

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
November 6, 2014**

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland

Topic: During the morning session, the committee met to discuss new drug application (NDA) 205353, panobinostat capsules, application submitted by Novartis Pharmaceuticals Corporation. The proposed indication (use) for this product is in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

During the afternoon session, the committee met to discuss NDA 206317, ferric pyrophosphate solution, for administration via hemodialysis dialysate, application submitted by Rockwell Medical, Inc. The proposed indications (uses) for this product are for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD) and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

These summary minutes for the November 6, 2014, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on January 14, 2015.

I certify that I attended the November 6, 2014, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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

 /S/
Deborah K. Armstrong, MD
Chairperson, ODAC

Summary Minutes of the Meeting of the Oncologic Drugs Advisory Committee November 6, 2014

The following is the final report of the Oncologic Drugs Advisory Committee (ODAC) meeting held on November 6, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and posted on the FDA website at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm394134.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 6, 2014 from 8 a.m. to 12 noon at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, and the Sponsor, Novartis Pharmaceuticals Corporation. The meeting was called to order by Deborah Armstrong, MD, (Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 150 people in attendance. There were five Open Public Hearing speakers.

Issue: During the morning session, the committee met to discuss new drug application (NDA) 205353, panobinostat capsules, application submitted by Novartis Pharmaceuticals Corporation. The proposed indication (use) for this product is in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Attendance:

ODAC Members Present (Voting): Deborah K. Armstrong, MD (Chairperson); Bernard F. Cole, PhD; Tito Fojo, MD, PhD; James Liebmman, MD; Bruce J. Roth, MD; Jane Zones, PhD (Consumer Representative)

ODAC Members Not Present (Voting): Harold J. Burstein, MD, PhD; Aman Buzdar, MD, FACP; Louis F. Diehl, MD; Michael Menefee, MD

Temporary Members (Voting): Wayne Taylor, MD (Patient Representative)

Temporary Members (Non-Voting): Roy D. Baynes, MD, PhD (Industry Representative)

FDA Participants (Non-Voting): Richard Pazdur, MD; Ann T. Farrell, MD; Barry W. Miller, MSN, CRNP; Nicole Gormley, MD; Chia-Wen Ko, PhD

Designated Federal Officer (Non-Voting): Caleb Briggs, PharmD

Open Public Hearing Speakers: Walter Capone, (The Multiple Myeloma Research Foundation); Michael Tuohy, Robin Tuohy, (International Myeloma Foundation); Kim Ryan, (Cancer Support Community); Diane Moran, (International Myeloma Foundation)

The agenda proceeded as follows:

Call to Order and Introduction of
Committee

Deborah Armstrong, MD
Chairperson, ODAC

Conflict of Interest Statement

Caleb Briggs, PharmD
Designated Federal Officer, ODAC

FDA Introductory Remarks

Ann T. Farrell, MD
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products
(OHOP)
Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS

Novartis Pharmaceuticals Corporation

Introduction

Renaud Capdeville, MD
Vice President, Global Program Head
Oncology Global Development
Novartis Pharmaceuticals

Multiple Myeloma

Keith Stewart, MB, ChB
Dean for Research, Mayo Clinic in Arizona
Vasek and Anna Maria Polak Professorship in
Cancer Research

Clinical Efficacy and Safety

Renaud Capdeville, MD

Clinical Perspective

Paul G. Richardson, MD
R.J. Corman Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute

FDA PRESENTATIONS

NDA 205353 – Panobinostat
(Farydak)

Barry W. Miller, MSN, CRNP
Senior Clinical Analyst
DHP, OHOP, OND, CDER, FDA

Nicole Gormley, MD
Clinical Reviewer
DHP, OHOP, OND, CDER, FDA

Clarifying Questions to the Presenters

Open Public Hearing

Questions to the Committee/Committee Discussion

ADJOURNMENT OF MORNING SESSION

Question to the Committee:

Trial 2308 is a randomized, placebo-controlled, double-blinded trial, with an add-on treatment design using bortezomib and dexamethasone as backbone therapy. The panobinostat treatment arm results included:

- Improvement in median progression-free survival of 3.9 months as assessed by investigators.
- Improvement in median progression-free survival of 1.9 months as assessed by a sensitivity analysis, which included the following as events: death, progression as assessed by investigators, initiation of another antineoplastic therapy, discontinuation of therapy due to disease progression, and disease progression that was documented after 2 or more missing assessments.
- 6% improvement in overall response rate.
- Increased incidence of deaths not due to progressive disease (7% vs. 3.5%) and adverse events of myelosuppression, hemorrhage, infection, and cardiac toxicity.
- No statistically significant difference in overall survival.
- No difference between arms in a time-to-treatment failure sensitivity analysis, which included the following as events: death, disease progression as assessed by investigators, and discontinuations due to adverse events.

