Dr. Srinivasachar said a [redacted] identification test should be added to drug product specifications. Dr. Simmons encouraged the firm to send any specific rotation data they have into the Division for review.

Carton Labels

Dr. Advani said carton labels are needed for all four strengths of Uniprost. The firm said they would supply these as artwork if that were acceptable to the Division. Dr. Advani said it was acceptable.

How Supplied section

Dr. Advani noted that the HOW SUPPLIED section of the draft labeling was incomplete (i.e., it did not include the storage statement and other information). The firm said they had inadvertently left out that information and would submit draft labeling correcting that omission.

Conclusion

Dr. Simmons expressed concern that the [redacted] of the manufacturing process of drug substance were not covered by GMP guidelines. He said that the Division would contact the Office of Compliance, to review in detail, the completed FDA inspection of the manufacturing facility. He said that the Agency would set up a telecon with the sponsor to discuss the FDA inspection as well as other issues needing clarification pursuant to the meeting with the sponsor.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
John Simmons, Ph.D.

ef/12-11-00/12-14-00/01-05-01

Rd: NNguyen-12/12/00
JVAdvani-12/13/00
Ksrinivasachar-12/13/00

cc: NDA 21-272
HFD-110
HFD-110/EFromm/SMatthews

Minutes of a Meeting between United Therapeutics and the FDA

Date: November 15, 1999

Applications: [redacted]
UT-15 Injection

Applicant: United Therapeutics

Subject: Pre-NDA Meeting

FDA Participants:

Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Douglas Throckmorton, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Xavier Joseph, DVM., HFD-110, Pharmacologist
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
Khin Maung U, M.D., Ph.D., Division of Scientific Investigations
Karen Storms, HFD-45, Consumer Safety Officer, Division of Scientific Investigations
Natalia Morgenstern, HFD-110, Chief, Project Management Staff (pre-meeting only)
Edward Fromm, HFD-110, Consumer Safety Officer

United Therapeutics

James Crow, Ph.D., President and Chief Scientific Officer
Roger Jeffs, Ph.D., Director, Research, Development and Medical
David Mottola, Ph.D., Director of Clinical and Scientific Affairs
Shelmer Blackburn, Director of Operations
Dean Bunce, Associate Director, Regulatory Affairs

Consultants

[redacted]

Background

UT-15, a chemically stable tricyclic benzindene analog of epoprostenol (prostacyclin), possesses potent pulmonary and systemic vasodilatory and platelet anti-aggregatory actions in vitro and in vivo. The ability of UT-15 to reduce the loading condition of the right ventricle suggests that this agent may have utility in the treatment of pulmonary hypertension. The acute hemodynamic profile of UT-15 in patients with pulmonary hypertension appears similar to that of epoprostenol (Flolan), which is approved to treat pulmonary hypertension. Unlike epoprostenol, however, which must be delivered by continuous intravenous infusion, UT-15 has sufficient chemical stability to allow for subcutaneous administration, offering patients and clinicians an alternative therapeutic route of administration.

UT-15 was designated an orphan drug for the indication of Pulmonary Arterial Hypertension (PAH), effective November 2, 1999. The firm plans to submit an NDA for UT-15 in June 2000 and is requesting the Division's feedback on the format and content of the proposed package.

Meeting

The firm opened the meeting by giving a brief background of pulmonary hypertension (PH). The firm noted that they are now requesting a change in designation of pulmonary hypertension to pulmonary arterial hypertension (PAH), per the September 1998 World Symposium on Primary Pulmonary Hypertension. They added that they were primarily concerned with the vascular forms of PH, both primary (PPH) and secondary. United Therapeutics noted that about 3000 patients per year were diagnosed with (PPH), and about 3 times that amount for secondary forms of pulmonary hypertension.

Carcinogenicity/Toxicology Studies

The firm said that they had completed 6 month toxicology studies in rats and dogs but have not done carcinogenicity studies. Citing technical problems with the 6 month rat study, they stated that standard two year rodent studies for evaluation of carcinogenic potential could not be done because of the increased mortality that would be expected with the required duration of continuous infusion. Dr. Throckmorton asked about the feasibility of doing a shorter term alternative assay for determining carcinogenic potential. The sponsor noted that such alternative assays, which are generally performed in mice, were not feasible due to the difficulty of continuously infusing such a small animal for 6 months or longer. Dr. Fenichel stated that carcinogenicity studies might not be feasible or necessary now but that if the Carcinogenicity Assessment Committee (CAC) requests that the studies be done then the sponsor would have to begin these studies prior to filing the NDA. He indicated that the sponsor should submit additional information to the Division supporting its view that carcinogenicity studies are not necessary for this drug. These should include data on the mortality of patients with secondary forms of pulmonary hypertension.

Pharmacokinetics

Dr. Joseph asked the firm if there was any data on protein binding. The firm said that it has not been able to determine the protein binding of UT-15 because UT-15 is an extremely potent drug and because the C-14 label UT-15 synthesized had so much radioactivity that it was unstable (i.e., self-degraded) even at –70 degrees C. Dr. Nguyen asked the firm if there were difficulties conducting the C-14 mass balance study due to the instability of the radiolabeled UT-15. The firm said that it will remount the C-14 study in December. All events will be synchronized to reduce the time the C-14 compound is stored, i.e., the preparation and sterilization of the C-14 UT-15 Injection, the start of the clinical phase (including obtaining IRB and radiation safety committee approval), and the analysis of various biological fluids. The excretion of radioactivity via both the biliary route and the renal route will be measured. Metabolites in the urine will also be examined. However, until the experiment is completed, it is unknown whether the metabolites have or have not been degraded due to the large amount of radioactivity in the C-14 labeled compound.

