FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Thursday, November 6, 2014
12:59 p.m. to 4:58 p.m.

Afternoon Session

FDA White Oak Campus
Building 31, The Great Room (Room 1503)
White Oak Conference Center
Silver Spring, Maryland
Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Caleb Briggs, PharmD
Division of Advisory Committee and Consultant Management
Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Deborah K. Armstrong, MD (Chairperson)
Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Bernard F. Cole, PhD
Professor, Department of Mathematics and Statistics
University of Vermont
Burlington, Vermont
Louis F. Diehl, MD (Afternoon Session Only)
Professor of Medicine
Duke University Medical Center
Durham, North Carolina

Tito Fojo, MD, PhD
Senior Investigator
Director, Medical Oncology Fellowship Program
Medical Oncology Branch, Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

James Liebmann, MD
Assistant Professor of Medicine
Department of Medicine
University of Massachusetts
Worcester, Massachusetts
Bruce J. Roth, MD
Professor of Medicine
Division of Oncology
Washington University School of Medicine
St. Louis, Missouri

Jane Zones, PhD (Consumer Representative)
Medical Sociologist (retired)
Member, Former Board Member
Breast Cancer Action
National Women's Health Network
San Francisco, California

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)
Howard Fingert, MD, FACP
(Industry Representative; Afternoon Session Only)
Senior Medical Director, Clinical Intelligence
Millennium, the Takeda Oncology Company
Cambridge, Massachusetts
TEMPORARY MEMBER (Voting) *(Morning Session Only)*

Wayne Taylor, MD *(Patient Representative)*

Hudson, Florida

TEMPORARY MEMBERS (Voting) *(Afternoon Session Only)*

Lakhmir Chawla, MD

Chief, Division of Intensive Care Medicine

Department of Medicine

Division of Intensive Care Medicine

Veterans Affairs Medical Center

Washington, District of Columbia

Michael Flessner, MD, PhD

Director of Inflammatory Renal Diseases

Division of Kidney, Urology, and Hematology Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

National Institutes of Health

Bethesda, Maryland
Linda F. Fried, MD, MPH
Chief Peritoneal Dialysis
Veterans Affairs Pittsburgh Healthcare System
Professor of Medicine, Epidemiology and Clinical
and Translational Science
University of Pittsburgh
Pittsburgh, Pennsylvania

Brian Rini, MD, FACP
Professor of Medicine
Cleveland Clinic Foundation
Lerner College of Medicine
Staff, Cleveland Clinic Taussig Cancer Institute
Glickman Urological and Kidney Institute
Cleveland, Ohio
ACTING INDUSTRY REPRESENTATIVE TO THE ONCOLOGIC 
DRUGS ADVISORY COMMITTEE (Non-Voting) 
Roy D. Baynes, MD, PhD (Morning Session Only) 
Senior Vice President 
Global Clinical Development 
Merck & Co., Inc. 
Rahway, New Jersey 

FDA PARTICIPANTS (Non-Voting) 
Richard Pazdur, MD 
Director Office of Hematology & 
Oncology Products (OHOP) 
Office of New Drugs (OND), CDER, FDA 

Ann T. Farrell, MD 
Director Division of Hematology Products (DHP) 
OHOP, OND, CDER, FDA
Barry W. Miller, MSN, CRNP  
*(Morning Session Only)*  
Senior Clinical Analyst  
DHP, OHOP, OND, CDER, FDA  

Nicole Gormley, MD  
*(Morning Session Only)*  
Clinical Reviewer  
DHP, OHOP, OND, CDER, FDA  

Chia-Wen Ko, PhD  
*(Morning Session Only)*  
Statistical Reviewer  
Division of Biostatistics V (DBV)  
Office of Biostatistics (OB)  
Office of Translational Sciences (OTS), CDER, FDA  

Kathy Robie Suh, MD, PhD  
*(Afternoon Session Only)*  
Clinical Team Leader  
DHP, OHOP, OND, CDER, FDA
Min Lu, MD, MPH
(Afternoon Session Only)
Clinical Reviewer
DHP, OHOP, OND, CDER, FDA

Lola Luo, PhD
(Afternoon Session Only)
Statistical Reviewer
DBV, OB, OTS, CDER, FDA
CONTENTS

AGENDA ITEM                                    PAGE

Call to Order                                    3
   Deborah Armstrong, MD                             12
Conflict of Interest Statement                   4
   Caleb Briggs, PharmD                             13
Opening Remarks                                  5
   Ann Farrell, MD                                 17
Applicant Presentations – Rockwell Medical       6
   Triferic Introduction                           10
      Ajay Gupta, MBBS, MD                         23
   Clinical Landscape                              11
      Steven Fishbane, MD                         26
   Triferic Mechanism of Action                    12
      Gary Brittenham, MD                         36
   Triferic Efficacy                               13
      Raymond Pratt, MD, FACP                    39
   Triferic Safety                                 14
      Vivian Lin, MD                               52
   Clinical Perspective                           15
      Steven Fishbane, MD                         61

A Matter of Record
(301) 890-4188
### CONTENTS (continued)

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Presentation</strong></td>
<td></td>
</tr>
<tr>
<td>NDA 206317 - Triferic</td>
<td></td>
</tr>
<tr>
<td>Min Lu, MD, MPH</td>
<td>69</td>
</tr>
<tr>
<td>Lola Luo, PhD</td>
<td>76</td>
</tr>
<tr>
<td>Min Lu, MD, MPH</td>
<td>84</td>
</tr>
<tr>
<td>Lola Luo, PhD</td>
<td>88</td>
</tr>
<tr>
<td>Min Lu, MD, MPH</td>
<td>92</td>
</tr>
<tr>
<td>Introduction of Committee</td>
<td>94</td>
</tr>
<tr>
<td>Clarifying Questions to the Presenters</td>
<td>96</td>
</tr>
<tr>
<td>Open Public Hearing</td>
<td>124</td>
</tr>
<tr>
<td>Questions to the Committee and Discussion</td>
<td>183</td>
</tr>
<tr>
<td>Adjournment</td>
<td>204</td>
</tr>
</tbody>
</table>
(12:59 p.m.)

Call to Order

DR. ARMSTRONG: I think we'll go ahead and get started.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings.
However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it on to Caleb Briggs, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 is
being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and
royalties, and primary employment.

This afternoon's agenda involves new drug application 206317, ferric pyrophosphate solution, for administration via hemodialysis dialysate, application submitted by Rockwell Medical, Incorporated. The proposed indications 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 and to reduce the prescribed dose of erythropoiesis stimulating agent required to maintain the desired hemoglobin levels. This is a particular matters meeting during which specific matters related to Rockwell Medical's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public
statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Howard Fingert is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Fingert's role at this meeting is to represent industry in general and not any particular company. Dr. Fingert is employed by Millennium Pharmaceuticals.

We'd like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ARMSTRONG: Thank you. We will proceed with opening remarks from Dr. Ann Farrell.
Opening Remarks - Ann Farrell

DR. FARRELL: Good afternoon. I want to especially thank the public, ODAC members, and Rockwell Medical to this important advisory committee meeting to discuss ferric pyrophosphate. The agency is interested in having safe and effective medicines to provide supplemental iron for those patients who truly need it through widespread marketing.

This application is a little different than our usual applications for iron treatment in several ways. Most applications submitted for an iron indication are for intravenous use and focus on the demonstration of an effect in patients who are iron deficient. Those are usually randomized controlled trials involving a comparison to an improved iron product.

This application does not provide evidence that ferric pyrophosphate is effective in patients who are iron deficient and is also not an intravenous product. This application involves a novel form of iron delivery as part of a dialysate.
This application attempts to provide evidence that this product, given as part of hemodialysis solution, can be used for the treatment of iron loss or iron deficiency to maintain hemoglobin levels, whereas the agency sees that this product could be used to provide iron.

Due to the novelty of the product, the administration, the clinical trial design, and results, we are bringing this application to the committee today. The review team members will present their findings from the submitted data, and we would appreciate the committee focusing on the following two issues, whether the benefit outweighs the risks, and whether additional trials should be performed to describe potential benefits such as a reduction in ESA dosing.

Patients with stage 5 chronic kidney disease usually have a multifactorial chronic anemia, which is managed by a combination of ESA use, vitamin supplementation, iron and folate, and if needed, transfusions. Many hemodialysis patients receive intravenous iron products as part of their dialysis...
treatment.

As stated before, Rockwell Medical planned their two identical phase 3, randomized, placebo-controlled trials to enroll patients who are iron replete and on a stable ESA dose. This development plan is consistent with the agency's recommendation that two adequate and well-controlled trials be conducted for an indication.

These trials enrolled patients based on a combination of hemoglobin, ferritin, and transferrin values. No patient underwent bone marrow biopsy procedure to look at adequacy of iron stores. As such, the trial criteria would have allowed the enrollment of patients who were both iron replete as well as those who are iron deficient.

The primary endpoint was a mean change in hemoglobin from baseline to end of treatment, and the protocol mandated that patients be withdrawn from the trial if their hemoglobin went above 12, which occurred in both the placebo and treatment
arms; went below 9, which occurred in both the placebo and treatment arms; or the serum ferritin went below 100, which occurred in both treatment arms.

This is kind of a contrived situation since we're not sure what would actually happen in real life. As a result, only 18 percent of patients remained on the trial at the end of 48 weeks. Trial results showed that both trials met the primary endpoint, however, in one of the key secondary endpoints, the mean change from serum ferritin, although the ferritin changed to a smaller degree in the ferric pyrophosphate arms compared with the placebo arms, the fact that the serum ferritin decreased for the ferric pyrophosphate arms suggests that ferric pyrophosphate supplied but did not maintain serum iron. This is also supported by the need for intravenous iron and for blood transfusions, which were administered to patients in both arms.

Safety issues identified during the trial include numerically higher depths in the ferric
pyrophosphate arm compared with those seen in the placebo arm, and they appeared to be principally due to cardiac causes. Among the AEs of note were the numerically higher number of hypotensive events and arteriovenous thrombosis of the fistula and AV graft.

The applicant also conducted an exploratory, single phase 2 study to assess whether ferric pyrophosphate could reduce ESA dose in patients on hemodialysis with a hemoglobin level between 9.5 and 12. The study enrolled 100 patients and randomized them to treatment with ferric pyrophosphate or placebo.

Although the study came close to achieving the endpoint, the study results showed a discrepancy between the prescribed ESA dosing and the actual dose delivered, which questions the validity of the primary endpoint. The review team has spent a great deal of time and energy trying to find the clearest way to understand the data from this trial as well as the randomized trials.

Again, the agency requests that you focus on
whether the benefit outweighs the risks of the product and that whether additional trials should be conducted to describe other potential benefits such as ESA sparing. Thank you very much.

DR. ARMSTRONG: Thank you, Dr. Farrell.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the
committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentation.

**Applicant Presentation - Ajay Gupta**

DR. GUPTA: Good afternoon. I'm Ajay Gupta, a practicing nephrologist, inventor of Triferic, and chief scientific officer for Rockwell Medical. We are pleased to present to you today a novel method of administering iron by hemodialysis using a novel iron salt. This salt is a pyrophosphate citrate chelate of trivalent iron. Its proposed generic name is ferric pyrophosphate citrex, and the proposed trade name is Triferic. Triferic has been under clinical development since 2002 when Rockwell licensed it.

Rockwell Medical is a leader in manufacturing and distributing hemodialysis products and has been serving dialysis patients for
20 years. Triferic is Rockwell's lead investigational drug. It's the first and only parenteral iron compound that is a salt, and therefore can be delivered via hemodialysate. Since Triferic does not have a carbohydrate moiety, it reduces the risk of hypersensitivity reactions. Triferic comprises ferric iron that is tightly bound to pyrophosphate and citrate, thereby generating negligible free iron in the circulation. Triferic delivers iron directly to transferrin. Here we see the X-ray crystallographic structure of transferrin crystallized in the presence of Triferic. The crystal comprises Triferic iron shown as orange spheres in the folds of the two lobes of transferrin. Diferric transferrin so formed is taken up rapidly by the erythroid precursors in the bone marrow, leading to more efficient erythropoiesis.

So how does this novel therapy help a hemodialysis patient? Hemodialysis patients lose iron through a combination of factors, amounting to
an average iron loss of 5 to 7 milligrams per hemodialysis session. Triferic added to the dialysis solution is infused slowly by diffusive transport during the course of hemodialysis, replacing about 5 to 7 milligrams of iron at each treatment.

As you will see today, Triferic maintains iron and hemoglobin levels without overloading iron stores. Effective delivery of iron improves the efficiency or erythropoiesis and reduces the need for ESAs. Importantly, there is no evidence of oxidative, inflammation, or anaphylaxis with Triferic.

Today, we will share data from the longest duration study ever conducted for any iron therapy in hemodialysis patients. Our two placebo-controlled, pivotal trials met their primary endpoint. And in an important supportive study, we observed that Triferic significantly reduced ESA dose by 35 percent compared to placebo.

The overall safety profile of Triferic was similar to placebo across nearly 800 patient-years
of exposure. Given these results, we are seeking approval for this proposed indication. Iron replacement therapy for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult hemodialysis patients and to reduce the doses of ESAs required to maintain hemoglobin levels. Upon approval, Triferic will be the first approved, maintenance iron therapy in adult hemodialysis patients.

This afternoon, we will review the clinical landscape and Triferic clinical program in hemodialysis patients and propose Triferic as a novel option to address the unmet need for maintenance iron therapy in hemodialysis patients.

We have here additional experts to address your questions, and now I'd like to invite Dr. Fishbane to present the clinical landscape and the unmet need. Dr. Fishbane.

**Applicant Presentation – Steven Fishbane**

DR. FISHBANE: Great. Thank you, Dr. Gupta.

Good afternoon. I'm Steve Fishbane. I am a paid consultant to the sponsor. I do not have a
financial interest in the outcome of this meeting. I am an academic nephrologist with longstanding interest in iron therapy and a member of the KDIGO anemia guidelines panel and previously the KDOQI anemia guidelines panel that develops anemia guidelines for the international population of people with kidney disease and on dialysis.

In the next few minutes, I would like to discuss with you the unmet need that view in terms of iron management and some background on our disease. Currently, there's over 20 million U.S. adults who have chronic kidney disease of which 400,000 are on hemodialysis. The majority of these patients are anemic, and there are a number of factors that lead to this. Certainly, one is the deficiency of erythropoietin, a second, which you'll hear about more in Dr. Brittenham's presentation, chronic inflammation. But we've known for a long time that iron deficiency and replacement of iron plays a very important role.

Patients lose iron with every hemodialysis treatment, and they do so primarily because at the
end of the treatment, there's iron and there's
blood that's left behind. That's retained within
the filter, within the apparatus, and the
dialysate. But there are additional causes of loss
as well. There's repetitive bleeding from the
vascular access. We draw a lot of blood from these
patients. They have surgery.

In addition, they have gastrointestinal
blood loss, which has substantially increased
compared to the general population. And when you
take this together, they have far greater losses of
iron, which makes iron repletion almost mandatory
in the vast majority of people who are on dialysis.

Our end treatment today in hemodialysis
really falls into two categories. We use these two
arbitrary terms a lot that nephrologists will
recognize. We talk about repletion, repletion
therapy, or administering what is essentially
1,000 milligrams of intravenous iron over
10 dialysis treatments in iron-deficient patients.
These patients in general have low ferritin values,
and we consider them to be strictly iron deficient.
The IV iron products that are currently approved in the U.S. are approved for this indication. But in point of fact, most iron therapy in the United States today is really conducting it by what we would term maintenance therapy, in which rather than waiting for people to become iron deficient, we replete iron on a regular basis. We give weekly doses of, say, 50 to 100 milligrams of intravenous iron weekly. But the IV iron products that we're using for this purpose to try to keep up with the iron losses of patients are not approved by the agency as maintenance iron therapies. We're using them off label and lack information on the efficacy of safety within this indication.

The amount of IV iron that's currently being used for hemodialysis patients in the United States is fairly substantial. You'll see on this figure that over the last couple of years, patients are receiving over about 300 milligrams per month. I'd like to point out that there is a very substantial mismatch, which is currently taking place between
the amount that patients are losing and the amount
that's administered. So this is about
3,600 milligrams of iron that we're giving per year
with losses of about 1,000 milligrams per year.

As a result, this causes an imbalance. As
we're trying to squeeze intravenous iron into a
role that it's really not designed for, we're
getting increasing levels of ferritin. So if you
look back at 1993, patients really suffered because
of iron deficiency and that resulted to anemia.
Average levels of ferritin were approximately
300 microgram per deciliter.

You'll see that over the years, as we've
tried to use intravenous iron in this maintenance
role that ferritin values have tended to grow
higher and higher into the 600's. And more
recently, serum ferritin concentrations have been
at approximately 800 micrograms per deciliter in
the dialysis population.

Now, anemia treatment practices more
generally have gone through extensive changes from
the '90s, when ESAs were first available until the
late 2000s. Hemoglobin levels and ESAs doses went up, as you'll see, in lock-step. It went up until hemoglobin levels were approximately 12 grams per deciliter in the United States. But please notice what's happened in the last couple of years, as we've seen hemoglobin and ESA dose decrease. And that's decreased in response to additional knowledge that we have gained through clinical trials and in terms of agency labeling in terms of how best to use these agents in the clinical setting.

Interestingly, as we've seen this drop off in ESA dose and hemoglobin levels, we've seen an important increase in blood transfusions. This is U.S. hemodialysis data for recent years, and you'll see that on the far right in that set of data that over the last four years, the rate of transfusion for these patients has increased by about 30 percent.

Transfusions is always an important issue for patients, but I'd like to remind at least those of you that don't work with dialysis patients that
it has very particular importance in our population in that the gold standard by far for these patients is kidney transplantation. And that by the sensitization that occurs with transfusion, we are depriving patients, in many cases, of the ability to subsequently undergo kidney transplantation.

When we relate hemoglobin levels to clinical outcomes, there have been a variety of published observational studies that have shown what Regidor and his colleagues showed in the current study, that there's a direct relationship between hemoglobin concentration and the risk for mortality.

Small decreases in hemoglobin under 11 -- by the way, this is most closely related to what was seen in the studies that you'll hear about today -- there's approximately a 40 percent reduction in risk for mortality. We'll be careful here. It's an observational study, but the strength of this association is something that we'll need to consider.