1. **VOTE:** Given this benefit:risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

Vote Result: Yes: 2 No: 5 Abstain: 0

Committee Discussion: *The majority of the committee voted “no.” Those committee members who voted in the negative described unease regarding the lack of additional data, such as improvement in overall survival or quality of life endpoints, to support the observed improvement in progression-free survival (PFS). While these committee members generally agreed that Trial 2308 demonstrated that panobinostat shows activity in patients with myeloma, concerns with the toxicity and uncertain magnitude of PFS improvement were cited as contributing to a negative benefit:risk profile overall. Some members hypothesized that toxicities exhibited on Trial 2308 may be better managed in the United States as compared to the international sites from the trial, but that the data under consideration does not provide evidence of this. One committee member specifically questioned whether the dose and combination of agents from the trial was ideal for maximizing benefit while minimizing toxicity. With regard to magnitude of improvement in PFS, some committee members referred to the censoring and missing data as raising questions about this magnitude, particularly in light of the lack of supportive data from other assessed endpoints. Several committee members who voted “no” encouraged the applicant to continue to pursue clinical development of this agent in hopes of better elucidating a population of patients with multiple myeloma who would safely benefit from treatment with panobinostat in combination with other treatment.*

Those committee members who voted “yes” described a judgment that the demonstrated magnitude of improvement in PFS was sufficient to support a positive benefit:risk profile for the use of panobinostat in this complex and challenging population of patients.

Please see the transcript for details of the committee discussion.

The morning session was adjourned at approximately 12:00 p.m.

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 6, 2014 from 1:00 p.m. to 5:00 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, and the Sponsor, Rockwell Medical, Inc. The meeting was called to order by Deborah Armstrong, MD., (Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 75 people in attendance. There were two Open Public Hearing speakers.

Issue: During the afternoon session, the committee met to discuss NDA 206317, ferric pyrophosphate solution, for administration via hemodialysis dialysate, application submitted by Rockwell Medical, Inc. The proposed indications (uses) for this product are for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD) and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

Attendance:

ODAC Members Present (Voting): Deborah K. Armstrong, MD (Chairperson); Bernard F. Cole, PhD; Louis F. Diehl, MD; Tito Fojo, MD, PhD; James Liebmman, MD; Bruce J. Roth, MD; Jane Zones, PhD (Consumer Representative)

ODAC Member Present (Non-Voting): Howard Fingert, MD, FACP (Industry Representative)

ODAC Members Not Present (Voting): Aman Buzdar, MD; Harold J. Burstein, MD, PhD; Michael Menefee, MD

Temporary Members (Voting): Brian Rini, MD, FACP; Michael Flessner, MD, PhD; Linda F. Fried, MD, MPH; Lakhmir Chawla, MD

FDA Participants (Non-Voting): Richard Pazdur, MD; Ann T. Farrell, MD; Kathy Robie Suh, MD, PhD; Min Lu, MD, MPH; Lola Luo, PhD

Designated Federal Officer (Non-Voting): Caleb Briggs, PharmD

Open Public Hearing Speakers: Paula Dutka, RN, MSN, CNN; Charlene Berry

The agenda proceeded as follows:

Call to Order and Introduction of
Committee

Deborah Armstrong, MD
Chairperson, ODAC

Conflict of Interest Statement

Caleb Briggs, PharmD
Designated Federal Officer, ODAC

FDA Introductory Remarks

Ann T. Farrell, MD

Director

Division of Hematology Products (DHP)

Office of Hematology and Oncology Products
(OHOP)

Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS

Rockwell Medical, Inc.

Introduction

Ajay Gupta, MBBS, MD

Chief Scientific Officer

Rockwell Medical, Inc.

Clinical Landscape

Steven Fishbane, MD

Chief, Division of Kidney Disease and
Hypertension

North Shore University Hospital and

Long Island Jewish Medical Center

Professor of Medicine, Hofstra North Shore-LIJ

School of Medicine

Clinical Efficacy

Raymond Pratt, MD, FACP

Chief Medical Officer

Rockwell Medical, Inc.

Clinical Safety

Vivian Lin, MD

Senior Director Clinical Research

Rockwell Medical, Inc.

