Summary Minutes of the
Oncologic Drugs Advisory Committee Meeting
September 14, 2011
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the September 14, 2011 Meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on 10/11/11.

I certify that I attended the September 14, 2011 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Caleb Briggs, Pharm.D.
Designated Federal Officer, ODAC

/S/
Wyndham Wilson, M.D., Ph.D.
Committee Chair

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 14, 2011 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Prior to the meeting, members and invited consultants were screened and cleared for conflict of interest, and provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Wyndham Wilson, M.D., Ph.D. (Committee Chair); the conflict of interest statement was read into the record by Caleb Briggs, Pharm.D. (Designated Federal Officer). There were approximately 100 persons in attendance. There were twelve (12) speakers for the Open Public Hearing session.

Issue: The committee discussed new drug application (NDA) 021825, with the proposed trade name FERRIPROX (deferiprone) film-coated tablets, application submitted by ApoPharma, Inc., represented by CATO Research Ltd. (authorized U.S. agent). The proposed indication (use) for this product is for the treatment of patients with transfusional iron overload (excess iron in the body related to blood transfusions), when current chelation therapy is inadequate. (Chelation therapy in these patients binds iron in a form that allows it to be eliminated from the body).

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting):
Deborah Armstrong, M.D., Ralph Freedman, M.D., Ph.D., William Kelly, D.O., Brent Logan, Ph.D., Mikkael Sekeres, M.D., M.S., Wyndham Wilson, M.D., Ph.D. (Committee Chair), Antoinette Wozniak, M.D.

Special Government Employee Consultants (Temporary Voting Members):
Dawn Aldrich (Patient Representative), Ann Zimrin, M.D., Jane Zones, Ph.D. (Acting Consumer Representative)

Regular Government Employee Consultants (Temporary Voting Members):
Gregory Kato, M.D., Susan Shurin, M.D.

Oncologic Drugs Advisory Committee Member (Non-Voting):
Gregory Curt, M.D. (Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present:
Frank Balis, M.D.
Patrick Loehrer, Sr., M.D.
Julie Vose, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Ann Farrell, M.D., Kathy Robie-Suh, M.D., Ph.D., George Shashaty, M.D., Tejashri Purohit-Sheth, M.D.

Designated Federal Officer:
Caleb Briggs, Pharm.D.

Open Public Hearing Speakers:
Maria Hadjidemetriou
Amy Celento, Vice President, Cooley's Anemia Foundation
Teresa Turchi
Anthony J. Viola, National President of the Cooley's Anemia Foundation
Nunzio D. Cazzetta
Alicia Somma
Thomas D. Coates, M.D.

Michelle Chieco
Peter Chieco
Gargi Pahuja, M.P.H., J.D.
Ralph Colasanti, Cooley's Anemia Foundation
Richard Ward

The agenda was as follows:

Call to Order Introduction of Committee	**Wyndham Wilson, M.D., Ph.D.** Chairperson, ODAC
Conflict of Interest Statement	**Caleb Briggs, Pharm.D.** Designated Federal Officer, ODAC
Industry Presentation Introduction	**ApoPharma, Inc.** **Dr. Michael Spino** President, ApoPharma Inc.
Medical Need	**Dr. Ellis Neufeld** Associate Chief Division of Hematology/Oncology Children's Hospital Boston
Efficacy & Safety Benefit / Risk Risk Management	**Dr. Fernando Tricta** Vice President Medical Affairs ApoPharma Inc.
Clinical Perspective	**Dr. Renzo Galanello** Professor Head of Pediatric Clinic and Thalassemia Unit University Hospital Cagliari Sardinia, Italy
Conclusion	**Dr. Michael Spino**
FDA Presentations	
Ferriprox (deferiprone) NDA 021825	**Kathy Robie-Suh, M.D, Ph.D.** Medical Team Leader Division of Hematology Products (DHP), Office of Hematology Oncology Products (OHOP), OND, CDER, FDA
	Ann Farrell, M.D. Acting Director DHP, OHOP, OND, CDER, FDA
	Tejashri Purohit-Sheth, M.D. Acting Director Division of Good Clinical Practice Compliance, Office of Scientific Investigations (OSI)