Hemodialysis patients are generally a sick
population. They do not have good outcomes. The mortality rate remains disturbingly high. The quality of life for patients tends to be greatly diminished. Patients spend an average of 12 days per year in the hospital.

One thing that's really interesting -- you'll note on this slide -- is that we've been fairly successful in terms of reducing the rate of hospitalizations. But please note that one area of very grave concern is that in recent years, the rate of infection in patients has gone up, and not just gone up, gone up by 43 percent. And it's been something of a mystery until now why is it that the rate of infections has increased so sharply.

As you'll see -- this is from an editorial we published just this much -- that as serum ferritn values have risen over the years and intravenous iron treatment has increased, you'll see that the rate of hospitalizations due to bacteremia have increased in lock-step. And as ferritin values temporarily leveled off with a
little bit of a lag, bacteremia leveled off as well. And unfortunately, we don't know with the most recent increase in ferritin what has been the impact in terms of infections.

Now, this doesn't prove causality, but it does suggest the relationship. And over the last year and a half, we've seen I think a very alarming number of studies now that have very strongly indicator relationship between the rapid injection of iron with intravenous iron and the rate of infections that these patients experience.

Taken together, this association has further substantiated. This is a meta-analysis published in the British Medical Journal I think last year in which Litton and colleagues looked at all studies, RCTs of IV iron, and they found that there was a fairly strong relationship in terms of relative risk between treatment with intravenous iron and rate of infections.

So what is the unmet need in dialysis patients? Patients require iron replacement to maintain hemoglobin levels. It's a basic health
need of these patients. We need to be able to
match the amount of iron that's lost with every
dialysis treatment to replacement. That is true
maintenance therapy. We've never been able to do
that to date as we've tried to squeeze IV iron into
that role.

Currently, we're using IV iron to try to
address this need, but it's not ideal. The
majority of IV iron gets sequestered, and that
leads to this mismatch between the amount of
administered iron and the amount of iron that is
lost. And this has led to the increase as we've
seen in serum ferritin, and I believe to the risk
for infection that we've seen in recent years very
strongly demonstrated. Iron remains a very
important need for these patients, but there are
important concerns, and there's an unmet need
related to that.

I thank you all very much for your
attention, and I turn over now to Dr. Brittenham to
speak about how the mechanisms of action of
Triferic address the unmet need that I've
discussed.

Applicant Presentation - Gary Brittenham

DR. BRITTENHAM: Good afternoon. Thank you, Dr. Fishbane. I'm Gary Brittenham, a hematologist. And I'm a paid consultant to the sponsor, but I have no financial interest in the outcome of the meeting. In the next few minutes, I would like to discuss a new physiologic approach to replacing iron losses in patients who receive chronic hemodialysis.

First, let us consider the distribution of iron in the body in health. Most iron is present in functional pools as hemoglobin within circulating red blood cells and in the erythroid marrow as myoglobin and muscle and in the enzymes within hepatocytes and other cells throughout the body.

In healthy individuals, the body has iron stores within reticuloendothelial macrophages in the spleen, bone marrow, and liver, and within hepatocytes. This storage iron can be mobilized to compensate for iron losses. Transferrin is the
transport protein that carries iron to the
erythroid marrow and to other tissues.

The body treats iron like a precious metal.
There's no mechanism for iron excretion and almost
95 percent of the iron for red blood cell
production is derived from recycling of iron from
red blood cells at the end of their life span.
Only minute amounts of iron are physically lost
each day, and in health, these losses replaced by
absorption of dietary iron.

In patients treated with hemodialysis, iron
homeostasis is more complex. Dialysis and uremic
blood losses ultimately result in anemia. At the
same time, the inflammation of chronic kidney
disease results in a marked increased in the iron
regulatory hormone hepcidin, which blocks both
recycling of iron and absorption of iron from the
diet. As a result, transferrin saturation falls,
restricting iron delivery to the marrow. So the
marrow is unable to produce enough red blood cells
to maintain the circulating hemoglobin
concentration, and anemia worsens.
At present, IV iron is administered to replace these iron losses, but much of this iron is retained within the reticuloendothelial system because of the hepcidin block to iron release. Thus, with each IV iron treatment, iron stores increase further, eventually leading to iron overload.

Triferic and iron salt added to hemodialysate bypasses the hepcidin block. Triferic contains no carbohydrate, minimizing the risk of anaphylactic reactions. The iron in Triferic is tightly bound to pyrophosphate and to citrate, minimizing the risk of formation of non-transferrin bound iron and of oxidative injury. Triferic crosses the dialyzer membrane into the systemic circulation, where it directly donates iron to transferrin, circumventing the hepcidin block.

Once bound to transferrin, Triferic iron helps restore red blood cell production in the marrow. The increased iron supply helps improve erythropoiesis and maintains circulating...
hemoglobin concentrations. By improving the supply of iron to the erythroid marrow, Triferic also improves the response to erythropoiesis stimulating agents.

Now, I would like to invite Dr. Raymond Pratt to the podium to discuss the efficacy results seen in the Triferic clinical development program.

**Applicant Presentation - Raymond Pratt**

DR. PRATT: Thank you, Dr. Brittenham. My name is Raymond Pratt, and I'm the chief medical officer at Rockwell Medical. I'll be presenting the pivotal and supportive efficacy results of the Triferic clinical program. As Dr. Gupta mentioned in his introduction, Triferic successfully met the primary endpoint in two adequate identical, placebo-controlled, phase 3 trials plus successfully reduced ESA dose in placebo-controlled phase 2 study.

The Triferic clinical program included 7 phase 2 and 3 studies. The duration of the trials were the longest of any conducted with iron in CKD hemodialysis patients. There were two adequate and
well-controlled pivotal trials named SFP-4 and SFP-5, and there was one well-controlled supportive efficacy study called NIH-1. The controlled clinical studies enrolled over 1,400 patients, and long-term safety was studied in three open-label extension studies, where patients could be exposed to Triferic for up to 18 months.

The patient population of the Triferic program is consistent with the overall chronic dialysis population in the United States. All studies enrolled adult patients undergoing chronic in-center hemodialysis 3 or 4 times per week. All patients met guideline recommended hemoglobin levels between 9.5 and 11.5 grams per deciliter at study entry and were iron replete according to transferrin saturation and serum ferritin measurements. ESA doses were required to be stable prior to randomization.

This is the first phase 3 program designed to study iron as a maintenance therapy in hemodialysis. In discussion with the FDA, placebo was selected as the control because there are new
approved treatment options for maintenance iron therapy. The primary clinically meaningful endpoint was hemoglobin concentration. In order to isolate the effect of Triferic on hemoglobin, ESA doses needed to be held constant and no supplemental iron was allowed during the trial. As Dr. Brittenham noted, both ESA and iron can independently affect hemoglobin concentration.

The hemoglobin range for the trial was set between 9 and 12 grams per deciliter to ensure patient's safety. We performed 2 identical randomized, single-blind, parallel-group, placebo-controlled studies, utilizing different investigative sites. The studies had three stages. First, a run-in period of up to 4 weeks, then a randomized treatment period during which patients in the Triferic arm were dialyzed with hemodialysate containing two micromolar Triferic iron and placebo patients received standard hemodialysate.

The dose was chosen based on a dose ranging study, where it delivered the maximum amount of
iron while not over-saturating transferrin. In this stage, the patient's dose of ESA could not be changed and no supplemental iron, either oral or intravenous, was allowed.

Patients completed randomized treatment and could move to the open-label extension stage when they met 1 of 4 criteria: their hemoglobin became less than 9 or increased to greater than 12 grams per deciliter; or their serum ferritin became less than 100 microgram per liter; or their hemoglobin concentration was 11.5 grams per deciliter with a rise of greater than 1 gram per deciliter over a 4-week period; or if they did not meet one of the first three criteria, they completed study after 48 weeks.

Patients who completed randomized treatment continued in the open-label stage, receiving Triferic for up to 18 months total time regardless of treatment allocation during the randomized stage. Given this study design, we had some constraints on the magnitude of the effect that could be observed. For example, if patients'
hemoglobin decreased to less than 9 gram per
deciliter, they completed the randomized stage and
were then able to have an increase in their ESA or
receive IV iron in the open-label stage. Likewise,
if hemoglobin increased to greater than 12 grams
per deciliter, they completed the randomized stage
and were able to receive a reduction in ESA dose in
the open-label study.

The primary endpoint was assessed by taking
the average of the hemoglobin concentrations
obtained during the last one-sixth of the time
patients were treated in the randomized phase of
the study. This allowed an assessment of the
durability of Triferic therapy. Supporting
secondary endpoints included whole blood
hemoglobin, reticulocyte hemoglobin, and serum
ferritin concentrations over time.

We employed a conservative testing approach
in our statistical analysis plan. The primary
endpoint used an ANCOVA model with a baseline
hemoglobin as covariate. The prespecified analysis
population was the mITT population defined as all
patients who were randomized received at least one
dose of study drug and had at least one post-
baseline hemoglobin value. We used all patients' 
observed data for the mITT and ITT populations.
The sensitivity analysis included the ITT 
population and a mixed-models repeated measures 
analysis. Post hoc analyses included a multiple 
imputation model and an analysis of the change from 
baseline in hemoglobin for patients who completed 
the study due to the protocol mandated changes in 
anemia management.

A total of 599 patients were randomized with 
299 receiving Triferic and 300 receiving placebo. 
Sixty-seven percent of the patients completed the 
randomized treatment by meeting one of the 
protocol-specified criteria. The majority of these 
patients entered the open-label stage, and 
80 percent of them provided follow-up data for a 
total of up to 18 months.

Thirty-three percent of patients actually 
withdrew for reasons, including transplantation, 
adverse events, transfusions, or protocol
violations. The proportions and timing of these withdrawals were similar between the Triferic and placebo groups, and all hemoglobin values from this group were included in the primary analyses.

Here we see patients who completed the randomized treatment according to the protocol. More patients received Triferic completed for hemoglobin levels greater than 12 gram per deciliter and more patients receiving placebo completed for hemoglobin levels less than 9 grams per deciliter. This tells us that more patients on Triferic required a decrease in ESA dose, while patients on placebo required an increase in their ESA dose. The majority of these patients and these groups transitioned to the open-label extension phase.

The patient demographics in the new studies were well balanced and reflected the current makeup of the U.S. chronic hemodialysis population. Patient populations were also similar with respect to underlying cause of renal disease, dialysis vintage, cardiovascular and inflammatory conditions, and baseline laboratory
characteristics.

The study met its primary endpoint. It demonstrated consistent and statistically significant effective Triferic to maintain hemoglobin concentrations relative to placebo. At the end of treatment, patients receiving Triferic maintained their hemoglobin concentrations. That is, they showed no change from baseline in the average of the hemoglobin concentrations during the last one-sixth of study participation.

The placebo group showed a decline in hemoglobin concentration as expected for a group deprived of iron and without changes in ESA dose. The difference between Triferic and placebo groups was a statistically significant 0.36 grams per deciliter in each study with a p-value of 0.011.

These results were robust. The Triferic demonstrated maintenance of hemoglobin in all populations, subgroups and sensitivity analyses evaluated, including the ITT population. With the exception of the multiple imputation analysis for the efficacy evaluable population for SFP-4, all
analyses showed statistically significant effects favoring Triferic. The post hoc analysis of patients who completed the study due to protocol mandated changes in anemia management showed a similar mean difference when compared with placebo.

Now, I'd like to turn to our secondary endpoints. Given the similar results seen across the two trials, we pooled these for data presentation. The individual study results are in your briefing document. Reticulocyte hemoglobin is the earliest indicator of iron-restricted erythropoiesis, and Triferic maintains reticulocyte hemoglobin while placebo shows a decline in reticulocyte hemoglobin. The reticulocyte hemoglobin content parallels the hemoglobin level, and this indicates that Triferic provides effective erythropoiesis while the placebo groups develop iron-restricted erythropoiesis.

Serum ferritin is an index of body iron stores and inflammation. Patients receiving Triferic maintain their hemoglobin while they do not increase their serum ferritin. This tells us
that the iron is being used directly and not being
sequestered. These results demonstrate that
Triferic can provide sufficient iron to maintain
erthropoiesis. Placebo patients showed declines
in ferritin and hemoglobin indicating that they are
unable to mobilize sufficient iron to maintain
hemoglobin synthesis.

Now, I'd like to turn your attention to our
ESA sparing trial, the NIH-1 study. And by ESA
sparing, we mean that either the decrease in ESA
dose or the absence of an increase in ESA dose in
response to a change in therapy. The primary goal
of this study was to determine whether Triferic
could spare the need for ESA while maintaining iron
balance. Additionally, the trial explored the
effective Triferic on patients with ESA
hyporesponse.

This was a randomized, double-blind,
placebo-controlled, parallel group study. Patients
who were iron replete with stable ESA doses during
a 2-week run-in period were randomized to dialysate
containing Triferic or placebo for up to 36 weeks.
The objective was to maintain hemoglobin concentrations between 9.5 and 11.5 gram per deciliter by adhering to a common ESA and IV iron algorithm.

A blinded central anemia management group facilitated ESA dosing based on the patients' weekly trends in hemoglobin values. IV iron could be administered only for development of iron deficiency as determined by a serum ferritin of less than 200 microgram per liter.

The primary endpoint was the percent change from baseline to the end of treatment in prescribed ESA dose with end of treatment defined as the last 2 weeks on study, and 80 percent of the patients completed this 36-week treatment period.

Like the pivotal trials, the NIH study met its primary endpoint. At the end of treatment, there was a statistically significant 35 percent reduction in prescribed ESA dose relative to placebo in the Triferic group. It's important to remember that there's a clinical benefit for reducing ESA dose due to the risks associated with
ESAs.

Here we see the changes in hemoglobin on the top line and the ESA use on the bottom line amongst placebo patients. The hemoglobin in the placebo group starts to decline, which corresponds with an increase in prescribed ESA dose to keep the hemoglobin within the target limits.

Now, when we look at the Triferic group in red, we see that there is no hemoglobin change and no increase in prescribed ESA dose. The difference in the ESA dose is between Triferic and placebo at the end of treatment is statistically significant at 35 percent. I would like to note that the maintenance of hemoglobin in the Triferic group and the decline of hemoglobin in the placebo group are similar in magnitude to what was observed in the SFP-4 and -5 pivotal clinical studies.

We also looked at ESA hyporesponsive patients defined as patients whose response to ESAs is typically suboptimal, that is greater than 13,000 epoetin units per week. These patients used approximately twice the amount of ESA as the
average patient. This subgroup demonstrated a 74 percent reduction in ESA dose compared with placebo.

Similar to the SFP-4 and -5 studies, serum ferritin levels do not increase in the Triferic group, but they decline in placebo. This shows that Triferic can effectively replace iron losses with each dialysis treatment to maintain hemoglobin levels and decrease ESA dose without increasing iron stores.

Now, to summarize the efficacy results, Triferic administered by a dialysate matches the iron need, maintains hemoglobin without increasing iron stores while reducing ESA. The primary endpoint was met in each study, maintenance of hemoglobin and reduction in ESA, and these results were consistent across multiple analyses.

The difference between Triferic and placebo groups was statistically significant at 0.36 grams per deciliter in each study with a p-value of 0.011. This is a clinically relevant and meaningful result. As Dr. Fishbane noted earlier,
a change in hemoglobin of this magnitude in the
hemodialysis population is associated with a
decreased risk of blood transfusions and mortality.

I would like to now introduce Dr. Vivian Lin, our senior director of clinical research at
Rockwell Medical to summarize the safety profile of Triferic.

Applicant Presentation – Vivian Lin

DR. LIN: Thank you, Dr. Pratt. I'm Vivian Lin, senior director of Rockwell Medical. I will
now discuss the Triferic safety data, which showed that the tolerability profile of Triferic is
similar to placebo.

The Triferic safety profile was analyzed using two safety populations. The first, the
controlled phase 2 and phase 3 included all patients who received at least one dose of study
drug, Triferic or placebo, in three blinded, randomized, placebo-controlled studies. All
Triferic patients received the same dose, 2 micromolar and dialysate. This was the primary
population for evaluating the safety profile of
Triferic.

The second, the all phase 2 and phase 3, included all patients in phases 2 and 3 received at least one dose of Triferic, 1411 patients, the vast majority of whom received the 2 micromolar dose. In this population, we looked only at the Triferic treatment group. So the data for this group in the following slides is labeled all Triferic.

The Triferic safety profile is characterized by a large clinical trial database. The mean duration and total exposure in the Triferic and placebo grouped in the control population, shown in the first two columns of the table, were essentially identical. The total exposure in both groups was about 160 patient-years. In the graph, we can see that the Triferic patients, in red, and placebo patients, in black, left the control studies at the same rate, suggesting that the overall tolerability of Triferic is similar to placebo.

Finally, the total Triferic exposure was 780 patient-years, 5 times that in the control
studies shown in the all-Triferic group in the last column of the table. Most of the exposure in this group came from the 3 long-term open-label extension studies, which had a completion rate of 80 percent. Some patients, 55 percent of those originally randomized in the phase 3 efficacy studies, received Triferic for 18 months. This large database allows us to really understand the safety of Triferic.

Overall adverse events were similar between the two groups. This column show the number and percentage of patients in the controlled Triferic and placebo groups. Relatively few patients experienced related adverse events or adverse events relating this study discontinuation. There were also relatively few deaths, 4 percent for Triferic and 2.9 percent for placebo. I'll go into the mortality in greater detail later in the presentation. Finally, the proportions of patients experiencing serious adverse events were also similar between the two groups.

The common adverse events were similar
between the Triferic and placebo groups.

Procedural hypotension, the most common AE, was experienced by 23 percent of the Triferic group and 22 percent of the placebo group. This term primarily consisted of cases of intradialytic hypotension or IDH. Since IDH is a possible indicator of iron toxicity, it's reassuring that the rates are the same.

The common serious adverse events were also similar between the Triferic and placebo groups. You can see that the proportions of patients who had serious events of CHF, pneumonia, and fluid overload were about the same between Triferic and placebo. The rates of cardiac-related SAEs in general was likewise similar. Also, given the concern that iron may promote bacterial growth, it's reassuring to note that the proportions of patients with infection-related SAEs was also about the same.