Clinical Perspective

Steven Fishbane, MD

FDA PRESENTATIONS

NDA 206317 - Triferic

Min Lu, MD, MPH

Clinical Reviewer

DHP, OHOP, OND, CDER, FDA

Lola Luo, PhD

Statistical Reviewer

Division of Biostatistics V (DBV),

Office of Biostatistics (OB),

Office of Translational Science (OTS),

CDER, FDA

Clarifying Questions to the Presenters

Open Public Hearing

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

Efficacy:

Ferric pyrophosphate is intended to treat iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD). In the two pivotal studies conducted for this use, patients were randomized (1:1) to treatment with ferric pyrophosphate or placebo at each dialysis session for up to 48 weeks. Efficacy was assessed as the mean change in hemoglobin (Hgb) from baseline up to end-of treatment compared between the ferric pyrophosphate and placebo treatment groups. Results showed the following:

- Statistically significant difference between groups (ferric pyrophosphate better than placebo) for primary efficacy endpoint of mean change in hemoglobin from baseline to end-of-treatment.
 - SFP-4: 0.06 g/dL vs -0.3 g/dL for ferric pyrophosphate and placebo, respectively; p=0.01
 - SFP-5: -0.04 g/dL vs -0.39 g/dL for ferric pyrophosphate and placebo, respectively; p=0.01

Statistical issues were identified including: (1) Although treatment duration was planned for up to 48 weeks, only 18% of patients completed 48 weeks and 44% completed 24 weeks treatment; (2) Because the end of treatment Hgb values represent various time values, it is difficult to draw inferences about effects during the complete 48 weeks; (3) Differential reasons for treatment discontinuation could impact the magnitude of effect on Hgb level.

The applicant also asserts that the product reduces the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels. This claim is based on a single exploratory study (NIH-FP-01) which showed no significant difference between the ferric pyrophosphate group and the placebo group in the mean percent change in prescribed ESA dose from baseline for the intent-to-treat (ITT) population (5.0% vs 37.3% for ferric pyrophosphate and placebo, respectively; p=0.052). Also, the mean percent change in actual ESA dose from baseline was not significantly different between the ferric pyrophosphate group and the placebo group in the ITT population (11.1% vs 40.7% for ferric pyrophosphate and placebo, respectively; p=0.111). Statistical issues were identified for this study including: (1) A single trial, no replication of the result; (2) No formal sample size or power calculations planned or conducted; and (3) Difficulty in the interpretation of the efficacy of ferric pyrophosphate over the placebo at the end of treatment.

Safety:

Observations from the safety evaluation in the pivotal trials in which 292 patients received ferric pyrophosphate and 296 received placebo include:

- More observed deaths in the ferric pyrophosphate treatment arm as compared to the placebo arm in both pivotal studies (SFP-4: 5 vs 3 for ferric pyrophosphate and placebo, respectively; SFP-5: 7 vs 3* for ferric pyrophosphate and placebo, respectively). [*one placebo patient was randomized but not treated].
- Overall deaths in the pivotal trials included 6 cardiac arrests and 4 sudden deaths in ferric pyrophosphate group and 2 cardiac arrests and 1 sudden death in placebo group.
- Hemodialysis (HD) vascular access thrombosis events observed in 5.1% of patients receiving ferric pyrophosphate and 3.7% of patients receiving placebo
- One patient with a suspected hypersensitivity event in the ferric pyrophosphate group and none in the placebo group.

Observations from the safety evaluation in the NIH-FP-01 trial (in which 54 patients received ferric pyrophosphate and 49 received placebo) include:

- 2 deaths in the ferric pyrophosphate group and 3 deaths in the placebo group

Question #1 was revised to the following based on the committee discussions that transpired during the meeting:

1. Ferric pyrophosphate is proposed for use for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD).

VOTE: Do the efficacy and safety results in Studies SFP-4 and SFP-5 support a positive benefit/risk for use of ferric pyrophosphate to treat iron loss?

Vote Result: Yes: 8 No: 3 Abstain: 0

Committee Discussion: *The majority of the committee members voted “yes.” Those committee members who voted positively described confidence that the trial supported that ferric pyrophosphate was superior to placebo in the context of the trials and that it was effective in delivering iron to those patients. Many of the same members also acknowledged a somewhat artificial setting from the trial as compared to clinical practice, but cited comfort with the demonstrated safety profile of this agent and an unmet need for maintenance iron replacement in dialysis patients as supportive factors. Those committee members who voted “no” described difficulty in translating the conclusions from the trials to clinical practice, given the differences in treatment in this setting. Individual committee members who voted negatively also stated concerns regarding appropriate dosing and the low rate of patients who completed the planned 48 week treatment duration.*

2. The applicant proposes to include in the label a claim that use of ferric pyrophosphate reduces the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

DISCUSSION: Considering the limitations of the NIH-FP-01 study, should additional studies be required to establish efficacy of ferric pyrophosphate for this claim? Discuss important aspects of trial design for studies to substantiate clinical benefit for this use.

***Committee Discussion:** Committee members generally agreed that additional studies would be necessary to establish the efficacy of ferric pyrophosphate to reduce the prescribed dose of ESA. Committee members suggested that a larger trial would be necessary, and further stated that a double-blind, randomized structure would be appropriate. Several committee members asserted that it would be critical to standardize the ESA that was used as a comparator, since there is significant variability among the available ESA products, particularly in regards to dosing and half-life. Another committee member emphasized that any additional trials should be designed to assess clinical endpoints, rather than laboratory measures.*

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:58 p.m.