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APPLICATION NUMBER:

022231Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
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Attention:	Candice Teuber
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Subject:	Meeting Minutes IND 68,582
Date:	December 11, 2006
Pages including this sheet:	7

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Pre-NDA Meeting with Sponsor

Application Number: IND 68,582

Sponsor: Orphan Therapeutics, LLC

Drug: Terlipressin

Type of Meeting: Pre-NDA

Classification: B

Meeting Date: November 22, 2006
Preliminary Responses Sent: November 20, 2006
Briefing Package Received: October 9, 2006

Meeting Chair: Robert Temple, M.D.
Recorder: Dianne Paraoan

List of Attendees:

Division of Cardiovascular and Renal Products

Robert Temple, M.D.	Director, Office of Drug Evaluations I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Salma Lemtouni, M.D., M.P.H.	Medical Officer
Robert Kumi, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Jialu Zhang, Ph.D.	Statistician
Dianne Paraoan	Regulatory Health Project Manager
Paul Maher, M.D.	Office of Orphan Drug Product
John Senior, M.D.	Associate Director for Science, Office of Surveillance and Epidemiology

(b) (6)

On behalf of Orphan Therapeutics

Peter Teuber, Ph.D.	President and Managing Partner
Arun Sanyal, M.D.	Clinical Consultant, Principal Investigator

(b) (4)

Elizabeth Diaz, M.D.	Chief Medical Officer
Dror Rom, Ph.D.	Statistician
Candice Teuber, Pharm.D.	Director, Regulatory Affairs

(b) (4)

BACKGROUND

Orphan Therapeutics requested a pre-NDA meeting with the Agency to discuss the findings of their Phase 3 trial, OT-0401, and to seek our feedback on their proposal to submit their NDA for accelerated approval.

Orphan Therapeutics conducted their trial on their drug terlipressin for the treatment of hepatorenal syndrome (HRS) type 1. The sponsor has received Orphan and Fast Track Designations.

Previous meetings with the sponsor include a pre-IND meeting (January 22, 2004) and a Guidance meeting (March 17, 2004).

Preliminary Response

CLINICAL AND STATISTICAL

1. Does the Agency agree with the sponsor's proposal to submit a NDA for (b) (4)

We would be happy to discuss this issue further at the upcoming meeting, but we do not believe that the findings of OT-0401 adequately support the approval of terlipressin under (b) (4)

2. If yes, does the Agency agree that the principal design of the proposed study would be acceptable as the ongoing postmarketing study commitment? Specifically, dose FDA agree with:

- **a. HRS reversal on treatment as the primary endpoint?**
- **b. Open-label, single arm design?**

3. If the Agency will not consider an (b) (4) **at this point, is the principal design of the proposed trial acceptable to the Agency as a second study to support a NDA submission?**

In response to questions 2 and 3, we believe that the proposed study would not be an adequate design to support approval. You should plan on demonstrating effectiveness on the primary end point in two studies at $p<0.05$.

Additional Comments
To facilitate a discussion of the findings in OT-0401, the Division would like you to be prepared to address the following:

1. As the days progressed after randomization, the number of subjects at each time-point including Day 14 (figure 4, page 22) varied. Could you explain why?

2. Baseline SCr and gender were found statically significantly to predict the primary outcome. Could you present data showing how these factors affect the rate of treatment success and HRS reversal?

3. You summarized safety at Days 7 and 30, but not Day 14 (primary time point), could you present a summary of safety data at Day 14?

Discussion during Face to Face Meeting

(b) (4)

Outcome of the trial

Dr. Stockbridge informed Orphan Therapeutics that their findings are not compelling. Orphan Therapeutics conducted a placebo-controlled trial in which the primary endpoint failed to show statistical significance of $p<0.05$. The sponsor claimed that they were too ambitious in the design of their primary endpoint, but Orphan Therapeutics informed the Division that they had learned a lot from this trial and are willing to conduct another study, taking into consideration any guidance from the Agency in the design of the study.

Should Orphan Therapeutics plan on a confirmatory study, Dr. Temple recommended that they not conduct an open-label study. Blinding greatly enhances study credibility and should be used unless it is impossible.

The sponsor explained that their "success" endpoint was too ambitious in that it called for improved serum creatinine (≤ 1.5 mg/dL) at 14 days. What was used by many researchers to describe HRS reversal was a creatinine ≤ 1.5 mg/dL at any time and they asked whether the Agency would accept this endpoint. Dr. Temple agreed that HRS reversal was a reasonable endpoint, but it cannot be defined as a one-time SCr improvement that then goes away. The sponsor agreed that it should be something between the ambitious endpoint they chose for the completed study and the one-time SCr improvement. For example, a patient with SCr ≤ 1.5 mg/dL at day 8 who goes to transplant should be counted. Orphan Therapeutics would be welcomed to discuss a second study with the Agency.

The sponsor thought that the reason that their findings did not reach statistical significance was that the placebo group responded unexpectedly favorably to albumin, and by bad-luck, a number of severe cases that deteriorated quickly happened to cluster in the terlipressin arm. Dr. Temple thought that it would be a good idea to get a full account on each subject.

Other studies looking at terlipressin

Orphan Therapeutics informed the Agency that they may be able to obtain the rights to another study in which an investigator looked at terlipressin with albumin versus albumin alone in 3-4 sites. The sponsor claimed that the investigator stopped his study early because of the findings of OT-0401 but that the findings were similar to OT-0401. The Agency encouraged the sponsor to obtain these data and include them in their package.

Rolling Review

The Division discussed the best way to give an opportunity to review the data to see whether it might be supportive. Because Orphan Therapeutics has Orphan and Fast Track Designation, Drs. Temple and Stockbridge discussed the possibility of Orphan Therapeutics submitting an NDA for rolling review. The sponsor would provide the clinical portion for review first, including full data on study OT-0401 and the other terlipressin study. They would provide the other sections (i.e., CMC and Pharmacology/Toxicology) of the NDA later, if the clinical data seemed satisfactory.

CONCLUSION

Drs. Temple and Stockbridge encouraged Orphan Therapeutics to consider the recommendations above, specifically to submit their NDA as a rolling review rather than to conduct another study at this time. Orphan Therapeutics is welcome to contact the Division for further discussion.

Recorder: Dianne Paraoan
Chair, Concurrence: *{See appended electronic signature page}*
Robert Temple, M.D.

Draft: 11/30/06 Final: 12/12/06
RD:
Temple: 12/11/06
Stockbridge: 12/8/06
Lemtouni: 12/08/06
Kumi: ROK 12/07/06
Zhang: 12/6/06
Senior: 12/6/06
Maher: 12/4/06

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/s/

Robert Temple

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