The proportions of patients with specials safety events were likewise similar between the two groups. For these events, the rates in the
controlled population are shown in the first two columns, and the rates in the all-Triferic group are shown in the last column. As you can see, for each of these events, the rates in the controlled Triferic and placebo groups were pretty similar.

For the 2 cases of suspected hypersensitivity that were considered related to Triferic, these were non-serious events that resolved within minutes without epinephrine or other drastic measures. Further evaluation showed that one of the events was more likely due to hypovolemia rather than hypersensitivity. Finally, looking at the all-Triferic group in the last column, it's reassuring that the rates overall were similar to those observed in the controlled studies, as one could have expected to see more events when patients were followed out longer.

The overall mortality was similar between Triferic and placebo. For completeness, the analyses of the controlled studies shown on this slide also include the phase 3 SFP-6, randomized,
double-blind, placebo-controlled, crossover safety study, which is also included in the all-Triferic group.

There were relatively few deaths in the controlled studies, 14 in the Triferic group and 13 in the placebo group, about one-third the predicted rate from the 2013 U.S. Renal Data System report. As these were small numbers, in order to get a better estimate of the mortality rate, we looked at the all-phase 2 and phase 3 population and calculated the exposure adjusted mortality across all patients who received Triferic. None of the events occurred during administration of Triferic, and none were felt by the investigator to be due to Triferic.

A tabular summary of all deaths on Triferic is provided in table 11.2 of the briefing book. The exposure adjusted mortality rate in the all-Triferic group was 6.5 per 100 patient-years. This is similar to the 7.2 per 100 patient-years in the placebo group of the controlled studies.

We carefully evaluated each of these cases,
and the data did not show anything unusual about
the Triferic patients compared to the placebo
patients. The causes of death were similar in the
two groups and as expected were mostly cardiac
related. On evaluation of the case narratives, the
reported terms of cardiac arrest, sudden death, and
death generally described similar types of events.

As the outcomes of these types of events
depend in part on whether they are witnessed, we
also looked at non-fatal events. There were 2
additional cases of non-fatal cardiac arrest that
occurred in the placebo group. Taken together,
however, there is still a slightly numerical
imbalance in the two groups in the subset of
events, 11 in the Triferic group and 8 in the
placebo group.

The Independent Data Safety Monitoring Board
for the pivotal studies reviewed 10 of the cases
that occurred in the Triferic group and felt that
the events were unrelated to Triferic. We also
performed a careful review of the cases and did not
see any differences between the Triferic and
placebo patients. We evaluated the rates of serious arrhythmias and cardiovascular ischemic events in the overall controlled safety population, and there were no differences between Triferic and placebo. Also, as we discussed, there were no differences in composite cardiovascular events or other special safety events.

The independent assessments of the investigators' DSMB and our internal case review were consistent. In these patients with multiple cardiovascular risk factors, the fatal events were most likely due to underlying disease rather than Triferic. The assessment of the FDA medical reviewer, as presented in the FDA briefing book, was also consistent, indicating that the cases could most likely be attributed to comorbid disease or disease progression.

The totality of the data suggests that a numerical imbalance in the subset of deaths does not constitute a cardiovascular safety signal and that the cardiovascular safety of Triferic is similar to placebo.
Turning to labs and vitals, no safety signals were observed in the chemistry or hematology safety labs or in vital signs. Specifically, there were no changes from baseline to end of treatment in liver function tests, and no patients met Hy's law criteria. There were no changes in mean calcium or phosphorus. Mean ferritin did not increase, and the incidence of individual ferritin greater than 1200 micrograms per liter was the same in the Triferic and placebo groups.

For markers of inflammation, we also looked at CRP, and there were no mean increases relative to placebo. In the NIH-1 study, we looked at markers of oxidative stress and, again, changes were about the same as placebo. And finally, there were no changes in pre-dialysis or post-dialysis mean blood pressure. Additionally, in the phase 3 efficacy studies, about half as many Triferic patients needed transfusion as placebo patients.

In summary, the Triferic safety profile supports the use of Triferic 2 micromolar as a
maintenance therapy for CKD-HD patients. This is based on a larger safety database with over 1400 patients representing nearly 800 patient-years of exposure. The overall adverse event profile, including adverse events of special interest, was similar to placebo.

There were no cases of anaphylaxis in over 100,000 doses administered. There was no evidence of iron-related toxicity or iron overload. And finally, there was no evidence of increased inflammation or oxidative stress. Across the clinical program, Triferic demonstrated a consistent and well-defined safety profile suitable for use as a long-term maintenance therapy. Thank you.

Next, Dr. Fishbane will present his clinical perspectives on the use of Triferic.

**Applicant Presentation - Steven Fishbane**

DR. FISHBANE: Thank you, Dr. Lin. I'd now like to conclude the presentation by offering my clinical perspective on the use of Triferic and its benefits and risks in this setting. I've been
actively treating patients on hemodialysis for 20 years. I've had the opportunity to serve as an investigator in the phase 2 and principal investigator in the phase 3 studies.

My experience with Triferic has demonstrated its utility for the dialysis patients and treating physicians. What we've seen is that Triferic effectively maintains iron balance. It has a novel mode of delivery. It met its primary endpoints in two replicate phase 3 clinical trials. It maintains hemoglobin levels. Triferic reduces ESA dose requirements. It does not increase iron stores. It matches iron needs with replacement while decreasing the need for blood transfusions. And all of these outcomes are clinically important.

In the placebo treated patients from the phase 3 studies, if you deprive patients of iron, what you find is that hemoglobin concentrations progressively decline, whereas when we look at the Triferic group, hemoglobin is maintained. And I'll remind you that this occurred despite no changes in ESA dose and no use of intravenous iron.
How important is the change in hemoglobin that we observed? I want to return to the Regidor study that we saw earlier. I remind you that our patients generally started around at 11 hemoglobin, and in the placebo group declined to approximately 10.5 grams per deciliter. You see that effect in terms of mortality is approximately 40 percent.

Let's be conservative about this. It's an observational study, but let's recall that by the time these patients develop end-stage renal disease, they have extensive heart disease, left ventricular hypertrophy, coronary artery disease, and are very sensitive to the hypoxic insults that occur with dialysis patients. And this makes these patients substantially more sensitive to small changes in hemoglobin response. Overall, these data suggests that changes in hemoglobin at this magnitude may be clinically relevant.

In addition, another clinical benefit demonstrated was that related to blood transfusion. This was related to 50 percent reduction or greater than 50 percent reduction in the Triferic group.
compared to placebo. And I'll just remind you again, the transfusions in our patient population is highly important as it helps patients get to transplantation.

In addition, we saw a positive effect in terms of ESA dose sparing, so we've seen, as presented by Dr. Pratt, a 35 percent reduction in ESA dose requirement. ESA dose is strongly associated with adverse outcomes. The agency reminds us to use the lowest dose possible in order to try to avoid that type of outcome.

When we compare Triferic with intravenous iron -- and this is where the unmet need truly emerges -- Triferic makes for a better option in terms of maintenance therapy. And most hemodialysis patients require this because of their ongoing, every dialysis treatment loss of iron. IV iron only has an indication and testing for repletion therapy. Triferic will have the proposed maintenance indication if approved and was studied specifically for this purpose.

As to quantitative iron needs, Triferic
simply matches iron loss with every treatment with the amount of iron the patients require. In contrast with intravenous iron, we're injecting 100 milligrams of iron directly into the blood stream, in a couple of minutes overwhelming the ability of transferrin to bind it. And we think that's related to a number of the problems that we've been seeing with intravenous iron.

The rate of infusion with Triferic is slow. It's given over the length of the dialysis treatment. Iron sequestration and overload have become an important concern with the use of intravenous iron, in a classic article by Ro Stocker last year, that with the extensive use of intravenous iron off label, that we see a substantial overload. Triferic directly binds to transferrin, therefore iron sequestration and overload should never be a problem with this agent.

The most important safety issue that has evolved with intravenous, and much of this has evolved just in the past two years, and frankly three of the key studies have been in the previous
month -- but there is now a very sizeable, convincing, and strong body of evidence that indicates that intravenous iron is related to infections.

Now, with Triferic, we can't be entirely conclusive and want to be conservative in terms of this. But when you're only giving enough iron to match losses, there should never be free iron in the circulation available to microorganisms. Biologically that makes sense, and in the phase 3 clinical trials, we see that there is similar rate of infection slightly less but let's call it the same, between placebo and patients treated with Triferic, not even a hint of a signal.

Finally, anaphylaxis. All of the carbohydrate-based intravenous iron drugs are associated with anaphylaxis. It's a relative rare event but still continues to occur and occasionally be a catastrophic reaction for patients. We had one just about a month and a half ago that required hospitalization from one of our patients. Triferic has no carbohydrate moiety, and there hasn't been
anaphylaxis observed with it.

The benefit of Triferic has been clearly established and outweighs potential risks.

Efficacy, the benefit, is based on the totality of the evidence and is highly directionally consistent for all variables. Triferic maintains hemoglobin levels, reduces ESA dose requirements, reduces the need for intravenous iron, and reduces transfusion needs. Efficacy is clearly established by this consistency in the totality and directionality of the results.

We saw low-risk potential in the safety profile. It does not increase iron stores, which has been such a problem with the use of intravenous iron. No anaphylaxis cases have been observed in over 100,000 doses that have been administered, and the rate of infection, as we've seen, is similar to placebo. Taken together, we see an overall very favorable benefit to risk profile.

The results presented today match what I've observed since working with Triferic in phase 2 through the phase 2 program. I believe we have
tried to squeeze intravenous iron into a
maintenance role. We have potentially hurt our
patients with iron overload infections,
anaphylaxis, and similar risks. Now we have the
opportunity to provide maintenance therapy by
giving small amounts of iron as required simply to
maintain iron balance.

As a practicing nephrologist, I truly
believe this is an improved therapy that will
greatly benefit hemodialysis patients. Thank you
for your attention.

DR. ARMSTRONG: Thank you to the sponsor.
We'll now proceed with the presentation from FDA.
I'd also like to apologize. We haven't introduced
the panel members, which we will do after this
presentation and before the panel questions.

DR. ROBIE-SUH: Before we start, I just have
one comment regarding the FDA briefing document.
On page 52 of that document, there is a sentence
that refers to an Appendix 1. That sentence was
left over from an earlier version of the document
and should be deleted. There is no appendix for
FDA Presentation — Min Lu

DR. LU: Good afternoon. My name is Min Lu. I'm a medical reviewer in the Division of Hematology Products. I will summarize the major findings from the Triferic NDA review. [Indiscernible] we'll present the mean efficacy results and the statistical issues from the clinical trials.

DR. ARMSTRONG: Excuse me. Can you just speak a little bit more into the microphone?

MS. LU: This slide acknowledges the FDA Triferic review team. I'll start with the proposed indication and the key issues for each indication, a brief comment on current FDA-approved iron products for patients with hemodialysis-dependent chronic kidney disease, followed by a brief summary of Triferic products. Then we will present the efficacy and safety results in the clinical trials for each indication in sequence. Dr. Luo will describe the mean efficacy results during the presentation. At the end, I will provide a brief
summary of study findings and all questions for the panel.

In the Triferic NDA, applicant proposed two indications. The first indication is for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease. The second is to reduce the prescribed dose of erythropoiesis stimulating agent required to maintain desired hemoglobin levels.

This slide lists the key issues for the proposed first indication. In the two phase 3 trials, about 50 percent of study patients discontinued the study treatment prior to 48 weeks due to protocol mandated changes in anemia management, mostly due to ESA dose changes. There were differential reasons for treatment of discontinuation between Triferic and the placebo groups that may impact the study results. There were more observed deaths in the Triferic group as compared to the placebo group in the phase 3 trial.

This slide lists the key issues for the
proposed second indication to reduce the ESA dose in this population. It was based on a single phase 2 trial. There was no formal sample size or power calculations planned in the study. There is difficulty in the interpretation of efficacy results. No phase 3 trials were conducted for this indication.

The currently approved iron products for us in hemodialysis-dependent chronic kidney disease are intravenous iron products. This includes iron dextran, sodium ferric gluconate complex, iron sucrose, and ferumoxytol. They were approved for indication for treatment of iron deficiency anemia and administered by intravenous iron injection or infusion. The dose ranged from 100 to 510 milligram per dose. Serious and life threatening anaphylactic or anaphylactoid reactions are the major safety concerns.

Triferic is a ferric pyrophosphate and is also referred to as SFP. The product does not have a carbohydrate moiety unlike other intravenous iron products. Triferic is supplied as 5 milliliter
ampule containing 27 milligrams of iron. For use, 1 iron pill is added to each 2.5 gallons of bicarbonate concentrate. The final concentration after further dilution is 110 microgram iron per liter dialysate.

Now I will present the findings for the first indication for the treatment of iron loss or iron deficiency to maintain hemoglobin. To support this indication, two phase 3 clinical trials, RMTI-SFP-4 and the RMTI-SFP-5 were conducted. The two trials had identical study design. They were randomized, single-blind, placebo-controlled, multicenter trials. Patients received either dialysis with Triferic or placebo dialysis for up to 48 weeks.

The primary efficacy endpoint was a mean change in hemoglobin from baseline to the end of the treatment period that was defined as the last one-sixth of treatment period in the randomized phase. No intravenous iron or oral iron was allowed, and no significant change of ESA dose was allowed in the randomized study.
The mean inclusion criteria of study included patients undergoing hemodialysis at least 4 months, hemoglobin level between 9.5 to 11.5 gram per deciliter, transferrin saturation of 15 to 40 percent, and serum ferritin level 200 to 800 microgram per liter. Patients also should have adequate dialysis, stable dialyzer blood flow rate, and a stable vascular access for dialysis for the last 3 months.

In the two phase 3 trials, the protocol provided criteria as is shown for protocol-mandated change in anemia management. This included hemoglobin criteria for ESA dose change and the serum ferritin level for intravenous iron administration. For both phase 3 studies, any patient requires a significant ESA dose change or IV iron administration would be removed from randomized phase of study at that time.

This slide shows a number of randomized patients in the studies. A total of 305 patients were randomized in the first study and 294 patients were randomized in the second study. The majority
of patients in both studies were from the United States.

The demographics of study populations are summarized here. The median age of study patients was about 60 years in both treatment groups in the two studies. The majority of subjects were male and most were Caucasian. This was comparable between the SFP and the placebo groups in the SFP-4 study. There were slightly more males and Caucasians in the placebo group compared to SFP group in study SFP-5.

The baseline mean hemoglobin level was about 10.9 grams per deciliter in both studies comparable between the SFP in the placebo groups. The baseline mean transferrin saturation was about 28 percent, and the serum ferritin level was about 500 microgram per liter in the study population. There were similar between the two groups in both studies.

This slide shows the hemodialysis parameters during the study. Almost all study patients were undergoing hemodialysis 3 times a week. There were
no apparent major differences in duration of
dialysis, blood flow rate, and dialysate flow rate
between the SFP and the placebo group in both
studies.

This slide shows the subject disposition in
two trials. Less than 20 percent of study patients
completed 48 weeks of study treatment. About 50
percent of study patients were removed from
randomized phase prior to 48 weeks due to protocol
mandated changes in anemia management. There were
more patients removed for this reason in the
placebo group as compared to SFP group in both
studies. Other main reasons for early withdrawal
were protocol violations for ESA dose change,
intravenous iron use, deaths, blood transfusion,
adverse events, and withdrawal consent.

This slide summarizes the final hemoglobin
and serum ferritin level in patients who are
removed from randomized phase due to
protocol-mandated changes in anemia management.
Both treatment groups had a patient with a final
hemoglobin more than 12 gram per deciliter as well
as patient with hemoglobin less than 9 grams per deciliter that required an ESA dose change. However, slightly more patients had a final hemoglobin more than 12 grams per deciliter in the SFP group than in the placebo group, and slightly more patients had a final hemoglobin less than 9 grams per deciliter in the placebo than the SFP group in both studies.

Also, most subjects had a final serum ferritin level less than 100 microgram per liter in the placebo as compared to SFP group that required IV iron treatment in both studies.

Next, Dr. Luo is going to present the efficacy results for the SFP-4 and the SFP-5 studies.

**FDA Presentation - Lola Luo**

**DR. LUO:** Thank you, Dr. Lu. Good afternoon. My name is Lola Luo. I'm the statistical reviewer for this NDA. In this section, I will review the statistical analysis plan, report the efficacy results, then I will discuss the statistical issues related to the large
extent of subjects who discontinued the treatment early.

Again, the primary efficacy endpoint for the two pivotal studies was the mean change in hemoglobin from baseline to end of treatment. End of treatment was defined as the last one-sixth of the randomized period for each subject. If a subject completed the whole 48 weeks of the study, then the end of treatment is about 8 weeks.

Subjects were randomized in a 1 to 1 ratio to either SFP or placebo. Randomization was stratified by the pre-randomization hemoglobin value and by the baseline prescribed ESA dose. The study was a single-blind trial. Only the subjects were blinded to the treatment group assignment.

The study was designed to detect a treatment difference in mean change from baseline between treatment groups of 0.5 gram per deciliter, assuming a standard deviation of 1.25 gram per deciliter. Under this assumption, 132 subjects per group were required for each study to assure a 90 percent power. This sample size was rounded up
to 150 subjects per group to account for loss to follow-up.

An interim analysis was planned to occur after approximately 50 percent of the 300 subjects were randomized for the purpose of verifying assumptions and possibly re-estimating the sample size. No change to the sample size was needed as the result of this interim analysis.

An analysis of covariance ANCOVA model was used for the primary efficacy endpoint analysis. The mean change in hemoglobin from baseline to end of treatment was the response variable. The treatment group was the factor, and the baseline hemoglobin level was the covariate. The model also included an indicated variable for the baseline ESA dose stratum.

The intent-to-treat or ITT analysis population was defined as all randomized subjects. A test of the treatment effect was performed at the two-tailed 5 percent significance level comparing the least square mean values between the two treatments. The difference in hemoglobin change
was evaluated using least-square means. Least square means are means adjusted for covariates using the ANCOVA model. They are considered better estimators compared to raw means when the treatment groups are unbalanced and covariates are present. For the primary endpoint, no missing values were imputed.

