18, 2016 (e-mail exchange attached). Further clarification on requested information for the SC linker, and the accelerated approval proposal by Sigma-Tau was discussed during the telephone conference on October 19, 2016.

DISCUSSION

The questions outlined in your September 21, 2106, Meeting Package are presented in **bold** font, our responses sent in the October 12, 2016, Meeting Preliminary Comments are in *italic* font, and meeting discussion is in regular font.

Regulatory

1. **Based on the regulatory history of the product as outlined in Section 6.1.2.2 and discussed in more details in Section 6.2, the current situation of the drug supply (considering that (b) (4) has not entered into a supply agreement with Sigma-Tau (b) (4) requires a definitive solution, which ultimately consists of successfully completing the clinical development of EZN-2279 and the BLA approval by the FDA. Considering also that it continues to be increasingly difficult to enroll patients into Study STP-2279-002, it was agreed with the FDA for Sigma-Tau to submit a BLA for accelerated approval. The BLA (Module 1, Clinical Sections of Module 2, and Module 5) is planned to be submitted in eCTD format as listed in Section 101, with more details in Sections 10.2 and 10.3.**

   Does the FDA agree that the Module 1, Clinical, and Nonclinical Sections of the BLA content and format is acceptable for the filing of the BLA?

   FDA Response:
   Module 1, Clinical and Nonclinical Sections of the proposed BLA content and format are acceptable.

   Meeting Discussion:
   The Division stated that if Accelerated Approval will be used as a regulatory pathway to approval for this product, it needs to be clear that the surrogate endpoint for this product would be measurement of the therapeutic level of the ADA activity (a minimum of 15 mmol/hr/ml) with an assessment of the health of the patients' immune system. Accelerated

Approval would not be used simply to add more patients to the database subsequent to approval. The Division suggested that Sigma-Tau submit information on all patients who have received EZN-2279 even for shorter periods than in Study STP 2279-002 for whom information is available on therapeutic levels of EZN-2279 (surrogate endpoint) and this information would be reviewed to support accelerated approval. The long-term follow up (e.g., one year) on safety and effectiveness in these patients, including clinical endpoints of morbidity or mortality can be submitted to the application when collected and would be reviewed to support the full approval.

The Division noted that there has been internal discussion including with the Rare Disease Program on how much can be learned from the experience of the 3 evaluable patients: whether this very limited database contains sufficient information to make a determination that the product is safe and effective. Therefore, we wanted to have an early discussion with Sigma-Tau regarding the challenges such a small number poses in evaluating this product.

Sigma-Tau stated that they now plan to postpone submission of the BLA from their original timeline of March 2017 to the current planned submission timeline of June 2017. The expectation is that at the time of a June 2017 submission, the database would contain information on the 3 patients in the Japanese study, adding more safety and pharmacokinetic data. The Japanese protocol differs from the US protocol in that while US patients were switched from Adagen to EZN-2279, this was not the same for Japanese patients.

(b) (4)

The Division recommended that both patients converted from Adagen and treatment-naïve patients should be studied, and the indication and labeling would reflect the population studied. Sigma-Tau initially wished to receive accelerated approval based on data from patients converted from Adagen, and then study treatment-naïve patients. Acknowledging the challenge with enrollment, the Division noted that making decisions on such a limited number of patients presents a number of challenges to determine safety and efficacy.

Nonclinical

2. **As discussed with the FDA on 16 December 2015, Sigma-Tau is requesting the FDA's guidance on the nonclinical development of EZN-2279 for BLA approval. The nonclinical development program is summarized in Section 10.2, which contains a tabular summary of completed animal studies, including a recent toxicology study conducted for high impurities of the drug product, and more detailed discussion surrounding the ongoing enhanced embryo-fetal development study in rats.**

   Does the FDA agree that the nonclinical development plan as presented in the current briefing package is sufficient for the filing of the BLA?

FDA Response:

If there are no outstanding CMC issues (i.e, impurities, product comparability) that require nonclinical qualification, we agree that the overall nonclinical development plan appears sufficient to support BLA filing. However, the adequacy of ongoing embryofetal development studies to support the application will be a review issue (see Question # 3).

Meeting Discussion:
None.