Office of Compliance (OC), CDER, FDA

Clarifying Questions from Committee

Open Public Hearing

Questions to the ODAC and ODAC Discussion

Questions to Committee:

NDA 021825
Ferriprox (deferiprone) film-coated tablets

APPLICANT: ApoPharma, Inc.
represented by Cato Research Ltd.
(authorized U.S. agent)

PROPOSED INDICATION: for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate

Patients with some inherited anemias, most notably β-thalassemia, require chronic red blood cell transfusions for their disease and consequently develop iron overload (transfusional hemosiderosis). The iron deposits in tissues, mainly heart and liver, and results in morbidity and mortality. Iron chelation therapy (with deferoxamine) to remove iron from the body improves survival in these patients. ApoPharma (a division of Apotex, Inc) has submitted a New Drug Application (NDA) for deferiprone for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate. Deferiprone has been marketed in the European Union (EU) (since 1999) and other countries for a similar indication.

In support of its application, the applicant provided the report and data from a single, retrospective, uncontrolled, multi-institutional study (LA36-0310) entitled "Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate". The study selected from the total clinical trial database for deferiprone those patients who had failed prior treatment with an iron chelator as assessed based on (1) serum ferritin >2500 µg/L, (2) liver iron concentration (LIC) >7 g iron/g dry weight and/or (3) cardiac MRI T2* value <20 milliseconds [taken as reflecting elevated cardiac iron content]. This retrospective, non-randomized study showed that over a treatment period of up to 1 year (76% of patients 6 months or longer; 27% of patients, 1 year or longer) 52% of study patients had a 20% or greater decrease in serum ferritin, consistent with a decrease in body iron load. LIC in the study patients evaluable for that parameter also declined and Cardiac MRI T2* change was in a direction consistent with a beneficial effect of deferiprone. The major safety concern identified was agranulocytosis which occurred in 1.7% of patients in the clinical studies. While agranulocytosis is generally reversible with deferiprone discontinuation, there have been deaths in the post-EU approval marketing experience.

1. VOTE: Is there a favorable benefit/risk profile for deferiprone in the treatment of patients in whom current chelation therapy is inadequate?

YES: 10 NO: 2 ABSTAIN: 0

Overall, members agreed that the strength of the data in support of the drug was not ideal, expressing concerns over the retrospective nature of the data, heterogeneity of the study population and lack of ongoing confirmatory trials. Several of those who voted in favor of accelerated approval cited the unmet need for tolerable therapies in this population, particularly administration inconveniences with the other therapeutic options. Many stated they believed that the safety of the drug had been shown to be acceptable, particularly owing to the extensive patient use in other countries. Those who voted against approval voiced concerns over the low quality of the supporting data and the lack of ongoing confirmatory trials. Many members of the committee expressed that confirmatory trials must be initiated quickly and must be carefully designed to encourage successful completion. Members from both sides of the vote stressed the importance of the drug being used as labeled, as they expressed concerns with data in off-label use.

**Additionally, members discussed possible study designs for confirmatory trials to satisfy accelerated approval requirements. Members expressed interest in studying Ferriprox against other agents for up-front use. One member suggested a non-inferiority study in which untreated patients would be randomized between Ferriprox and one or both of the currently marketed treatments. Another member discussed the value of studying the impact of Ferriprox on iron in various body tissues, specifically cardiac as compared to other therapies. A few members discussed interest in studies specifically in sickle cell patients and support of the sponsor's currently planned trial in this population. However, one member expressed concern over accrual in this population after drug approval, and encouraged the sponsor to begin this trial very quickly.*

Please see transcript for detailed discussion.

The morning session adjourned at approximately 12:17 p.m.

========== Lunch Break ==========

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 14, 2011 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Prior to the meeting, members and invited consultants were screened and cleared for conflict of interest, and provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Wyndham Wilson, M.D., Ph.D. (Committee Chair); the conflict of interest statement was read into the record by Caleb Briggs, Pharm.D. (Designated Federal Officer). There were approximately 50 persons in attendance. There were two (2) speakers for the Open Public Hearing session.