The primary efficacy results for SFP-4 and SFP-5 using the ITT population are presented in this table, for study SFP-4, the subjects receiving SFP had a mean increase of 0.06 gram per deciliter in hemoglobin at the end of treatment, while the placebo group had a mean decrease of 0.3 gram per deciliter. The mean difference in change from baseline in hemoglobin level between the two groups was 0.35 gram per deciliter, and it was statistically significant with a p-value of 0.01. Study SFP-5 had a similar results.

This table summarizes three of the key secondary endpoints, ferritin reticulocyte hemoglobin content and TSAT. While numerically the changes seem consistent with the pattern seen in
the primary analysis, these results are based on data using the last observation carried forward, LOCF technique, which is likely not appropriate, biasing the result. Also, no multiplicity adjustment was done, making the results difficult to interpret.

Now I will discuss the statistical issues. Many subjects had to discontinue the study early and did not complete the planned 48 weeks of the randomized treatment. In SFP-4, only about 18 percent of the total 305 subjects completed 48 weeks and 44 percent completed 24 weeks.

Due to the extent of subjects that discontinued early, the end-of-treatment hemoglobin values represent various time points; hence, it is difficult to draw inference over the entire 48 weeks.

Next, I will discuss the differential discontinuation patterns seen from the data as the result of protocol-mandated anemia management changes. The following points are illustrated in the table on the next slide. As Dr. Lu showed
earlier in study SFP-4, 151 out of 305 subjects discontinued the study early due to protocol-managed anemia management changes.

In general, more subjects from the placebo arm discontinued early due to protocol-mandated changes, 54 percent versus 45 percent in the SFP arm. More subjects in the SFP arm discontinued early due to a hemoglobin greater than 12 gram per deciliter, 27 percent versus 21 percent in the placebo arm. More subjects in the placebo arm discontinued early due to hemoglobin less than 9 gram per deciliter, 18 percent versus 11 percent in the SFP arm.

In consideration of this differential discontinuation pattern, several sensitivity analyses were performed to explore its impact on the primary efficacy result. The difference in means in change from baseline between SFP and the placebo groups and the associated 95 percent confidence interval for these analyses are shown in this forest plot for study SFP-4.

The difference in means in the modified ITT
population had a similar magnitude and a 95 percent confidence interval as the ITT population. Modified ITT is defined as all randomized subjects who took at least one dose of study drug and had at least one post-baseline hemoglobin value. There were 6 subjects who were in the ITT population but excluded from mITT.

The third plot shows the effect estimated by a mixed effect repeated measurement MMRM model using all data points after baseline instead of only data points at end of treatment. The difference in means between the two treatments appear to be reduced by using early data.

The last plot shows the variability in estimating the mean difference associated with imputing a large amount of data using multiple imputation techniques. Since so much data were imputed, a large standard deviation was observed, and this estimate might not be reliable. Similar patterns are seen in study SFP-5.

In summary, the primary endpoint mean change in hemoglobin from baseline to end of treatment was
statistically significant favoring the SFP arm. However, the difference in mean change between the two groups was marginal in both studies.

The changes from baseline for the secondary endpoints presented were numerically smaller in SFP group than in the placebo group. However, the secondary endpoint analyses were not adjusted for multiplicity; hence, it is difficult to draw valid statistical inference from the results.

After reviewing the data, FDA had the following statistical concerns: 1) the extent of subjects who discontinued the study treatment before the planned 48 weeks; 2) the end-of-treatment hemoglobin values represent various time points, and it is difficult to draw inference over the entire 48 weeks; 3) differential reasons for treatment discontinuation due to protocol-mandated anemia management changes could impact the estimation of the magnitude of the treatment effect on hemoglobin level.

Now, Dr. Lu will continue to present the safety results of these two studies.
DR. LU: Thank you, Dr. Luo. I'm going to summarize the major safety findings from the SFP-4 and SFP-5 studies. The overall report adverse event rate was slightly high in the SFP group than in the placebo group for the phase 3 trials. There were 12 deaths in the SFP group as compared to 5 deaths in the placebo group. The number of patients with no fatal serious adverse events was similar between the two groups. A few more patients in the SFP group experienced adverse events leading to treatment discontinuation than in the placebo group.

This slide summarizes all cause due to any cause in the two phase 3 trials. The age of patients ranged from 44 to 79 years. Most of the patients were male. Treatment duration ranged from 8 days to more than 300 days. The time between the last study treatment to the event leading to death ranged from 1 to 15 days in the SFP group and 1 to 3 days in the placebo group.

The most common event leading to death was
cardiac arrest, which had 6 deaths in the SFP group and 2 in the placebo group. Additional 7 deaths or unknown cause of deaths were reported in 4 patients in the SFP group and 1 in the placebo group. Among those, 6 SFP-treated patients and the 1 placebo-treated patient died at home or in nursing home without the detailed information available.

Almost all patients had significant underlying cardiac conditions. Myocardial infarction was a cause of death in 1 patient in the SFP group and 2 patients in the placebo group. One patient in the SFP group died of pneumonia.

This slide shows the most common nonfatal serious adverse event that was reported in the SFP group than in the placebo group. This event was arteriovenous fistula thrombosis, pulmonary edema, and a diabetic foot infection.

This slide shows a reported adverse event of special interest for Triferic. About 20 percent of patients in both treatment groups experienced intradialytic hypotension. There was one suspected hypersensitivity reaction reported in the SFP group.
and none were in the placebo group. About
9 percent of patients in both treatment groups had
a cardiovascular event.

Hemodialysis vascular access thrombotic
event occurred in 15 patients in the SFP group and
11 in the placebo group. Most of these occurred in
the AV fistula graft. Systemic or serious
infection was reported similarly between the SFP
and placebo group.

This slide shows the most common adverse
event that was reported more frequently in the SFP
group than in the placebo group. The event
reported more than 5 percent of SFP-treatment
patients with procedural hypotension, muscle
spasms, headache, peripheral edema, pain extremity,
and dyspnea.

In summary, for the proposed indications for
the treatment of iron loss or iron deficiency to
maintain hemoglobin, the mean change of hemoglobin
from baseline to the end of a treatment period was
.06 gram per deciliter in the SFP group as compared
to .3 to .39 gram per deciliter decrease in the
placebo group after adjusted for baseline hemoglobin in the ESA dose. The difference in mean changes in hemoglobin between the two groups was statistically significant in both studies.

With regard to safety, there was imbalance in all-cause deaths between the two groups. One hypersensitivity reaction was reported in the SFP-treated patients. There were 10 arteriovenous fistula thrombosis events in the SFP group as compared to 6 events in the placebo group.

Next, we will present the results for the proposed secondary indication to reduce the prescribed dose of ESA. One phase 2 study was conducted for this indication. Study NIH-FP-01 was a randomized, double-blind, placebo-controlled study. Patients with a hemoglobin level of 9.5 to 12 gram per deciliter were enrolled. Study treatment was up to 3 weeks. The dosing and the concentration for Triferic was the same as phase 3 trials.

This study allowed intravenous iron administration and the ESA dose change based on
ferritin level and the hemoglobin value after 4 weeks of study treatment. In this study, 54 patients each were randomized to SFP or placebo groups. The demographics were similar to those in the phase 3 trials and were comparable between the two treatment groups. The baseline hemoglobin ESA dose category was similar to the phase 3 trial and is balanced between the two treatment groups.

Dr. Luo will now present the efficacy results in this study.

**FDA Presentation - Lola Luo**

DR. LUO: Thank you again, Dr. Lu. For my report, I will summarize the statistical analysis plan, present the efficacy results, and discuss the statistical issues.

The primary efficacy endpoint was the percent change from baseline to end of treatment in the prescribed ESA dose required to maintain hemoglobin in the target range and adjusted for baseline hemoglobin. End of treatment was defined as the last two weeks of the randomized period. Randomization was stratified by baseline ESA dose.
Subjects were randomized in a 1 to 1 ratio to SFP or placebo within each stratum.

There was no sample size calculation because the statistical tests were considered exploratory, not conclusive, by the sponsor. Approximately 50 subjects were randomized to each treatment group. A one-way ANCOVA model was used for the exploratory treatment comparison, where the percent change from baseline in prescribed ESA was the response variable, the treatment group was the factor, and the baseline hemoglobin was the covariate. The model included an indicator variable for the baseline ESA dose stratum. Missing values were not imputed. Twenty-one percent of subjects discontinued the study prematurely. These prematurely discontinued subjects were balanced between the two treatment arms.

The primary efficacy result using the ITT population is presented in this table. Sponsor has presented the results in mITT population, which included all subjects randomized after December 2,
2010 who received at least one dose of study drug and had any ESA dose information available during the treatment period. At a baseline, the SFP and the placebo groups were comparable with respect to the prescribed ESA dose. At end of treatment, after adjusting for baseline hemoglobin level, the subjects receiving SFP had a mean increase in ESA dose of 5 percent while the placebo group had a mean increase of 37.3 percent. This difference between the two groups had a nominal p-value of 0.052.

A sensitivity analysis was conducted to evaluate the percent change from baseline in the actual ESA dose between the two treatment groups. The result in the ITT population is presented in this table. The subjects receiving SFP had a mean increase of 11.1 percent while the placebo group had a mean increase of 40.7 percent. This difference between the two groups also had a nominal p-value of 0.111.

This figure shows the primary endpoint, the percent change from baseline, in prescribed ESA
dose by study week. It raises concern on the interpretation of the efficacy of the study drug over placebo at the end of treatment because the mean percent change from baseline in prescribed ESA dose was higher in SFP group than in the placebo group for the first 24 weeks of the 36-week study period. In other words, for the first two-thirds of the study, subjects in SFP group needed more prescribed ESA dose than the subjects in the placebo group. After week 24, the percent change of prescribed ESA dose in SFP group started to decline and became lower than the placebo group.

In summary, at the end of the treatment, subjects in SFP group had a numerically smaller increase in the mean percent change from baseline in both prescribed and actual ESA doses. However, both analyses had nominal p-values greater than 0.05.

After reviewing the data, FDA had concerns over the interpretation of the results expressed as follows. There is no replication of the results. There is no formal sample size or power calculation.
presented. The statistical tests were described as exploratory, not conclusive in the protocol. It is difficult to draw inference to the efficacy of Triferic on reducing the prescribed ESA dose to maintain desired hemoglobin level because subjects in the SFP group had a higher mean percent change from baseline in prescribed ESA dose for the first two-thirds of the 36-week study period. In addition, the difference between the two treatment groups had a nominal p-value of 0.052 using the ITT analysis population.

Now, Dr. Lu will continue to present the safety results of this study.

**FDA Presentation - Min Lu**

DR. LU: Thank you, Dr. Luo. This slide shows the safety results of the NIH-FP-01 trial. The SFP and the placebo group had similar frequency of total adverse events reported. There were 2 deaths in the SFP group and 3 deaths in the placebo group during the study. One additional placebo patient died after completion of study participation. Serious adverse events was
reporting at least one-third of patients in both study groups. There were 4 patients who discontinued treatment due to adverse even in the SFP group and 1 in the placebo group.

In summary, study NIH-FP-01 was a single, exploratory, phase 2 trial and no formal sample size of power calculations planned in the protocol. Therefore, there is difficulty in the interpretation of efficacy results.

Finally, our questions to the AC panel. The first question, 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. Do the efficacy and the safety results in studies SFP-4 and SFP-5 support a positive benefit/risk for use of ferric pyrophosphate for any indication?

The second question is for discussion. The applicant proposed to include in label a claim that use of ferric pyrophosphate reduces the prescribed dose of ESA required to maintain desired hemoglobin
level. Considering the limitation of 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. Thank you.

**Introduction of Committee**

DR. ARMSTRONG: Thank you both.

As I mentioned before, we neglected at the beginning of this session to introduce the panel members, so I'd like to start with Dr. Fingert and have you introduce yourself.

DR. FINGERT: I'm Howard Fingert. I'm a hematologist/oncologist. And I'm the nonvoting industry representative, and I'm employed at Takeda Pharmaceuticals.

DR. CHAWLA: My name is Lakhmir Chawla. I'm an intensivist and nephrologist at the Washington, D.C. VA here.

DR. FLESSNER: Michael Flessner. I'm a nephrologist at the NIDDK.

DR. RINI: My name is Brian Rini. I'm a
medical oncologist at Cleveland Clinic.

DR. FRIED: Linda Fried. I'm a nephrologist at the Pittsburgh VA, University of Pittsburgh.

DR. ZONES: Jane Zones. I'm the consumer rep, and I'm a medical sociologist.

DR. ROTH: Bruce Roth, medical oncologist at Washington University in St. Louis.

DR. FOJO: Tito Fojo, medical oncologist, NCI.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

DR. ARMSTRONG: I'm Deb Armstrong, medical oncologist at Johns Hopkins.

DR. BRIGGS: Caleb Briggs, designated federal officer, ODAC.

DR. DIEHL: Lou Diehl, medical oncology, Duke University.

DR. LIEBMANN: James Liebmann, medial oncology, University of Massachusetts.

DR. LUO: Lola Luo, statistical reviewer.

DR. LU: Min Lu, clinical reviewer, DHP.

DR. ROBIE-SUH: Kathy Robie-Suh, clinical
team leader, Division of Hematology Products, FDA.

DR. FARRELL: Ann Farrell, division director, Division of Hematology Products.

DR. PAZDUR: Richard Pazdur, office director.

Clarifying Questions to the Presenters

DR. ARMSTRONG: Thanks, everyone. So we'll start now to take clarifying questions for the sponsor and for the FDA from the panel. Please remember to state your name for the record before you speak. And if you can, please direct questions to a specific presenter, and please let Caleb know if you have -- and he'll keep a list of -- so we'll start with Dr. Fojo.

DR. FOJO: I had one question for the FDA. You were talking about the secondary efficacy points. Can you explain again why you thought the results were biased? You said it, but I didn't understand.

DR. LUO: I believe for the secondary efficacy endpoint, the sponsor used IOCF technique to impute the missing data, and generally -- the
analysis resulted from using IOCF's concept made biased results.

DR. FOJO: Okay.

DR. LUO: One more thing, I want to stress, for the secondary endpoints, sponsor did not adjust for any multiplicity. Hence, it is difficult to draw conclusions from them.

DR. FOJO: Okay. I don't know if Bernard wants to say -- could I see what he has to say about it?

DR. COLE: So as I understand it, where there was incomplete or missing data, the previous value that was measured was substituted for anything that was missing. And it's unclear, really, how valid that is in all settings. I think that's where -- depending on how the actual mechanism unfolds, that could result in a bias.

DR. ARMSTRONG: Dr. Chawla?

DR. CHAWLA: This question is for Dr. Fishbane, which is that as I understand this, the way the drug is delivered is for reverse clearance. So as the drug ends up in the
dialysate, it reverse clears through the filter into the blood. And my question is how does one
dose the drug if you don't know the clearance of
B12 for each patient on a given day? And the
preliminary data, at least based on the FDA
briefing, suggests that there's pretty significant
differences in drug delivery based on that
clearance.

DR. PRATT: This is Ray Pratt. I'm the
chief medical officer, and we'll get Dr. Fishbane
up in a minute to address your question. We didn't
present this core slide, however this is the pre-
to post-dialysis incremental increase in serum
iron, the decrease in unsaturated binding capacity,
which is an index of free sites on transferrin, and
the increase in TSAT that you observe in
the -- this is in the phase 3 studies here, alone.

Very consistent, approximately 100 microgram
per deciliter increase, pre to post-dialysis, which
has remained constant at each of the times that it
was measured across the study. There is some
variation in the amount that's given to each
individual patient, and it's estimated that, again, as we showed in our pivotal studies, we are able to deliver enough iron to maintain hemoglobin concentration stable at baseline over a period of time where, again, in the placebo group where we're not administering any iron and we're trying to make them a little bit of iron restricted -- to restrict their erythropoiesis there, you see a steady monotonic decline in the hemoglobin concentration.

DR. CHAWLA: Do you have these data based on the Kt/V subsets or the different filters?

DR. PRATT: Yes. We looked at a variety of different effects on this. And if we could bring up the slide that shows all the effects on iron, on the intradialytic iron transfer with all the different groups that we looked at. We did see an effect on very low Kt/V and again very low dialysate flow rates in terms of reducing the amount of iron administered. However, none of the other effects that we looked at, including the membrane type, membrane surface area, any of the other subgroups that we looked at -- I think we can
I'm sorry it's so small, but we looked at very, very many different subgroups here. The Kt/V less than 1.6, greater than 1.6, or in the middle, and there's a slight difference between the two groups, but really not statistically different between the groups. The cellulosic dialyzers, which look like they have a little bit lower iron delivery, was the smallest subgroup of hemodialysis dialyzers that were actually used in this trial. But again, we can see that it's pretty consistent across the way: catheters, fistulas, blood flow rates, dialysate flow rates, dialyzer membrane type. And again, we looked very carefully at dialyzers that were re-used versus dialyzers that were single use, and we see a pretty consistent range. Again, there's a range of values that we see in this population.

DR. CHAWLA: On page 38 on the FDA briefing, if you look at the differences between the dialysis adequacy of the Kt/V 1.6 above and below and the various membranes, it appears as though all the
hemoglobin benefit is in the Kt/V 1.6, because what you have is the deltas are consistently across this dose range.

Let me just say up front that I think the drug works as advertised from the data that's available. I think this is a very slick way to do what needs to be done, and I agree with the general notion that currently the way iron is given is problematic. So I don't want to come off as being uber negative here.

However, I think that the way the drug gets dosed in any individual patient on any given day, it's highly variable. And based on the individual clearance of the B12 on that day through -- for the B12 clearance, essentially, because it's the same size. I think we can agree it's all around 1300 daltons.

DR. PRATT: Yes. So on a patient who happens to come in with a large filter, on a Monday, who's getting a lot of back filtration, you could potentially give them 2 or 3X dose of this drug, whereas on another day, for a patient who has
very little UF and has a very small filter, the very low cutoff, you would give them almost none.

So I'm trying to understand at the bedside as a clinician how I'm going to decide how much of this drug to give on any given dialysis patient on any given day since we do not routinely do the TSATs pre and post and have real-time metrics for this.