3. **The nonclinical development of EZN-2279 is discussed in Section 10.2. As discussed, following the FDA's recommendation for Enzon to conduct reproductive toxicology studies for EZN-2279, Sigma-Tau evaluated the nonclinical development, including assessing Enzon's justification for not conducting reproductive toxicity studies submitted in the original IND submission (provided in Attachment 1.6.2-1). Given the 25 year successful history with Adagen, the structural, pharmacological, and toxicological similarity of Adagen and EZN-2279, and the absence of any significant adverse effects of EZN-2279 in 4-week toxicology studies in both rats and dogs, Sigma-Tau does not anticipate that full reproductive toxicology studies (to include fertility studies) will provide additional beneficial information needed for the toxicology profile of EZN-2279. However, in order to consider fetal development with the use of EZN-2279, an enhanced dose finding embryo-fetal toxicology study, (enhanced to include more rats, more assessments, and is conducted under good laboratory practice [GLP]), was recently initiated in July 2016 and is scheduled for completion by the end of the year; refer to Module 4.2.3.5.2 for the Protocol (Study STPI20098870). Preliminary results are positive as no test article related effects were noticed for clinical and macroscopic observations on test animals, on pregnancy status, or during external examination of fetuses. Considering these results, additional information obtained from the endotoxicity study for high impurities, the previous toxicology studies conducted, and the history of use with Adagen, this study should conclude the reproductive toxicology nonclinical development of EZN-2279.**

   Does the FDA agree that the ongoing enhanced embryo-fetal reproductive toxicology study is sufficient to conclude the EZN-2279 reproductive toxicology profile needed for the BLA filing?

   FDA Response:
   The question is premature. The adequacy of the on-going dose-finding embryofetal toxicity study to support this application, in conjunction with other supporting data, will be a review issue.

   In addition to the justification for not conducting the full battery of reproductive toxicology studies, the BLA should include pharmacovigilance evidence of successful pregnancies and lack of infertility in ADA-SCID patients treated with Adagen®.

Meeting Discussion:

The following response was provided in the October 18, 2016 email (ATTACHMENT):

Given more than 25 years of marketing experience with Adagen, we would like you to provide any information you have on successful pregnancies or any information you may have collected regarding fertility. This might include spontaneous report(s) or any other source of information.

We refer you to the Meeting Discussion for Question 3 of the July 10, 2007, meeting for IND 100687, held between Enzon Pharmaceuticals, Inc. and the FDA for this IND, which states:

"... there were indeed some patients that had reached reproductive age. However, there is limited information on the adult Adagen patient population. No information on their offspring is available. Enzon indicated that they will do some follow-up on their offspring."

4. **During the pre-IND meeting with the FDA, Enzon presented a nonclinical development plan that included their intention of completing 13-week toxicology studies. As further discussed in Section 10.2, given the 25 year successful clinical history with Adagen, the structural, pharmacological, and toxicological similarity of Adagen and EZN-2279, the safe use of the stable PEG SC linker in the pediatric population with other chronic use medications, the absence of any adverse effects in 4-week toxicology studies of EZN-2279 (including the recent toxicology study concluded to assess high impurities (Study STPI130260A), and the immunogenic properties of EZN-2279 in both rats and dogs that could be a limiting factor in the utility of the animal model system in the investigation of potential toxic effects after chronic treatment, Sigma-Tau does not anticipate that longer term toxicology study will not provide additional beneficial information for the toxicity profile of EZN-2279.**

   Does the FDA agree that additional long-term toxicology studies (13 week repeat dose toxicity study) are not necessary for the BLA filing?

   FDA Response:

   As noted under the response for Question # 2, if there are no CMC uncertainties regarding the comparability of both products, we agree that longer-term studies may not be required for BLA filing. In the BLA, provide all available information to support safety of the PEG SC linker.

   Meeting Discussion:

   The Division stated that there is currently no information in the application regarding how the PEG SC linker in EZN-2279 may change the profile of the product from that of Adagen. It was mentioned during the July 10, 2007, meeting for this IND that Enzon had plans to implement changes in the PEGylation manufacturing process based on process development as previously submitted to PIND 100594. Any data that provide information on the SC-linker for EZN-2279, or other products, as well as a comparison between Adagen and EZN-2279, such as *in vivo* or *in vitro* data, should be submitted.

   Sigma-Tau stated that there are data available, such as stability data, on how the PEG SC linker characteristics of EZN-2279 differ from those of Adagen. During the upcoming CMC

pre-BLA meeting with the Agency that is currently scheduled for next week, Sigma-Tau plans to discuss comparisons of the different linkers, including pharmacokinetic data.