Issue: The committee considered the development of products for the treatment of patients with non-metastatic castration resistant prostate cancer (CRPC) who have a rising serum level of prostate-specific antigen (PSA) despite being on androgen deprivation therapy (ADT). There are no products currently approved for this indication. No specific products were presented or discussed; rather, the committee was asked to consider possible trial designs and suitable clinical endpoints to establish efficacy that would support a labeled indication for treatment of non-metastatic CRPC after PSA progression on ADT. Because ADT is an unproven therapy for this condition with serious long-term toxicity, the committee was asked whether approval of a new therapy in conjunction with continued ADT would be appropriate for patients with non-metastatic CRPC.

Attendance:
Oncologic Drugs Advisory Committee Members Present (Voting):

Deborah Armstrong, M.D., Ralph Freedman, M.D., Ph.D., William Kelly, D.O., Patrick Loehrer, Sr., M.D., Brent Logan, Ph.D., Mikkael Sekeres, M.D., M.S., Wyndham Wilson, M.D., Ph.D. (Committee Chair), Antoinette Wozniak, M.D.

Special Government Employee Consultants (Temporary Voting Members):
James Anderson (Patient Representative), Mario Eisenberger, M.D., Marc Garnick, M.D., David Penson, M.D., Derek Raghavan, M.D., Ph.D., Jane Zones (Acting Consumer Representative)

Regular Government Employee Consultants (Temporary Voting Members):
Timothy Donahue, M.D., Bhupinder Mann, M.D.

Oncologic Drugs Advisory Committee Member (Non-Voting):
Gregory Curt, M.D. (Industry Representative)

Guest Speakers (Non-Voting, Presenting Only):
Joel Nelson, M.D., Howard Scher, M.D.

Oncologic Drugs Advisory Committee Members Not Present:
Frank Balis, M.D.
Julie Vose, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Robert Justice, M.D., John Johnson, M.D., Paul Kluetz, M.D., Yang-Min (Max) Ning, M.D., Ph.D.

Designated Federal Officer:
Caleb Briggs, Pharm.D.

Open Public Hearing Speakers:
Scott T. Williams, Vice President, Mens Health Network
Matthew R. Smith, M.D., Ph.D.

The agenda was as follows:

Call to Order Introduction of Committee	**Wyndham Wilson, M.D., Ph.D.** Chairperson, ODAC
Conflict of Interest Statement	**Caleb Briggs, Pharm.D.** Designated Federal Officer, ODAC
FDA Presentation Issues Concerning Development of Products for Treatment of Non-Metastatic Castration-Resistant Prostate Cancer (NM-CRPC)	**Paul Kleutz, M.D** Medical Officer, Division of Oncology Products 1 (DOP1) OHOP, OND, CDER, FDA,
Guest Speaker Presentation Development and Features of Non-Metastatic Castration Resistant Prostate Cancer	**Joel B. Nelson, M.D** Frederic N. Schwentker Professor & Chairman Department of Urology, University of Pittsburgh School of Medicine

Guest Speaker Presentation Trials in the Non-Metastatic Rising PSA Castrate State: The Realities of Implementation and Completion	**Howard I. Scher, M.D** Chief, Genitourinary Oncology Service; D. Wayne Calloway Chair in Urologic Oncology Memorial Sloan Kettering Cancer Center

Questions to Presenters

Open Public Hearing

Questions to the ODAC and ODAC Discussion

Questions to Committee:

STUDY PATIENT POPULATION:

Non-metastatic castration-resistant prostate cancer (NM-CRPC) is a result of the use of androgen deprivation therapy (ADT) in patients with a rising serum prostate-specific antigen (PSA) after primary local therapy for prostate cancer. NM-CRPC is characterized by asymptomatic increases in PSA with no radiographic or clinical evidence of metastases despite continuation of ADT. There are no randomized clinical trials demonstrating that early use of ADT in patients with non-metastatic, PSA-only recurrent prostate cancer provides clinical benefit. In contrast, long-term use of ADT can result in serious adverse reactions, including increased risks of developing diabetes, osteoporosis or fracture, fatal cardiovascular disease and decreased muscular mass contributing to frailty.