DR. PRATT: Right. I'd like Gupta to come up and address that issue. But in the meantime, while he's coming up, we did look at this consistently across the population. I mean, we were doing this serially in all of the studies. And we did see a consistency in delivery, and it did show that -- again, you're correct in the hemoglobin values in the very low Kt/V patients.

Dr. Gupta, please, enlighten us.

DR. GUPTA: Ajay Gupta, Rockwell Medical. We measured the pre-dialysis and the post-dialysis transferrin saturation every month, and we do not see this inconsistency in patients over time.

DR. CHAWLA: But the hemoglobin delta you
have to agree is primarily driven in the high Kt/V group, right? Can we agree to that?

DR. PRATT: It's driven by patients who are adequately dialyzed, which is one of the requirements for coming into this study.

DR. CHAWLA: Well, adequate dialysis is now 1.2, right? So 1.6 is considered a higher metric, and in hemo, randomized controlled data, that didn't make a difference in outcome. So we agree that by and large, middle molecule and at least common U.S. dialyzers are correlative with B12 middle molecule clearance. But that's not always the case, and there are deviations based on the filter, the clearance, and the way the patient is set up, and the back filtration.

DR. PRATT: Yes.

DR. CHAWLA: So do you have any guidance for the clinician on how to dose this appropriately?

DR. PRATT: Well, the dose as we've studied it is set up for a single concentration for all the patients. Now, having said that, again, there may be some patients who may get a little bit less one
time and a little bit more the next time. On the average, because this is a chronic therapy, it will be administered over -- all the time that they're on dialysis, they should have enough coming in to maintain their hemoglobin.

There will be some patients that will ultimately have more blood loss that will decrease, so they may need a supplementation of intravenous iron when they become iron deficient. However, for the day-to-day usage of the patients and to make it easier for the dialysis unit, it was chosen to do a single concentration of Triferic.

DR. CHAWLA: So I agree with that, that treating it as a population, when you look at the population metrics, it works in a given population. There's no disputing this, and I agree with that completely. My concern is that any drug, even water in a dialysis patient can be lethal at too high a dose. Right? So all drugs have toxicity. So there's going to be a group of patients who get little to none of which they get an exposure or no benefit. And you're going to have a cohort of
patients who get a lost. And you're going to have
some people who are in between.

So generally when we dose drugs, we want to
identify who those groups are. And I want to know
how do we do this if this drug gets approved.

DR. PRATT: One thing I can say, and then
I'd like Dr. Gupta to come back up to the podium,
is that we did look very carefully at the maximum
iron concentrations and transferrin saturations
that we saw across the entire program, and we
actually never -- again, we designed the drug so
that you always had a buffer for unsaturated iron
binding capacity so that any additional iron was
there. And we never saw a transferrin saturation
that exceeded 90 percent at any time in the patient
group.

DR. GUPTA: Ajay Gupta. Just an additional
point. The drug is tailored to be delivered as a
function of a combination of factors, which is the
dialysate flow rate, the blood flow rate, and the
surface area of the dialyzer. So we all understand
that in this patient population, we strive to
deliver a certain adequacy of dialysis, which we
monitor on a monthly basis using either urea
reduction ratio or Kt/V.

Inasmuch, we ensure in these patients that they have adequate dialysis with the urea going from the blood to the dialysate compartment, and shows that we have a proportional diffusive transport of Triferic from the dialysate to the blood compartment.

DR. CHAWLA: I don't think that you can say that assuredly. Patients who have a Kt/V X do not necessarily have the same B12. I can put up a very small cutoff filter and give you a Kt/V of 1.6, and give you zero middle molecule clearance. So the Kt/V, which is a small molecule -- urea is extremely small -- does not necessarily correspond to middle molecule, and you have that in the available data that you've presented.

The polyethersulfone and the polysulfone is hugely different than polyamide. And there's also sorts of filters that are out there. And the KOA for B12 is available for every filter on every
patient, everyday. And so, I don't know if it's
too late in the process, what I would like to
see -- I think you have the ability to go in and do
the B12 coefficient of clearance for every patient
and see what the hemoglobin effect is, and allow
people to make that analysis thoughtfully. I mean,
the data are available.

DR. PRATT:  Dr. Fishbane, I think we can get
you up here now to answer the question.

DR. FISHBANE:  Dr. Chawla, thank you for the
question. Two comments that I want to make. First
is that in relation to your question related to
overtreating patients with iron, let's just
recalibrate ourselves in terms of quantitatively
what we're doing so that if somebody let's say were
to have -- in one of our small patients that has a
Kt/V, say, of 2.2 or so, or if you're looking at
higher molecule weight clearances as hard
clearance, we're giving the patients 5 to
7 milligrams of iron. And it will go up in those
patients, and maybe it will go up to 10 milligrams
that will be absorbed.
Right now, you're injecting in your patients 100 milligrams of iron intravenously. Quantitatively, we will never see in hemodialysis patients where you will over-deliver iron. And I think that the clinical study with a wide variety of patients with different types of clearance and different sizes speaks to that fact.

Your other question haunted me at the beginning of the clinical trials because it was my question, too, is what happens when you have patients where the clearances are going to be lower, and therefore drug delivery lower. I think here is where the important contextual issue comes into play.

The point of this is that I hope that -- the drug is not being looked at as a replacement for intravenous iron, that it is creating what has been a really important need for us. I've been studying these drugs for 20 years, and intravenous iron has had its place. What we have needed is to be able to maintain iron stores overtime, but there will certainly be patients who will continue to require
treatment from time to time with intravenous iron.

We think that that will be substantially decreased. I would hope so because I think there are substantial safety issues with intravenous iron. But to your point of people that have lower clearances, they'll probably need a little bit more intravenous iron. I think they're important points you raise, and I think that quantitatively they're well managed within protocols that I could see designing very easily. Thank you for the question.

DR. ARMSTRONG: Dr. Fojo, did we move away from you too quickly?

DR. FOJO: Yes, but that's okay.

DR. ARMSTRONG: Do you have another question?

DR. FOJO: Can we have some clarity on the end-of-treatment hemoglobin values, how that differed between the placebo arm, or the control arm, and the SFP arm? I could see how that would make a difference if one arm was very bias to early time points, and the other one was very bias to late time points.
DR. PRATT: Could you repeat the question?

I really didn't get the entire --

DR. FOJO: The end-of-treatment hemoglobin values --

DR. PRATT: Yes.

DR. FOJO: -- that could occur at any time. It's when treatment was ended, but that varied.

DR. PRATT: That varied. That's correct.

DR. FOJO: I wanted to know, again, when that happened, not the amount but when it happened. So how long were they on treatment before the EOT was obtained, were on observation.

DR. PRATT: Patients completed the trial at various times when they actually met one of those four criteria. So we had patients completing early within the first month of treatment and patients who went for the entire 48 weeks of treatment. There were balanced between the two groups, but the reasons that they were actually completing were different, as we've demonstrated, between the two groups because the more patients in the placebo group completed when their hemoglobins dropped
below 9, and then they needed to change an anemia management to either increase their ESA or add IV iron to the therapy, whereas more patients in the Triferic group completed at that. But the actual times in which patients completed were very, very similar across the way, as were also the timings for patients who were true withdrawals who actually withdrew from the study because they had an adverse event. They died. They had received a transplant, or any of the other reasons that people truly withdraw from clinical studies. So we felt that this was a very -- that there was no differential in terms of the withdrawal rates.

DR. FOJO: Right. So you're saying that timing was similar.

DR. PRATT: Was very similar, yes.

DR. FOJO: What was that timing?

DR. PRATT: The mean time of patients in the trial was six months in terms of exposure. So that was the mean time that patients in both groups, in both studies, remained in the study prior to
DR. FOJO: Okay. And then the other thing that I had a question about were the deaths on the study. One could say, well, these aren't very great differences, but this was a study of only a few hundred patients. And as was noted at the beginning, 400,000 patients or so are dialyzed. So even small differences could be an enormous difference in terms of death.

So what are the thoughts that you all have on deaths, and how do you view that, vis-a-vis with the FDA has on their overall safety and the pooled phase 3 trials?

DR. PRATT: Okay. Dr. Lin, if you could come. And while Dr. Lin is coming up here, again, we looked at the totality of the data in all of our clinical studies, which enrolled the similar population, which is reflective of the U.S. chronic, hemodialysis population. And yes, there were imbalances that you saw in the phase 3 studies, but there were also imbalances in the other studies, which we cannot discount.
DR. LIN: As Dr. Pratt mentioned, overall, the mortality was very similar between the Triferic and placebo arms. We consider all of the controlled studies of the Triferic 2 micromolar dose. So the FDA presented the SFP-4 and SFP-5 studies, and certainly we saw imbalance there. But in the NIH-1 study that had the same population and same dose of Triferic and a similar duration of treatment, we saw 2 cases in the Triferic group and 4 in the placebo group. In the SFP-6 study, again, it was the same population and same Triferic dose 2 micromolar. We saw zero taxes in Triferic and 3 in placebo.

So taken together, if we look at all the clinical studies of Triferic, we end up with 14 cases in the Triferic group and 13 in the placebo group. And you can see the exposure adjusted events down at the bottom. If we take a look to get the best sense of what the mortality rate might be, if we look at the all-Triferic group, which has 5 times the exposure in NIH-1 and SPF-4 and SPF-5 studies combined, the rate is 6.5 per hundred
patient-years of exposure, which ends up looking very similar to the placebo group. Thank you.

DR. FOJO: One last quick question. Why is it so difficult to do studies in this patient population? 400,000 of them, and if we're looking at a study for the ESA with 50 some-odd patients, 54 in each arm. Why? What? Am I missing something?

DR. PRATT: Dr. Fishbane, would you like to -- Steve, I think you're probably the best person to comment because you've been doing this for a long time.

DR. FISHBANE: Yes, Dr. Fojo, you're quite right. We've struggled with this in the dialysis population. I think that, in general, for the dialysis population, no matter what issues that we've looked at, we just haven't done as many studies and as large studies as we've liked to. It's very hard, given the organizational structure of dialysis in the United States today with corporate ownership and related to issues, to be able to get the size of the studies' consistency
that we would like. But I think it's more of a general question that you raise. It's a good one.

DR. ARMSTRONG: Dr. Liebmann?

DR. LIEBMANN: I want to ask Dr. Fojo's first -- one of his most recent questions slightly differently. Could you put up slide CE-14? His question, which I'm going to restate slightly differently was when did people drop out? So you have a number of graphs like this showing changes over time. What we're kind of used to seeing in a lot of trials is a number on the bottom showing number of risks. Do you have that?

DR. PRATT: I don't have a slide that actually has the number of risks, but I can provide that to you at the break.

DR. LIEBMANN: I think it's kind of important.

DR. PRATT: We do have it in -- can we put this next slide up, please? We do have this slide, which is a little bit busy but actually gives you the number at risk at each of the time points along the way there. And you can see that patients in
the placebo group and in the Triferic group completed the study or, again, withdrew for other reasons at the same rate over time.

DR. LIEBMANN: Okay. Thank you.

DR. ARMSTRONG: Before you move on, I think the FDA may have a slide that shows --

DR. LIEBMANN: I noticed it out of the corner of my eye.

DR. ARMSTRONG: Go ahead.

DR. LUO: Hi. We actually prepared a slide. If you look at the backup slide 57, we plotted a mean observed hemoglobin values over time for 4 weeks. You can see at week 48 -- for SFP-4 at week 48, SFP group had about 34 subjects and placebo group had about 35 subjects.

DR. LIEBMANN: Then my next question I'm afraid may be a little bit involved, and I'll be happy to hear from either Dr. Fishbane, Brittenham, or Pratt. And I may need a primer on iron kinetics in renal failure patients. I absolutely believe your slide, but there seems to be an association between very high ferritin levels and bacteremia.
It appears that over the last two decades, ferritin levels in patients on dialysis have been going up, and their risk of bacteremia is going up, and so presumably that's bad. I believe your other slide that says that anemia is associated with mortality, and so that seems to be bad.

If you look again, though -- let's go back to, again, CE-14. The entry mean hemoglobin or median in your populations -- or ferritin was 500. So the mean ferritin in your treated patients always stayed up around 450. And it fell below 450 in this population of patients somewhere around week 8 or 12. I think that if you go back to -- and then similarly, the difference in hemoglobin seemed to fall after that.

I guess my question -- and by the way, a very, very similar number was in the NIH-01 study, so I think CE-19. Go to CE-21.

DR. PRATT: The others have both the hemoglobin and the ESA dosing on it.

DR. LIEBMAN: I thought that there was one with ferritin also.
DR. PRATT: Yes, there is one. That's the next --

DR. LIEBMANN: Thank you. So again, the ferritin level here falls, again, below 450 or gets down around 450 somewhere by study week 12 or so. And it's after that that you begin to see the need for increasing ESA and fallen hemoglobin.

So I guess my question is, why -- I have two questions. Number one, why are people being pushed to ferritin of 800 anyway? And number two, why couldn't you just let the ferritin level dwindle down to 450 or so, and then give them a dose of IV iron and be done with it?

DR. PRATT: I think Dr. Fishbane is the best person, place, to answer that question for you right now.

DR. FISHBANE: I jumped out of my seat and didn't wait for an invitation on it. It's two different questions. I want to answer the second first if you'll allow me.

The reason -- so that initially when we -- after epo drugs were approved, what we found
was that we weren't very smart about this, that as you started to raise hemoglobin levels, you used up a lot of iron and patients became iron deficient. So in 1993, there was widespread really severe iron deficiency in this population that was problematic for patients. So initially, the concept that we had was exactly what you've proposed: Let the ferritin levels drop, then treat with intravenous iron.

There are two problems that we've learned over time that you get when you do that. One of them is that you get this tremendous cycling of hemoglobin results so that you treat with intravenous iron. And as a result of that, the hemoglobin level starts to rise very substantially. And then as you back off on your repletion, you get an immediate drop in the hemoglobin response. So you get this very cyclical movement, which creates all kinds of management issues.

The second that I think -- right now, a more substantive issue for us is that Alan Brookhart, using a really outstanding analysis, probably one
of the most important studies from 2013, showed us exactly that type of treatment. So again, it's repletion of iron deficiency. Wait until people become iron deficient, and then replete the iron as opposed to as you lose that small amount over time, replace that amount of iron.

Alan's group demonstrated, really very convincingly with an instrumental variable analysis, a great cluster analysis, that when you give iron that way, when you just replete iron by giving large amounts over a short period of time, to grab the ferritin after it's dropped, as opposed to giving iron over time, that you increase the rate of infections very substantially. So it seems that by giving iron in the large quantities that IV iron requires puts you at that risk. And biologically, it makes all the sense in the world based on all the animal studies and human studies that have been done.

Your other question, though, gets I think to -- and I'll try to be brief here; I apologize about this one -- why are levels 800s? And I think
there are two reasons for that. One of them is that what we've been trying to -- because we really haven't had other agents available. I'm the first person in the United States that did a study, an RCT of intravenous iron, and I've done a lot of studies of this. When there wasn't anything else available, we've tried to squeeze IV iron into maintenance therapy to make up for that regular loss. And I think that inevitably it creates that tremendous mismatch because of sequestration that leads to higher and higher ferritin values.

But the other part is I think a response to the fact that we have concerns about ESA therapy so that we're trying to use higher doses of iron to lower ESA dose. There are also economic issues and resend errors, which I could go into if you're interested. But I do think there were just going a little bit too far right now in terms of treatment.

DR. LIEBMANN: I'll just say the reason I wonder about that is the second question that we're being asked about is, with the current data that we have, does it justify the reduction in ESA? And
I've got to say that in the absence of knowing how these patients would do if you just gave them a little iron, I don't know.

DR. PRATT: I think one of the other issues, a -- and Dr. Brittenham I think could talk a little bit about the hepcidin story here, which will give a little bit more insight into the fact as to why these high doses of iron actually leads to the sequestration and the reticuloendotheliosis.

DR. BRITTENHAM: Let me say there's a reciprocal relationship between the hepcidin concentration and the iron availability. First, maybe what I should explain that the way that hepcidin works is by binding to ferroportin and restricting the iron exit from cells. The cells, the macrophages, and enterocytes that can provide iron into the circulation are unable to do so.

So if you stimulate the marrow with ESAs, then there's a hormone that's produced by the marrow called erythroferrone, identified just this year, that decreases the hepcidin level. So if you drive the system by adding ESAs, you can bring down
the hepcidin level enough to release more iron from stores.

So if you give iron conversely, you can provide -- when you give intravenous iron, there's a portion of it with all intravenous iron products, some 2 to 6 percent of the iron that's not bound within the carbohydrate but is a label iron portion that goes out into the circulation and oversaturates transferring. That's likely related to the reason why there's an increased risk of infection. But it momentarily provides iron for erythropoiesis.

I think those are the factors that are involved in the iron homeostasis relationships between the hepcidin, the intravenous iron, and the SFP, which is bypassing the hepcidin block and donating directly to transferrin.

DR. ARMSTRONG: All right. We actually have several more people who have questions, but we're approaching time for the break. What I'd like to do is go ahead and have our break. We'll come back at 3:30. We'll have the open hearing. We only
have two people, and we've allotted 30 minutes. So we'll have plenty of time to ask questions again when we come back before we actually address the two questions from FDA. So everybody please be back at 3:30.

(Whereupon, a recess was taken.)

Open Public Hearing

DR. ARMSTRONG: I'd like to go ahead and get started. We're going to begin with the open public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for informing-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if
known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your
cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. DUTKA: I'd like to declare that Rockwell Medical is supporting my travel to present at these proceedings. Good afternoon, and I would like to thank you for the opportunity to address this committee. My name is Paula Dutka, and as a nephrology nurse that has seen many changes and improvements in the care of our patients with kidney disease over the past three decades, I feel compelled to speak out in regard to ferric pyrophosphate, which is being reviewed for possible approval.

For the past 25 years, I have had the gratifying opportunity to work in nephrology research and assist in bringing new medications and technology to aid in the care of renal patients. Much of this work and my clinical experience has been in the area of anemia, of chronic kidney
disease. We've witnessed the vast improvement that erythropoietic stimulating agents have brought to the quality of our patients' lives and general well-being, a dramatic difference from the 1980s when a hemoglobin of 7 was commonplace along with all of its physical consequences and frequent transfusions, sometimes bi-monthly.