Dr. Nguyen asked if the firm had done pK analyses of the studies. The firm said that in P01:04 and P01:05, steady-state plasma samples were collected from individual patients during the weeks 6 and 12 visits, at which time clinical assessments were also made. The plasma clearance levels will be determined from the steady-state plasma concentration (and UT-15 dose). The multivariate analysis will investigate whether various patient factors (i.e., demographics and concomitant medications)

would explain some of the variability in UT-15 plasma clearance values. Dr. Nguyen indicated that this was acceptable.

Dr. Nguyen inquired whether there had been an analysis of drug-drug interactions. The firm said limited studies have been done.

Safety/Efficacy

Dr. Throckmorton inquired how many patients United Therapeutics would have at the time of filing of the NDA. The firm indicated that they will have 301 patients treated for the Efficacy population and is expecting and approximate total of 852 volunteers and patients exposed for the Safety population. Dr. Throckmorton thought it would be beneficial to use confidence intervals when analyzing the mortality data. The firm said that it could calculate confidence intervals for relative risk ratio and risk difference for mortality and transplantation in the randomized, placebo controlled studies. Dr. Fenichel noted that the confidence intervals could have broad limits if needed.

Dr. Fenichel said, if feasible, the firm should follow patient failures (e.g., those that went to Flolan) through the 12 week endpoint, to gather a combined endpoint of mortality, lung transplantation, and switch of therapy.

Dr. Throckmorton noted that outlier analyses of safety parameters (e.g., ALT, AST) would be important with this drug. He said shift tables would be helpful in analyzing the safety information. Dr. Fenichel remarked that the small numbers of patients in the studies are conducive to using data-graphical displays to identify outliers.

Dr. Throckmorton asked the firm if the ECG's were abnormal in the patients studied. The firm said in the context of shifts from "normal to abnormal" or "abnormal to a different type of abnormal" ECG, they did not notice anything significant. They also mentioned that they had not studied QT interval changes.

Dr. Fenichel commented that approval guidelines contain three essential elements; that the drug is safe, is effective, and has reasonable instructions for use. He noted that there were no instructions for physicians on how to discontinue the drug. He was particularly concerned about rebound pulmonary hypertension as this event was associated with Flolan. The firm responded by saying that at least one subject died after withdrawal, but that the death occurred about 48 hours later and therefore did not appear to be attributable to a rebound worsening of pulmonary hypertension. United Therapeutics also noted that the half-life of Flolan was about 2 minutes whereas UT-15 had a much longer half-life. The firm was encouraged to include a discussion of 'rebound' in their NDA.

Statistical

Dr. Fenichel inquired about the analyses of PAH and the subset analysis of PAH and whether the firm needed to accept a penalty for the two analyses. The firm explained that the primary analysis is a combined analysis of all patients in studies P01:04 and P01:05. If the combined analysis is significant (two-sided $p<0.049$), that will serve as justification to look at each study separately. If each protocol has two-sided $p<0.049$, this would be considered acceptable. If one study is $p<0.049$ and one study is $p>0.049$, then United Therapeutics will go back to the combined analysis to determine if it is clearly and robustly below $p<0.01$. If combined study analysis is $p\leq 0.01$, this will be considered acceptable. If not, then the firm will look at the subset for PPH for significance (two-sided $p<0.001$). Dr. Fenichel indicated that this approach did not need to have any penalties of the different types of analyses.

The firm indicated that they would submit a detailed statistical plan to the Division towards the end of January 2000. They said that a data lock would be set for the end of March and asked if the Division could review the plan and provide feedback to the firm by the end of February. Dr. Hung said he would be able to this.

Format

The Division indicated that the following items should be submitted in electronic format:

- Annotated Case Report Forms (SAS files with SAS variables)
- Integrated Safety and Efficacy
- Key pK studies
- draft labeling (4 or 5 copies on floppy disks)
- SAS data sets from clinical studies

The firm asked if Word 2000 documents were compatible with the Division's computers. Dr. Fenichel said that the Division used Word 97 now, but that Word 2000 was coming in, and that in any event this wouldn't be a problem, since Word 2000 can save files in Word 97 format.

Mr. Fromm asked the firm to include a pediatric section (i.e., how they plan to respond to the pediatric rule) in the NDA package.

Conclusion

The firm plans to submit this NDA in June of 2000. The firm plans on submitting a detailed statistical plan in January and the Division has promised a review of the plan by the end of February.

Addendum

Dr. Nguyen noted that with regard to protein binding, the sponsor could determine protein binding by an in-vitro methodology that does not require a radiolabel.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Robert R. Fenichel, M.D., Ph.D.

ef/11-17-99/11-26-99/12-6-99

Rd: KMaug U/11-19-99
DThrockmorton/11-29-99
XJoseph/12-1-99
NNguyen/12-1-99
JHung/12-3-99

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