Clinical

5. **Sigma-Tau will be submitting a BLA for EZN-2279 for accelerated approval based on the efficacy and safety evaluations of the first cohort of three patients enrolled into the ongoing study (STP-2279-002). The content and format of clinical sections are outlined in Section 10.1 with more details in Section 10.3. As described, the interim clinical study report (CSR) is planned to be written per ICH E3 format. However, as discussed, due to a very small number of patients, the creation of summary tables is not likely to be useful and is potentially misleading because of the lack of precision of the summary statistics with such a small sample size. As such, individual summary data tables per patient will be presented instead of summary tables for all patients, and patient profiles and case report forms (CRFs) for all patients will be included in the application.**

   Does the FDA agree with the presentation of the data as outlined in the briefing package is acceptable for filing of the BLA?

   FDA Response:

   Your proposed presentation of the data is acceptable.

   Meeting Discussion:

   See Discussion for Question 1.

6. **As this is a single study to be submitted for accelerated approval, formal Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) are not applicable. If additional data is available for the submission, summary data may be misleading and additional patients can exaggerate the impact on the summary statistics and subsequently interpretation of the data. Instead, the evaluation of both efficacy and safety is better served using individual patient profiles (to see all of a patient's data in context) and patient listings (to compare common data across patients), providing readily available data for both within and between patient comparisons. As such, if additional clinical data is available, formal ISS and ISE will not be included in the BLA for accelerated approval.**

   Does the FDA agree with this approach?

   FDA Response:

   Your proposal to use individual patient profiles (to see all of a patient's data in context) and patient listings (to compare data across patients) is acceptable.

   Meeting Discussion:

   See Discussion for Question 1.

ATTACHMENTS AND HANDOUTS

October 18, 2016, e-mail to Sigma-Tau

ATTACHMENT

From: Willard, Diana M
Sent: Tuesday, October 18, 2016 1:06 PM
To: 'Raven Jaeger'
Cc: GianFranco Fornasini (GianFranco.Fornasini@sigmatau.com)
Subject: FW: IND 100687/EZN-2279 - Meeting Preliminary Comments

Hi! Raven – in response to your e-mail below, we have the following comment:

Given more than 25 years of marketing experience with Adagen, we would like you to provide any information you have on successful pregnancies or any information you may have collected regarding fertility. This might include spontaneous report(s) or any other source of information.

We refer you to the Meeting Discussion for Question 3 of the July 10, 2007, meeting for IND 100687, held between Enzon Pharmaceuticals, Inc. and the FDA for this IND, which states:

> "... *there were indeed some patients that had reached reproductive age. However, there is limited information on the adult Adagen patient population. No information on their offspring is available. ENZON indicated that they will do some follow-up on their offspring."*

Regards,
Diana

From: Raven Jaeger [mailto:Raven.Jaeger@sigmatau.com]
Sent: Monday, October 17, 2016 4:20 PM
To: Willard, Diana M
Cc: GianFranco Fornasini; STPRegSci; Sumit Jain
Subject: RE: IND 100687/EZN-2279 - Meeting Preliminary Comments

Hi Diana,

Thank you for sending the FDA's preliminary comments for the pre-BLA meeting that is currently scheduled for this Wednesday, October 19th. We appreciate the FDA's advice, and for the most part, we understand the FDA's comments and do not need any further clarification. However, we would like further clarification on the FDA's Response 3 under the Nonclinical Section:

> *"In addition to the justification for not conducting the full battery of reproductive toxicology studies, the BLA should include pharmacovigilance evidence of successful pregnancies and lack of infertility in ADA-SCID patients treated with Adagen."*

We would like to discuss further with you what the FDA would like to be included in the BLA from a pharmacovigilance evidence perspective (e.g., from spontaneous reports or something more).
However, this discussion may not require the need for a face to face meeting. As such, we would like to know if the FDA agrees to discuss this topic either via email or teleconference on Wednesday instead of during a face to face meeting that may anticipate more time than is actually needed.

Please let us know if you agree that based on the reduced agenda for the meeting, the discussion is better to be discussed via email or teleconference on October 19th in lieu of a face to face meeting. If the FDA prefers the face to face meeting, we are okay with proceeding accordingly.

Thank you again for your guidance with this expedited development of EZN-2279.
Raven

From: Willard, Diana M [mailto:Diana.Willard@fda.hhs.gov]
Sent: Wednesday, October 12, 2016 4:49 PM
To: Raven Jaeger
Subject: IND 100687/EZN-2279 - Meeting Preliminary Comments

Hi! Raven – attached, please find the Division's Meeting Preliminary Comments for the pre-BLA meeting scheduled for October 19, 2016, for the above IND.

Please let me know if you have any questions.

Regards,
Diana

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
10/21/2016