Iron maintenance is an essential part of anemia management and is also seeing great improvements as well. I remember the days of having to administer iron dextran or INFed with its black boxed warning, which was wrought with many adverse effects and symptomatology for patients. More recent intravenous iron compounds are safer, but this method of administration is more difficult to maintain a steady state of iron balance.

Soluble ferric pyrophosphate is administered in a novel route of administration in the hemodialysis population via the dialysate or dialyzing fluid. This mode of administration offers slower, consistent infusion, potentially leading to more physiologic control, producing
steady iron indices. The technological ability to utilize the dialytic therapy to accomplish this is very exciting.

Our six years of experience with this investigational product showed us that soluble ferric pyrophosphate has the potential to allow nursing staff to utilize time required for IV medication administration to engage in other more patient-focused functions. Over the years that we've conducted five different protocols with soluble ferric pyrophosphate, we experienced administering it as a pre-mixed solution as well as mixing it ourselves with standard bicarbonate dialysate. Both methods were accomplished with ease and would be able to be integrated into routine hemodialysis practices.

Our patient experience was positive as well. I remember hearing comments such as, "It seems better getting iron this way." Actually, one of our patients has come today to give her perspective. Thank you.

DR. ARMSTRONG: Thank you. Will speaker
number 2 step up to the podium and introduce
yourself, and please state your name and any
organization you're representing for the record.
Thank you.

MS. BARRY: Hello. My name is Charlene
Barry. My travel was paid for by Rockwell
Pharmaceuticals. I am here today for the patients.
I was a patient in this trial. I have chronic
kidney disease, and anything that can help us with
iron is greatly appreciate. We are not, as some
think, the walking dead. We are very much alive,
and iron helps keep us that way. When we
have -- when I was on the trial, this way of
administering iron is great because it doesn't
break up the routine in what we're doing because it
happens and you don't kind of know what's going on.

I tolerated it very well. I had no side
effects, no headaches, no nausea, nothing that is
considered or comes from having iron treatments
sometimes. For me, being severely anemic before
this happened, and when I was first diagnosed of
having chronic kidney failure before that, I had
three blood transfusions. It is scary. It is time consuming. It is hard on your mind as well as your body because you don't quite know what's going on. My doctor didn't know where the blood was going out from. It's a very long process.

So having iron administered this way when you're having dialysis -- I'm on dialysis for 4 hours 3 times a week, and it's not a choice. Having iron administered this way lets me take that Zumba class and lets me live my life and not make -- I don't want to sleep all the time. I don't want to sleep everyday. After I finish dialysis, I want to go home and do things. I don't want to go home and go to bed. And that's what anemia does to you. It makes you sleep. You sleep your life away.

So this administration of iron for me was a wonderful advent because it kept my blood and body moving, and I really appreciated it. So if there's a way -- it worked for me. I'm not saying it works for everyone, but it worked for me. So that's my testimony for you.
DR. ARMSTRONG: Thank you very much to both of the speakers.

I'd like to go back now and continue with the discussions that we had before and move on to Dr. Roth.

DR. ROTH: I think Dr. Pratt could probably answer the first couple. The third question I have, I'm not quite sure who to direct it to.

First, going back, following up on Dr. Liebmann's comments on CE-13, 14 and then 21 with the ferritin, you look at these slides without numbers, and this suggests that people have reached steady state and this goes right into maintenance therapy, when in fact the median treatment time was only 160 days, and that end of treatment only represents one-fifth of the patients.

So the conclusions about not having any iron overload and things I think has to be put in perspective of how long patients actually treated.

The second is one of the pieces of the indication is in iron-deficient patients, and I'm not sure I've seen any data today on iron-deficient
patients. The mean ferritin level is 500. The minimum ferritin level to get on the trial was 200. So I'm not quite sure what the data is to support the indication for iron-deficient patients. I'll let you go with that.

DR. PRATT: Thank you. We did enroll patients who were iron replete by all measures, standard measures. But as the FDA actually commented, we did not do bone marrow assessments of irons. So there may have been some patients, even with elevated ferritin, who may have some iron deficiency.

Again, I'd like to point out that patients completed the trial. The end of treatment didn't just represent the patients who completed 48 weeks. It represented the last one-sixth of the time all patients were on the study, and it was the average of the hemoglobin values that were obtained during those last one-sixth of the time. And we did use all the observed data in calculating the primary endpoint that's defined as end of treatment.

DR. ROTH: My only other question -- I don't
know if you're the appropriate person or not -- is that when this trial was designed, it was designed as double-blind trial, and became a single-blind trial, allowing the investigators to know whether or not the patient was receiving study drug.

I wonder what the rationale behind changing that scenario was because I could imagine a scenario where the treating physician who's making the decision about whether to transfuse the patient; whether to rescue the patient with IV iron, whether to change the dose of the ESA, whether that person might not be better blinded to whether or not the patient is receiving study drug.

DR. PRATT: Let me address the issue of the single blind first, and then I'd like Dr. Fishbane to come up and address the second issue. With regard to the single blind, we could not make a matching placebo in the final market presentation. Triferic is a yellow-green concentrate solution. We don't have a dye that we can actually make there to add into the dialysate that would be safe for dialysis and would match that solution. Plus,
again, we're doing these studies in chronic dialysis units, some of which are running four shifts a day, mixing bicarbonate, getting things out to patients.

It just was logistically impossible to have a single blinded individual at each dialysis center that we used in the trial that would be responsible for dosing the solution. Again, we wanted to use the final market presentation our phase 3 trials. So that's why it's single blind instead of double blind.

Dr. Fishbane, if you can address the issue of blinded.

DR. FISHBANE: I was actually going -- I just wanted to respond Dr. Roth to your question about iron deficiency and the indications. When going by ferritin concentrations, what we've learned in the dialysis population -- and this is I'm guessing not true in the general population -- is two investigators, Gotloib from Israel and Stancu, and the Stancu in particular we made a lot of attention to in the KDIGO
guidelines -- they both showed the same thing, which was that even with higher ferritin concentrations -- so with patients sometimes with ferritin of 300, 400, there's a lot of people -- and these are bone marrow studies. When you do bone marrows, you find that they're completely deficient of iron.

So iron deficiency still does exist in this patient population and when you do have patients. It doesn't mean they all are, but there are a fair number of patients that are iron deficient.

DR. PRATT: You have your question, too, about the blindness, about did it influence your aspects on when to administer iron or transfusions.

DR. ROTH: The issue was whether the person treating the patient, knowing whether or not they're getting the study drug, whether that could affect their decision of whether to salvage the patient with IV iron or change the ESA dosage or transfuse.

DR. FISHBANE: Oh, yes. Good. Thank you. I apologize. I just wasn't paying attention
because I was trying to think about the initial question. So you're right. It was single blinded. It was by necessity. The protocol was interesting in that we weren't allowed to change the epo dose as well. We weren't allowed to give intravenous iron alone. And at the end of the randomization phase, in order to save patients, patients by criteria could receive transfusion or other therapy, but that removed them out of the randomization phase.

DR. ROTH: Correct. The patients came off of study, but that was still a decision of the treating physician of when to do that, correct?

DR. FISHBANE: Right. So patients remained in study but out of the randomization phase. And it was the decision of the treating physician. Thank you.

DR. ARMSTRONG: Dr. Fried?

DR. FRIED: I just wanted to expand a little bit to go back to some of the questions people asked Dr. Fishbane. As somebody who actually uses IV iron, and I tend to use the maintenance even
though it's not how it's approved. A similar to Dr. Chawla -- I mean, I think this drug works.

Truthfully, I don't think we know the safety of any of the drugs in terms of long term. I think they work, and I think the problem is that the infection analyses are incredibly biased because they're biased by indication.

Because what happens, when our patients start to get inflamed and start to get ill, the ferritin goes up, the transferrin sat drops. And as the transferrin sat drops, you give IV iron because you now have an indication when the ferritin is now less than 20 percent to give a dose IV iron. However, then those are the individuals who are getting sick, who are inflamed, then who get infections, and then get ill and die.

When you try to adjust for that, it's really the only very high doses. I don't think we know that the maintenance therapy or this therapy is going to be any better or different. But we haven't asked any of the other drugs to do this. I don't think we really know what we're doing in
dialysis in terms of whether or not we're improving ESA. And I believe this probably -- even though I don't think the NIH study was powered to do it, I think all iron therapies decrease the ESA dose. That's why we use them. It's one of the main causes for ESA resistance in our patients. And ferritin is a really horrible measure of whether or not somebody will respond to iron.

There was a study that was relatively small, but took individuals in dialysis -- I wasn't a part of it, but took individuals who had a transferrin saturation less than 25 percent and a ferritin between 1800 and 1200, and gave them a dose of iron and saw that the hemoglobins went up. But not everybody responds. There's a population that responds and a population that doesn't respond. And we don't really know -- we don't have a good measure to pick out who those people are who respond or if we're harming them because of no safety.

But given the biological plausibility -- back to this study -- in your early
studies, one of the concerns with giving intravenous iron is that you start seeing the ability of neutrophils to respond to E. coli, and other sorts of bacterial measures drops for about 48 hours. Do you have those studies, post-dialysis, in your slides, to see whether or not, let's say, neutrophil function is preserved?

DR. PRATT: We did not do any neutrophil function studies in the clinical program post-dialysis.

DR. ARMSTRONG: Any other questions, Dr. Fried?

DR. FRIED: No.

DR. ARMSTRONG: I had some questions. I guess one of my main issues with regard to this is I do think, as Dr. Chawla said, this is sort of a slick way of giving iron. Looking at the studies and the treatment duration, I'm not sure how you're going to have an indication for this in terms of dosing schedule, frequency, when you stop, when you restart, those kinds of issues. So I have a few questions that are based on that.
One of them is -- this is actually from the FDA summary, which I think this is the first time we've had an FDA summary this longer than the drug company's summary. In the randomized trial, they looked at the duration of treatment. And by the end of the 48 weeks, only about 20 percent of patients were still on study.

In the I guess what you guys call the NIH trial, that number was 75 to 80 percent at the end of that study, which was 36 weeks. Now, I realize that there were different reasons for having to stop the treatment, but what was the difference in terms of why could 78 percent of people on that small study be still on treatment at 36 weeks, whereas in the randomized trial, at 36 weeks, only about a quarter of patients were still on study?

DR. PRATT: Yes. There is a fundamental difference in the study design. In the NIH trial, remember that patients -- the goal in that study was to maintain hemoglobin at a target level, and patients' ESA dose was allowed to be changed and iron could be given when patients actually became
iron deficient, according to the definition that we had in the protocol, which was a ferritin less than 200 microgram per liter.

In the pivotal studies, the SFP-4 and SFP-5, the goal was to isolate the effect of Triferic on hemoglobin alone. And to that extent, we could not -- because ESA and iron both influence that, we had to maintain the ESA dose constant, and we had to prohibit any additional supplemental iron, oral or intravenous.

As a consequence, what happened was that you saw patients -- there are other factors that influenced hemoglobin level in the dialysis population that we weren't able to control, but those are the two main factors that we controlled. So patients stayed in the randomized part of the study until reached one of the pre-set endpoints in the clinical trial, again, to maintain that effect, be able to say that you had an effect between Triferic and placebo. Triferic, the goal was to maintain hemoglobin constant. The placebo group, the goal was to develop some iron restricted
erythropoiesis, have their hemoglobin drop, but not to make them terribly ill.

So again, if you look at just the kinetics here, we're saying that people lose on an average of 80 milligrams of iron per month. These patients were all iron replete when they came into this study. With the hemoglobin or the red blood cell lifespan that we have you expected to see a gradual decline over time. And that's what we observed in the placebo group in that study.

DR. ARMSTRONG: But that gets to the point of like are you going to say patients can get this once in their lifetime, and they have to go off if they need adjustments? How are you going -- this study, you presented very limited data. The patient representative sounds like she's actually been on this for a long time, but I'm not hearing any data about people being on this for a prolonged period of time.

What is the long-term safety? Can you get this multiple times or multiple cycles? Do we have data on patients who've had this treatment over the
course of years? We're not presented with that safety data.

DR. PRATT: Yes. Well, we actually did present you with the safety data for the all-Triferic population, which included all of the patients who were followed in the open-label treatment phases of the two pivotal studies as well as the SFP-6 study, which was 48 weeks of open-label treatment with patients on there.

Can I have the summary slide for the open-label treatment? And I can show you the effect here.

Again, when patients completed this study according to the protocol, we didn't stop following them. They moved to the open-label treatment phase of this study, where again their ESA could be adjusted. If they needed IV iron, they could get a dose of IV iron. In reality, patients in that phase of the study reverted back to the typical protocols that were ongoing in the units that were participating at the time.

So what we actually see here, thank you very
much -- and again, just to summarize it because this is the two open-label studies where, again, 80 percent of the patients -- 67 percent of the patients completed this study according to the protocol criteria, and they rolled over into the open-label study, where they were followed up to a total, in some cases, 18 months of continuous Triferic therapy.

What we actually see here is that the hemoglobin levels remained relatively constant in this group. This study was not designed for efficacy. It was an open-label trial, and people could get increased ESA or decreased ESA. People could get IV iron. But we're seeing is a consistency in the maintenance of the hemoglobin levels over this period of time, maintenance of the reticulocyte hemoglobin, and again, the ferritin dropped very gradually, a little bit, in the population over the time. And again, the mean time of patients in this study was 36 to 48 weeks of therapy, again, because they came in at different times when they completed the study.
DR. ARMSTRONG: So you have patients in the extension study up to a year almost?

DR. PRATT: Up to 18 months in some cases.

DR. ARMSTRONG: Eighteen months? Okay.

DR. PRATT: Again, depending on where they were randomized in the initial part of the SFP-4 and -5 study. And then everybody who completed, whether they were placebo or Triferic was maintained on the open-label trial.

Dr. Gupta would like to --

DR. GUPTA: Ajay Gupta. I'd just like to clarify that this therapy is for every hemodialysis treatment. So these patients get treated 3 or 4 times a week as in when they get hemodialysis. And this is a continuing treatment that continues for months. Like Dr. Pratt mentioned, we have patients who were exposed up to 1 and a half years.

DR. ARMSTRONG: But in your randomized study, only 20 percent of the patients were actually still on treatment at the end of 48 weeks.

DR. PRATT: Yes. They were only on -- those were patients who did not meet any of the criteria
to complete the study, those were very -- it was a small portion of the population that we expected to see because, again, the SFP-4 and -5 studies are not the way anemia is managed in chronic dialysis units. The NIH-1 study is much closer to what's going to happen in the population here because ESA doses are continuously adjusted, and iron can be given, again, a lot of times in the maintenance stage, but for our study here, when patients required it.

DR. ARMSTRONG: I guess you've sort of hit the nail on the head, which is the large amount of data that you presented us from the randomized study is a trial that doesn't reflect how you would actually be practicing the use of this clinically, and that the ESA study, which is a randomized trial of approximately 100 patients is more like how you would be treating these patients.

DR. PRATT: And the open-label studies are actually -- contribute long-term safety data to that population.

DR. ARMSTRONG: So if patients, when they
went off of the larger randomized study and went on
to the open-label study -- this is conglomerate
data, but we don't have a lot of toxicity data or
other data from patients in that situation. They
basically became patients like on the NIH study,
where it was, erythropoietin dosing, iron,
transfusion can be done at -- really ad lib.
Correct?

DR. PRATT: Well, we actually did follow the
ESA dosing in the assessed studies. Again, they
could be varied. They were not on a -- again,
unlike the NIH-1 study where there was a common ESA
dosing algorithm that all patients were treated on,
these were based on the individual dialysis units'
algorithms. So all generally similar. And we
actually saw here is -- again, you see a lot of
variability in the dosing, but again we see a
relatively constant ESA administration dose over
time that patients were in the study. And again,
this shows the duration up to 69 weeks of treatment
in the open-label studies, which were not, again,
powered for efficacy or with no control group.
DR. ARMSTRONG: I'm sorry. There were patients in the open label who got placebo?

DR. PRATT: No.

DR. ARMSTRONG: So this is --

DR. PRATT: The placebo group there --

DR. ARMSTRONG: Who had originally got placebo? Sorry.

DR. PRATT: -- is patients who were randomized in the parent part of the study and completed on placebo, and then moved to the open-label part. And the red ones were patients who were on Triferic and who maintained Triferic for the entire time that they were on this study.

DR. ARMSTRONG: Thank you.

DR. PRATT: Dr. Fishbane, please.

DR. FISHBANE: I just, Dr. Armstrong, wanted to make one point of clarification. In terms of hemodialysis, it's routine in the way that you would use this drug if you chose to, if a physician chose to use the drug. The way that it would work isn't that you would be starting or stopping therapy necessarily. So this is a background
therapy to try match the ongoing losses with every
dialysis treatment with certain amounts of iron to
replace that.

   It would be a chronic therapy. It would be
a treatment that patients would be treated with
over time. And dialysis unit routine is that
hemoglobin levels are measured either every 2 weeks
or every 4 weeks, so that we could make adjustments
based on that. An iron is, by regulation, measured
every 1 to 3 months. So that if for some reason a
patient required, for example -- it would be
inconceivable that a patient could possibly require
a reduction in the treatment. Just quantitatively,
that can happen because of the ongoing iron losses,
but you will have some patients who during
treatment will have a reduction in ion levels and
would require intravenous iron treatment on top of
that.

   I just wanted to give that clarification.

DR. ARMSTRONG: And I understand what you're
saying. I guess the issue is that we aren't being
presented data on continuous, ongoing, non-stop
treatment. We aren't really presented data, randomized trial data. We just aren't being -- and I understand what you're saying, but the way you're proposing using this is actually not the way it was used in your randomized trial.

DR. PRATT: We couldn't do it that way if we were going to isolate the effect of Triferic on hemoglobin to satisfy the regulatory requirement of showing an effect of Triferic alone on the patient population.

DR. ARMSTRONG: Dr. Fingert?

DR. FINGERT: Thank you. If you can help me understand better, some of the terms here are a bit confusing. There's been some discussion about completers that seem to be completers prior to 48 weeks. And then the FDA's table talks about 18 or 20 percent, completers 48 weeks. And there is difference in the numbers.

In the FDA briefing document, on their table 7, they were showing what looked like very interesting supportive data, the three to fourfold increase and IV iron administration in their
control group. And seven-fold increase in blood
transfusions given to the control group and SP-4.