1. **DISCUSSION:**
Issues Concerning Patient Population: Discuss what populations of patients with non-metastatic, PSA-only recurrent prostate cancer who have not received ADT and patients with NM-CRPC are appropriate for trials intended to support approval of products for these indications. If clinical trials should be limited to patients at high risk for prostate cancer morbidity or mortality, please discuss how the high risk population(s) should be defined.

Many members agreed that the most pressing need for study was in those patients with rapid PSA doubling times, as this subset typically experiences the worst prognosis. One member discussed a design in patients with rapid PSA doubling time who had not yet been treated with hormone therapy. These patients would be started on hormone therapy and those who continue to experience rapid PSA doubling would be randomized to either receive or not receive a new compound in combination with second line hormonal therapy.

One member stated that it would be important to divide hormone naïve patients and those who had progressed after receiving hormone therapy when conducting studies, to allow for relevant analyses. Another member suggested that cardiovascular health should be captured at the initiation of a trial, to allow for its impact to be considered in the analysis. One member indicated that, though high-risk patients should be the primary focus of drug development, it may be important to also randomize some low-risk patients to a subset to provide information to assist with off-label use of these drugs.

Please see transcript for detailed discussion.

TRIAL DESIGNS and ENDPOINTS:

Two types of randomized trial designs are proposed to assess the effectiveness of a product in these patient populations.

Trial Design 1 is a "Concurrent Comparison" that compares the product to placebo or an appropriate comparator. Possible endpoints include asymptomatic metastasis-free survival, symptomatic metastasis-free survival, and overall survival.

Trial Design 2 is an "Early versus Delayed" treatment comparing the efficacy of early treatment initiation of the product in the asymptomatic non-metastatic, PSA-only recurrent prostate cancer population who have not received ADT or the asymptomatic NM-CRPC setting to delayed treatment with the same product started after clinical metastases become evident. This design is not appropriate for investigational products with no known efficacy in metastatic prostate cancer. The question is whether early treatment with a product already approved in the metastatic setting is better than delayed treatment with the same product.

2. **DISCUSSION:**

Issues Concerning Trial Designs and Endpoints: Discuss the use of different study designs in asymptomatic non-metastatic, PSA-only recurrent prostate cancer who have not received ADT and asymptomatic NM-CRPC along with endpoints to be used for each type of design (e.g. overall survival, metastasis-free survival, and symptomatic metastasis-free survival) and patient population. For Trial Design 2, please also discuss potential disease progression criteria (e.g. evidence of metastasis, PSA progression, and symptoms) to initiate delayed treatment.

Much of the discussion focused on the suitability of various statistical outcomes in this population. Several members agreed that prevention or delay of bone metastases can be a clinically important outcome, but this is very much dependent on duration of prevention. Members discussed appropriate lengths of time for time to metastases measures, with varying perspectives. Generally, members felt that three months of metastases-free survival was certainly insufficient, but that it was difficult to establish a clear demarcation for what duration of metastases prevention would be acceptable to prove clinical benefit. One member suggested that one year would be an acceptable duration, conceding that it "may miss some small biological effects" but that it was reasonable to use this duration as the minimum to establish clinical benefit.

Several members discussed problems with using time to symptomatic metastases as an endpoint. One member mentioned that this measure requires complicated and extensive follow-up and can be difficult to use in trials. An additional member discussed that the most common symptom in patients with metastases is fatigue rather than bony pain, making it very difficult to gauge the time to presentation of symptoms.

Many members stated that overall survival and patient quality of life measures should be maintained as preferred outcomes in this patient population. Other members expressed some concern with measuring overall survival in these patients, with discussion of accrual difficulties, patient censoring, and heterogeneity of population cited as potential complications. One member discussed that measurement of overall survival may only be appropriate in high-risk patients, since other subsets may have life expectancies which make this measurement impractical.

Several members indicated that, though overall survival and quality of life measures are the ideal outcomes to measure clinical impact, trials should also be designed with alternate outcomes to assist with validating these measures.

Please see transcript for detailed discussion.

Meeting adjourned at approximately 5:00 p.m.