So I assume those happened off study -- or
it made the patient off part of the randomization
part of this study, and prior to 48 weeks. So can
the sponsor or the statistician explain to me how
would those kinds of patients be treated. Are they
completers and why are we hearing such different
numbers? And I think you mentioned 67 percent were
completers, and the agency and Dr. Armstrong talked
about 20 percent being completers.

DR. PRATT: Can I have the slide with the
completions from the core presentation? Patients
completed the study according to the protocol,
which meant they met one of the four criteria that
were prespecified in the protocol. And when you
add up those numbers of patients, 67 percent of
those patients completed the study by meeting one
of those four criteria were. And the patients who
completed 48 weeks were one of those subgroups of
criteria that were there. I think it may be
semantics, but this is how the protocol was
written, and this is how we treated these patients.

Patients who received transfusions, for the most part, were discontinued from the study because the attending physician required -- said they wanted to do a transfusion. Those patients were taken out of the study at that time. Some of them met criteria for completing, and them moved over to the open-label study, but some of them did not, and then they were treated with a transfusion. And that's where that data come, is in the follow-up period when they were terminated from this study.

The same thing with the IV iron. Patients who met requirement for ferritin less than 100 completed the study at that point, and then moved to the open-label study or they could be given a dose of intravenous iron to replete them, and then were on Triferic for the remainder of the time. I hope that clarifies that point for you and the difference between the two. It was approximately 18 percent of patients in both groups that completed 48 weeks without meeting one of the other three criteria in the protocol for completing this
study.

DR. FINGERT: I see. So is it fair for me to understand, then, that to evaluate the denominator for the benefit of treatment, it's not really just a small subset of 18 percent at 48 weeks.

DR. PRATT: Correct.

DR. FINGERT: It's really a larger denominator that enrolled and went through one of those completion events --

DR. PRATT: Correct.

DR. FINGERT: -- that we're really talking about here, to have confidence in what the two results show.

DR. PRATT: Yes.

DR. FINGERT: Okay. Thank you.

DR. ARMSTRONG: Dr. Diehl.

DR. DIEHL: So we are ultimately going to be asked to vote on the benefits and the risks, so I want to be sure that I have this correct. The benefits, as I understand them, notwithstanding all the discussion about the methods, is that there's
about a .3 increase in hemoglobin, and that there's
about a 3,000 unit difference in epo per week. And
there are theoretical benefits in terms of iron
storage and infection.

Now the problem with that that I have is
that they are compared to something, which I
understand from the nephrologists in the group is
not going to take place when this is actually
approved. In other words, you're comparing it to
placebo, and we don't actually use placebos in this
group. So I actually don't know what the advantage
is when this actually goes out into the community.

My second part of the question is that the
risks in this -- I have two questions. The first
is FDA slide 35. When I look at the side effects,
it appears to me, just looking down the list, that
there are more side effects in the Triferic than
there are in the placebo. And again, we have the
placebo problem there because you're not comparing
it to IV iron. But the second thing that I really
have a problem with is in the deaths. And there is
a numerical difference in the deaths, and we all
know that the iron, the ESA, the hemoglobin level, 
the cardiovascular events are all linked together.

So I would like to know that the patients 
that died did not have high hemoglobins, high epo 
doses, and the like, different from the placebo 
arm. Two questions.

DR. PRATT: Let me address.

DR. DIEHL: First, what's the advantage when 
you compare it to iron, IV iron? And second, what 
are the risks when you look at the epo dose, the 
hemoglobin level of the people that actually got 
Triferic?

DR. PRATT: We'll deal with the IV iron. We 
did not do an active comparator arm here because IV 
iron has not been studied in a long-term study. 
There are many different dosing regimens that are 
out there. Which would you choose to do the 
comparator trial with? Again, it does not have an 
indication. And if you go back and look at all of 
the approved product labeling for the intravenous 
iron products, the duration of the studies that 
they were approved on were perhaps up to 3 months
of follow-up after a few doses of intravenous iron, and they were done to increase the hemoglobin levels over and above in patients with anemia.

These studies that we've done here, we attempted to -- we've done the longest and largest studies of iron administration in a hemodialysis population to try and address the unmet need that was articulated by Dr. Fishbane, who is going to speak here in a minute. We believe that what we have here is that we have a product that maintains hemoglobin levels. And again, the change from baseline in hemoglobin and the Triferic group, when you look at the averages over the time period there, is no different from baseline. It's very stable across baseline.

We induced iron restricted erythropoiesis in the placebo group, so what you're seeing is a small decrease in the hemoglobin concentration in the placebo group that is actually reproducible in two separate studies and gives us -- yes, it's not going to be -- you don't use placebo in the dialysis units, but in order for us to demonstrate
that we have a significant effect by Triferic
alone, with nothing else, we had to do the studies
that way.

Steve, if you could please address.

DR. FISHBANE: Dr. Diehl, thank you. I
think the study should be done against placebo.
Intravenous iron is not a maintenance therapy. You
should not be comparing the drug not just because
of the lack of FDA regulation, but by necessity,
it's impossible to give intravenous irons in the
type of quantities that would allow you to do a
fair comparison. I think placebo is the right way
to do this study, but that's arguable.

In terms of your first question -- because
ultimately you're going to be asked to vote in
terms of the balance of risk and benefit, and we're
going to have to talk about safety because you
raised that question as well. But I did want to
speak about efficacy as well. The effects size in
this study was a hemoglobin change of .36 between
placebo and between the treatment arm. And as we
understand that kind of change, if were to
look -- I'd like to recall your attention to Regidor's analysis.

So there are a variety of studies that are like this in the dialysis population, that look at outcomes like death, hospitalizations, left ventricular hypertrophy. And what they show are that hemoglobin changes of about this size are associated with substantial benefits for patients for high-level outcomes. Outcomes are highly associated with hemoglobin changes of about the size that we saw in the decrement in hemoglobin in this patient population.

A second benefit in terms of hemoglobin changes of this size is what you achieve in terms of ESA dose requirements. We believe in the nephrology community that reducing on the FDA in terms of its labeling suggests using the lowest dose of ESA possible because of a lot of these adverse events associated with ESAs.

In the NIH-01 study, there was a 35 percent difference between groups. When we look at it on a population basis -- so Collins and others have
looked at this over the last couple of years as ESA use has decreased -- the change in hemoglobin that has driven very substantial changes in ESA dosing is exactly the magnitude of difference that was seen, for example, in the CRUISE study. And in fact, it's interchangeable because you could do the studies either way. You either can lock hemoglobin and look at ESA dose as essentially the NIH-01 study did or you could lock ESA dose and look at hemoglobin. But it's impossible to do both. So the second benefit, there's an effect in terms of outcomes. There's an effect in terms of ESA dose reductions.

The third benefit that relates to hemoglobin changes of this size in this population, where there's such decremented quality of life, is the relationship between a hemoglobin change of this type and quality of life. The largest study ever done in hemodialysis patients was an anemia study that looked at quality of life. And a hemoglobin change not near this amount but exactly this amount was associated with the strongest finding of that
study, which was a change in physical functioning
and quality of life for those patients.

Then finally, I'd like to recall your
attention, so not just outcomes, not just reduction
in ESA dose, not just quality of life improvement,
but in addition to that, something that's
tremendously important to us in the kidney disease
population, where we try very hard to avoid blood
transfusion, is that in the pivotal phase 3 CRUISE
trials here, you saw that the number of
patients -- I think Novartis had 50 percent
reduction. It's really more than that, 9 patients
transfused in the Triferic group compared to 23 in
the placebo group.

So by a variety of measures, efficacy here
is demonstrated by the totality of the effects that
were seen and by the very consistent directionality
that everything goes in the same direction and the
totality all move towards the demonstration of
efficacy. And I think you had a question about
safety.

DR. DIEHL: I grant all of that, but my
understanding is -- and correct me if I'm wrong -- that in the community, people would not be getting a placebo; they would be getting IV iron. Is that true?

DR. FISHBANE: Yes. It's not that you're wrong. It's just that -- so the method of treatment would be a little bit different. This is a -- to use the horrible cliche -- paradigm shift that what you're doing here is what we've been trying to do for the last 10 to 15 years is figure out a way to simply give the amount of iron that's lost with every treatment.

So you're not going to have patients that are being given intravenous iron and given this drug. If the doctors choose to give intravenous iron, that's the treatment they'll receive. If the doctors choose to give this treatment, then they will receive this treatment but may require maybe every 3 months a dose of IVR, and maybe every 9 months, maybe once every 18 months. It will be different for different patients. But it's ultimately not concurrent use of the two drugs.
Did I get the question right?

DR. DIEHL: Yes. If I could understand this, then, iron is important. It's very difficult to give in a regulated proper manner. This is a more efficient way to give it. Correct?

DR. FISHBANE: Yes.

DR. DIEHL: Okay. And then I have a question about the cardiovascular risk.

DR. FISHBANE: Yes. Let me get Dr. Lin to come up and talk a little bit and answer your question about the deaths and the safety in cardiovascular risk.

DR. DIEHL: Yes. I want to be sure that the iron that you gave in this very efficient way, which I grant, didn't raise the hemoglobin, didn't raise the cardiovascular risk because the curve that you showed actually shows that there are two tails to the hemoglobin curve; one when it's too low; and one when it's too high, which of course everybody in medical oncology knows.

DR. LIN: So first I'll show this slide, and then can we get up this slide showing the
laboratory results for hemoglobin in the patients who died? You've seen this slide a couple of times. I won't belabor the point too much. But overall, the number of deaths in the Triferic group in all control studies of Triferic is 14 compared to 13.

You raised the issue of the FDA slide 35, and I just want to point out that that slide showed only common adverse events that occurred in greater than 3 percent of the SFP-treated patients. And I'll get that slide up for you in a moment, too. But you also show the patients, the placebo patients, who had greater than 3 percent of cases, and you'll see a more balanced view. And overall, both for overall adverse events, common adverse events, and serious adverse events, numbers were balanced between the two studies.

This is the laboratory of the 14 Triferic patients who died in the controlled studies, NIH-01, SFP-4 and SFP-5. And you can see that end-of-treatment hemoglobin for those patients was no higher than the end-of-treatment for the Triferic
group as a whole or for the placebo cases.

The next slide shows serum iron. In the first column in the Triferic patients who died, again you're not seeing an increase -- if anything you see a slight decrease in the overall serum iron. So we do not believe that Triferic contributing to iron or hemoglobin has anything to do with the reason that these patients passed away. And finally, here's the slide on the overall adverse events.

Can we also line up the slide on the special safety, please, from the core? While we're getting that slide up, as you can see here, the overall adverse events for Triferic were similar to placebo. Here's the special interest adverse events. For composite cardiovascular events at the bottom of this slide -- these were things like hospitalizations due to a cardiac event, MIs, that sort of thing. You can see that in the controlled population, the rates were 8.7 percent for Triferic compared to 10.1 percent for placebo.

So the totality of the data overall do not
seem to show any problem in terms of cardiovascular
events with Triferic. Thank you.

DR. PRATT: Two points, again, and
Dr. Fishbane, can I call you back up here for a
moment? One of the other aspects that we didn't
spend a lot of time presenting here but we have in
your briefing book is the clearance of Triferic
iron is very, very rapid when administered. The
clearance is on the average of 1.2 to 2.2 hours so
that by the time, 8 to 10 hours, post-dialysis,
serum iron values are back to the baseline levels,
that they're there because you generate more
diferric transferrin, and it is cleared very
rapidly.

Steve, can you address the issue of the
mortality in this population with the randomness?

DR. DIEHL: I think you've
satisfactorily --

DR. FISHBANE: Just that on the issue of
deaths in the studies, I just want to recall the
attention to -- it's kind of a slicing and dicing
issue that the deaths in this population occur at a
high rate. Mortality rates have improved slightly, but they’re still very high. It’s been interesting that as I manage my dialysis units, which both have greater than 30 percent lower rates of mortality than national averages -- we have months where it’s zero. We have months where deaths are 3, 4. In May of this year, we had 6 deaths in one month.

The variability in deaths is difficult to address in studies, which I think makes it important to look at the totality of data. To recall CS-8, which is the slide in front of us right now, the total number of deaths when we take these studies together is higher in Triferic. There were 14 versus 13 in the placebo group. However, from study to study, this is what you get in the dialysis population, like I get in my dialysis unit. We've got a study where 3 placebo patients and zero die in the Triferic group.

In other studies, they go in the opposite direction. I think it is important for us to consider the totality of the information because of the randomness of mortalities and endpoints in
these patients.

DR. PAZDUR: Could I ask a question? Should those three patients in the placebo arm in that crossover study be actually in the Triferic arm?

DR. PRATT: Pardon?

DR. PAZDUR: Should those three patients in the placebo --

DR. PRATT: No.

DR. PAZDUR: Were they randomized to placebo?

DR. PRATT: They were randomized to -- two of the patients were -- I'll let Dr. Lin. She's the one that's the answer on this one.

DR. LIN: So two of the patients were actually randomized to placebo first and then Triferic, but unfortunately they passed away before receiving any Triferic. The third patient was a patient who last received Triferic on December 31, 2012, and then transferred over to the placebo arm and got a few doses, and then had a subdural hematoma on January 5th that was ultimately fatal. So by the rules of that study, the patient was
assigned to the placebo arm.

DR. ARMSTRONG: Dr. Rini?

DR. RINI: Thanks. I had a question about slide CE-19. This gets to the ESA dose, the second part of your requested indication. This is for anybody on the sponsor side, CE-19.

DR. PRATT: Yes, it's coming.

DR. RINI: So my question -- and I know this is a small study with larger error bars, but for the bottom curves, those seem like odd-shaped curves to me. It almost looks like ESA use is more in the Triferic arm up to about week 23, then there's just dramatic downturn while the placebo ESA use goes up. And I'm just wondering if that's related to the duration of Triferic use in this small study or something else. Am I missing something or how would you explain that?

DR. PRATT: Well, again, up to about week 20, remember we have to take into account the long lifespan of red blood cells, so that, again, I'll call your attention to the placebo group on the top there. Both groups maintain hemoglobin
levels for about that same period of time. There's variability in dosing of ESA because, again, we had an external blinded anemia management group that looked at the weekly hemoglobin concentrations and made recommendations as to what the next dose of ESA should be for these patients for the next weekly period.

So you've got some variability that's going on in the first 2 weeks. And again, by the time you're getting out to about 24 weeks, you're beginning to see the -- again, there's a small change in the placebo group that's dropping down. The Triferic group is maintaining constant.

I'll point out to you that the magnitude of the change here in the placebo group -- the goal of this study was to keep your hemoglobin in that target range, 9 and a half to 11 and a half by adjusting ESA doses. The hemoglobin levels were down, blinded, and the anemia management group said you need to give more ESA, need to give more SA, and that's where you started to see that monotonic rise in ESA use towards the end of this study.
there.

The magnitude of that effect of the difference between Triferic and placebo is very much close to the effect we see in the randomized placebo controlled trials, the efficacy SFP-4 and -5 studies because, again, in those studies, we were trying to induce iron-restricted erythropoiesis and show a drop in hemoglobin while we maintained hemoglobin in the Triferic treated group.

So both sets of studies are internally consistent in terms of the effective Triferic to maintain hemoglobin. It's in the placebo group that we're seeing either a drop, or because we're trying to maintain hemoglobin at a target level, you have to increase the ESA dose to increase hemoglobin.

DR. FISHBANE: I just wanted to add, Dr. Rini, that -- I love this study because this is complementary to the CRUISE studies, and this gets to I think Dr. Armstrong's questions, to an extent, in terms of what happens in real life when you do
this. So you start with patients in the current world of hemodialysis where there is a lot of iron in storage tissues. Just let them go for a while, but it takes a while.

So remember, you lose 5 to 7 milligrams of iron with every dialysis treatment, and the placebo group eventually breaks down. And that's exactly what would happen in real life, and that's what happened in the natural experiment, which was the early 1990s when we didn't treat patients with iron.

So what you see here is the gradual breaking down of erythropoiesis in the placebo group because of that repetitive loss of iron with the treatment. So it's exactly what I would have expected to have seen in this study, is hemoglobin will start to break down first. It will take a while because we're started patients in the modern area where they start off potentially iron overloaded, and then just let them go over time, better iron stores, safer iron stores. And then you get the benefit in terms of ESA dose sparing.
DR. PRATT: Thank you, Dr. Fishbane.

DR. ARMSTRONG: Dr. Rini, any more questions?

DR. RINI: No, I think that's fine. ESA changes on this study were prescribed. There was an algorithm, correct?

DR. PRATT: Yes.

DR. RINI: So at week 16, the hemoglobin is identical in both arms, yet there's more ESA use in the Triferic arm. So if it was mandated, how would that be different? You know what I mean?

DR. PRATT: There's some variability. We're looking at the Y-axis on the left side there. This is a difference of about a 1015 units, which comes across the way there. This is within the variability and the patient population that we've got. And these are just changes from baseline in the ESA. The baseline ESA usage in this population was approximately 9800 units per week of ESA. So this is on the order of a 10 percent, 12 percent variability, which is well within what you see in the chronic dialysis population today.
DR. RINI: Thank you.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: Leave the slide up. Just to be clear, the placebo here are not getting any iron at all. That was --

DR. PRATT: They could get iron if they had developed iron deficiency anemia. Twenty percent of patients in the placebo group developed iron deficiency with a ferritin less than 200, and 10 patients in the Triferic group.

Could have the IV iron slide, please? I'll just show you the time course in which --

DR. FOJO: Okay. I want to come back to this, though. You can show that in a second. Let me just finish here. There were no dropouts here. Everybody, all 54 in each arm are followed for the full length of the --

DR. PRATT: There was approximately 10 percent, 15 percent dropouts due to deaths, adverse events, and there. But they were equal across both of the groups. And the timing of the patients who left the study was the same.
DR. FOJO: And the study duration was how long?

DR. PRATT: It was 36 weeks.

DR. FOJO: And that end of treatment that's shown at the end, that's not 36 weeks, that period.

DR. PRATT: No. The end of treatment included all the ESA doses, the prescribed ESA doses during the last 2 weeks of participation in study for all study subjects. So if you dropped out at week 28, the last 2 weeks, week 26 and 28 of the ESA dosing would be included in that end-of-treatment analysis.

DR. FOJO: And the reasons for dropping out were what?

DR. PRATT: The reasons for dropping out -- do we have the -- the standard reasons that we had, we had -- again, you saw the deaths in the trial. There were 2 deaths in the Triferic arm. There were 4 deaths in the placebo arm. I'll just wait, if we get this slide up.

DR. FOJO: Okay. And then one last thing, which dovetails on to what Dr. Rini was saying.
What you're seeing in the red, in the Triferic, you're giving a lot of ESA in the middle there, which is then why the ESA -- then you get the expected hemoglobin response, and then the ESA requirements fall off, which is at that point when the statistical significance, if you will, begins to occur.

I think I'm bothered in some of the same ways that you were about this.

DR. PRATT: Do we have the graph?

DR. FOJO: It's okay.

DR. PRATT: Give my team a minute here, and we'll get that for you.

DR. ARMSTRONG: Since we're getting short on time, I think we need to move ahead.

DR. PRATT: Okay. Fine. Thank you very much.

DR. ARMSTRONG: Dr. Chawla? Were you done, Tito?

DR. FOJO: I was just going to ask, the FDA had the primary efficacy -- prescribe ESA dosage. It was slide 44, 45 and 46. You don't need to
bring it up. But you had p-values there of .052 and .111. Am I right to think that -- those p-values, we shouldn't think of those -- I know that, but I'm asking Dr. Cole also. Those p-values shouldn't be. They're not the same as a p-value on a Kaplan-Meier. This is a p-value for a hard amount, 9668.5 units of ESA. This is not an estimated PFS or an estimated OS. Just because it's .052 or .111, that doesn't mean it's not significant.

DR. LUO: Well, because this trial is designed for exploratory, not conclusive, so statistical tests were not adjusted for multiplicity, and the sample size, the power is not adequately -- the study is not adequately powered. Hence, we cannot really say whether 0.045 is statistically significant or not because this is all nominal p-values.

DR. FOJO: Okay. Thank you.

DR. SRIDHARA: I just wanted to add to that. This is Raji Sridhara again, division director, biometrics, FDA. The fact that we are also saying
that it is difficult to interpret or do any
analysis where you have this crossing of -- there
was an increase in ESA usage in the beginning in
the Triferic arm compared to placebo, and after
24 weeks, it crossed over.

So you are just simply averaging over it,
and it's pushed by what you're seeing at the end.
And if you're saying it's not different in the
beginning, then it's not really different at the
end, too. So it's difficult to interpret such
data.

DR. ARMSTRONG: We have two more people on
the list with questions, and then I think we want
to move on to actually asking the question and
voting. So Dr. Chawla?

DR. CHAWLA: I just had a quick question
about does the product affect conductivity, which
is important when we do these therapies in
patients. And secondly, when you do sodium
modeling in the bicarb, concentration's affected.
There will be a measured increase in the drug or
decrease on that, and has that been looked at?
DR. PRATT: It doesn't affect conductivity because, again, the concentration does not. It's very, very low. Again, remember, you're 2 micromolar iron in the final dialysate compared to millimolar sodium and other electrolytes. And yes, we did look in one of the studies where we actually dialed in a lower bicarbonate concentration. And we saw -- it was a lot of scatter in the data, but the quantitative delivery of iron was very similar at the lower versus the higher. We went down from 28 to 23, I believe, and we saw the same.

DR. ARMSTRONG: Are you done?

DR. CHAWLA: Yes.

DR. ARMSTRONG: Dr. Fingert?

DR. FINGERT: The safety profile here is -- I think sometimes we've been concerned about whether the trial entrants are going to be able to extrapolate the trial participation back to the -- how it's going to be used post-approval. Help me better understand this. The regions, the proportion in U.S. and the demographics, did I see
earlier data that you had people up to age 89, and proportion of African Americans?

How do these match with what is in the U.S., and was it mostly a U.S. trial? And how does the mortality data we've kept bringing up match with other known data sets in this renal dialysis population? I think there are epidemiology studies where you have -- to put it in context, basically.

DR. PRATT: I can tell you that the trials were conducted in the United States, and we have two sites in Canada for the SFP-5 study. Again, these demographics in this patient population really do reflect the chronic hemodialysis population in the United States today. We had adequate number of women, about 39, 36 percent women in the trial, so we were able to do good subgroup analysis on that. We had a good mix of non-white patients. And again, this is what we were able to enroll in the clinical study, which is very, very close to what the demographics of the U.S. dialysis population are.

What was your second question, Dr. Fingert?
DR. FINGERT: I wanted to know how the mortality overall ranks against other known mortality figures in this kind of population? In the renal dialysis population, I'm not an epidemiologist, but aren't there data sets that help us understand if this is higher than what's been seen or within the range of what's been seen, in this population?

DR. PRATT: Yes, sir. The best data set is actually the USRDS data set, which actually tracks all the Medicare patients. It's two years out of date, but it does reflect all the mortality. And that's about 20 deaths per 100 patient-years, is what you see in the USRDS data set.

Dr. Fishbane will tell you also that -- and I'm not going to put words in his mouth, but about 20 percent of patients with chronic renal failure on dialysis die each year. So we actually have a rate that's much lower, but again, we have to take it into the context. We were trying to do a study where we would have patients available for up to 18 months.
So, again, we're lower than the USRDS average, but this is very much comparable to the mortality rate that we've seen in other, longer term, say, studies of phosphate binders, for example.

DR. ARMSTRONG: I'm going to let Dr. Cole ask one question.

DR. COLE: I'd like to tell you what I'm interested in seeing, if it's possible, and that is an analysis of hemoglobin levels longitudinally over time, all patients for which those measurements are available regardless of whether they're in the first phase or second phase of the study.

The reason I ask that is because I'm not just interested in -- I think there's a potential problem when the endpoint is defined the way that you have in this study; that is you end up looking at the two treatments where they're going to be perhaps most different from one another, which is fine. I mean, that's how you define it. But whatever that benefit is, also there's interest in
whether it's persistent. And so this kind of analysis I'm suggesting, if you have it, would be helpful to answer that question.

DR. PRATT: I don't have that analysis, but we do have --

DR. COLE: That's okay. If you don't have it --

DR. PRATT: Right. No. But we did look at all these values. And actually the reason I didn't put a graph together is it was very monotonous. It was like one straight line all across the way because, again, patients, when they went to the open-label studies, where we actually followed them for up through the 18 months, became very much -- the hemoglobin levels were very constant across the way.

DR. COLE: Thank you.

DR. ARMSTRONG: One comment from FDA, and then we'll move on to the questions.

DR. LUO: Yes, Dr. Cole. We actually have observed hemoglobin value over time, but for the phase 2 stage only, if you would like to see them.
Questions to the Committee and Discussion

DR. ARMSTRONG: Thank you.

So we're going to move on to the discussion and the specific questions. We'll now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I'll ask the FDA -- I think we'll do these one question at a time, and we'll start with the first question. We'll do our voting. We'll go around, discuss it, and then we'll do the second question.

DR. FARRELL: Okay. Well, we've made a slight change to the question because we realized during the course of this conversation that there could be potential --

DR. PAZDUR: Ambiguity.

DR. FARRELL: -- ambiguity, right. Ferric
pyrophosphate is proposed for use in the treatment of iron loss or iron deficiency anemia to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease. Do the efficacy and safety results in studies SFP-4 and SFP-5 support a positive benefit/risk for the use of ferric pyrophosphate to treat iron loss?

DR. ARMSTRONG: Thank you. Are there any questions?

(No response.)

DR. ARMSTRONG: I guess I will ask a question because I think, based on the questions I asked before, you'll understand that we're presented a very limited amount of randomized trial data, and yet the proposed use of this will extend way beyond what we have observed. And so, the question is -- my question to the agency is, do you want us to respond to what we were presented in the randomized trial data or what we recognize would probably be the proposed use of this, which extends way beyond the data that are presented from the
randomized trial?

DR. FARRELL: Well, we asked you to look at
the randomized control data because we think that's
the best way of gauging potential risks. Compared
to placebo, one could have chosen IV iron, but I
think the randomized control data is the most
helpful.

DR. ARMSTRONG: Does anybody else have any
questions?

(No response.)

DR. ARMSTRONG: If there are no further
questions, we'll begin the voting process on the
first question. We will use an electronic voting
system for this meeting. Once we begin the vote,
the buttons will start flashing and will continue
to flash even after you've entered your vote.
Please press the button firmly that corresponds to
your vote. If you are unsure of your vote or you
wish to change your vote, you may press the
corresponding button until the vote is closed.

After everyone has completed their vote, the
vote will be locked in. The vote will then be
displayed on the screen. The DFO will read the vote from the screen and into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. So we'll have 20 seconds now.

(Vote taken.)

DR. BRIGGS: The vote is 8 yes, 3 no, zero abstentions.

DR. ARMSTRONG: So we'll go around the room. Dr. Chawla, I think you're the first voting member.

DR. CHAWLA: Yes, I compliment the sponsor for putting together a very difficult to do study with an epo change in the middle of the study. And I do think that these initial results are very interesting and the mechanism is interesting. But I am concerned about the ability to dose properly; hence, my vote.

DR. ARMSTRONG: And remember to please state your name.

DR. FLESSNER: Michael Flessner. I'm very
excited about --

DR. ARMSTRONG: Please repeat your vote.

DR. FLESSNER: Yes. I'm excited about this, the possibility of maintaining the iron levels in patients with this. I think that this study was well conducted although complicated. I had to read it over about five times to understand it. But I do think in this case, the applicants did show that this was an effective method of maintaining iron.

DR. RINI: Brian Rini. I voted yes.

Notwithstanding some of the trial design issues and a little bit of the artificial nature of the way they had to do the trial, I thought the totality of the data supported a benefit for a real unmet medical need it sounds like. And also in regards to the safety, I thought if you look across the entire program, I didn't think there was an adverse safety signal that mitigated that benefit.

DR. FRIED: Linda Fried. I voted yes. I think it's probably effective. You know what? I think the study is designed -- it was almost set up not to get people to 48 weeks. It's just sort of
artificial to expect that people are going to stay stable and not require ESA adjustment in our practice, particularly midway when the guidelines for prescribing and our scrutiny on how we're prescribing became even stricter.

I didn't see a clear safety signal, though the population is small. I do notice that the reasons that individuals dropped out also supported efficacy, wherein the placebo group, they tended to drop out when the hemoglobin was low, and they tended to drop out when the hemoglobin was high in the treated group, again supporting efficacy.

DR. ZONES: I'm Jane Zones, and I voted yes. I didn't feel like this was a real solid yes. I was concerned about methodological problems. And I thought the sponsor did a good job laying out the protocol, but it was so complex it I think made it quite difficult. Anyway, I would suggest that if the FDA does approve this product, that there be a phase 4 study or a post-approval follow-up.

DR. ROTH: Bruce Roth. I voted yes. I think the conundrum here is that the trial design
doesn't really reflect patterns of care, but by the same token, we can't ask the company to have a control arm with a non-FDA approved indication.

So is it better than placebo? Yes. And I don't think we can say much more than that. But I thought that it proved the point of what they were trying to do within the confines of that design.

DR. FOJO: Tito Fojo, and I voted no. In the end, I thought that the study wasn't all that well designed, and that made it difficult for us to come to a good conclusion. If you looked at the data, really, for me it was staying on study for 48 weeks that was really the issue, and that was for both the placebo and the treatment arm very similar, a hemoglobin less than 9; a ferritin less than 100, all those were failures. And maybe even a hemoglobin greater than 12 was a failure.

So I just wasn't happy with it. I know you tried to get the FDA to pony up as to whether this was long-term. I think that that's an important issue that you're concerned about, to say, "Oh, this is fine," but 696 patients have 780 years of
exposure. The average patient is one year. And for something that we'll do indefinitely just did not feel comfortable to me.

    DR. COLE: Bernard Cole. I voted no. It was not a strong no. I felt that the data show clearly that Triferic is active versus placebo. But when I only viewed in the sense where you're going to see the biggest difference between the two arms -- so I viewed the totality of the information as being we have proof of principal but not in terms of clinical practice. I would have liked to see a study that assessed it, the more realistic clinical setting.

    DR. ARMSTRONG: I'm Deb Armstrong, and I voted yes. As indicated by my questions, I think that the study as it was designed showed a benefit for the patients who received the treatment. My concern is that the actual use of the drug will be quite different than from the day it is presented. On the other hand, I'm actually trying to imagine a well-controlled, randomized, phase 2 trial, where
you mandate what's going on when the things you're
going to mandate are not things that are FDA
approved. And it sounds like both the
nephrologists on the panel here as well as from the
sponsors sort of grit their teeth and do things
that they don't really like doing such as giving
more IV iron.

I'm not even sure what the right trial
design would be, but it seems to me that the very
prolonged use of this agent, that there needs to be
some safety and potential efficacy studies looking
at much more prolonged use of the agent. But I
think for the very brief, the more limited
question, I thought the answer was yes.

DR. DIEHL: Lou Diehl. I voted yes. I
found this very challenging, but in the end, I
thought it did effectively deliver iron, which was
the main issue. And the safety profile and the
totality of the data, they answered all my
questions.

DR. LIEBMANN: James Liebmann. I voted yes.
Again, I think that the efficacy is believable. I
thought it appeared safe. I will disagree with all
the comments that you can't do a randomized trial
of this versus IV iron. I recognize that there is
not an FDA approval for that, but we have now heard
that for the last two decades, nephrologists have
been going ahead and giving IV iron on a
maintenance anyway. So it staggers the imagination
that the trial can't be done, and it should be
done.

DR. ARMSTRONG: So we'll move on actually to
the next question.

DR. FARRELL: The applicant proposed to
include in labeling a claim that the use of ferric
pyrophosphate reduces the prescribed dose of
erthropoiesis stimulating agent required to
maintain desired hemoglobin levels. Considering
the limitations of the NIH study, should additional
studies be required to establish the efficacy of
ferric pyrophosphate for this claim? Please
discuss the important aspects of trial design for
studies to substantiate clinical benefit for this
use.
DR. ARMSTRONG: Just to clarify, a yes answer here will be that further studies would be required.

DR. PAZDUR: We're just asking you to discuss it.

DR. FARRELL: To discuss it. I'm sorry. We didn't mean for you to vote.

DR. ARMSTRONG: Okay. Yes?

DR. FRIED: Just to start with trial design, it has to be larger. You can't take a hundred -- do I think it will work? Yes. From a clinical practice, we know that there are a lot of reasons that our individuals in our dialysis unit are epo resistant, but one of the main ones is iron. I do think you need a double-blind study. It needs to be a larger sample size. And essentially, you could use what are doses over time, recognizing that -- the question was, the early issues might depend -- I might standardize which ESA I used because the half-life of Epogen or Procrit, the two FDA-approved erythropoietins, or darbepoetin, are different. And that might make it
a little bit harder to look at hemoglobins over
time, particularly if you're worried about that
early change, given the half-life of the ESA.

DR. ARMSTRONG: Thank you. I'm hoping the
nephrologists here will help us out with this study
throughout this issue.

DR. FLESSNER: I agree with my colleague,
Dr. Fried. This study needs to be done again, and
it needs to be done with a biostatistician,
designing, helping to design the study and the
proper number of patients. And it will be an
important study because this -- and I believe, like
Dr. Fried, that eventually this will show that in
patients who aren't these epo-resistant type
patients -- and we have a certain percentage of
these very sick patients. They tend to actually
die a lot earlier than our normal patients -- that
it will show that there's a decrease in the use of
ESAs. However, I agree with her. I think it would
have to be carefully designed and some of the
things she mentioned, a single agent used as an ESA
and then a strict protocol.
DR. CHAWLA: I agree with those comments. And I think some sort of standardization, although it certainly -- as it was, this was a challenging series of studies to do, and this may be even more challenging. But the standardization is critical because all these ESAs, even though we have equivalence data, are not exactly the same. The dosing issue, I've made my comment previously. I won't continue to harp on that. But I do think that there is a potential for large groups of patients to be exposed to a drug who get no benefit. And I see no value in that except for potential harm.

I do think this will probably work for this. And I do think this molecule has a lot of potential, but it needs to be demonstrated in a larger set of patients because our experience collectively has been that smaller studies that show efficacy that get through, when they begin to get expanded to very large groups of patients, we have untoward surprises. And I think this would represent an opportunity to broaden the safety set.
DR. ARMSTRONG: Is there an agreement on the ESA-resistant patient, and the definition of that? And what frequency is that in the population?

DR. FRIED: There are varying definitions. Some people will use the dose for a particular hemoglobin or the weight. And so probably it varies, unfortunately, by study. It's one of those things right now, if you gave me a population, I could point them out, but I'm not sure I have a formal definition.

DR. ARMSTRONG: And again, what percentage do you think it is? I'm just curious if this is maybe a small population that --

DR. CHAWLA: No. So the issue is that it's highly dynamic. So if you're highly inflamed, your ESA resistance goes up. And so if a patient's coming off an infection or a hospitalization, then their ESA resistance is not static event. Some patients can be ESA resistant because they just are, but a whole subset of patients who get infected or have other events that are inflammatory are resistant for the time period for which they're
managing that inflammation.

We know that iron and iron sequestration is a highly adaptive event because iron is very beloved by bacteria and other microorganisms that infect us. So iron sequestration is a modality of adaptation. So being in a chronic anemia state, that's anemic chronic disease, is adaptive. It's just these patients are chronically in that state. And so forcing them out of it through vis a vis some form of iron, how you do it and what you do is really important.

So there are interesting mechanisms by which this drug looks like it might have a better modality, but to answer your specific question about ESA resistance, it's dynamic. So I think that you have to construct a very pragmatic design in order to accomplish this.

DR. ARMSTRONG: I'm just trying to think about potential -- study designs or patient populations where you could potentially answer this without having a huge number of patients. So one would be, for example, if somebody's just starting
dialysis, could you look at a population like that? Do people in the pre-dialysis renal failure setting get ESAs? So they will have already had ESAs at that point in time.

DR. FRIED: That's sometimes an insurance question. ESAs are extremely expensive, and if you --

DR. ARMSTRONG: Just know that, yes.

DR. FRIED: And if you're talking about -- I work in the VA. I give ESAs pre-dialysis. I'm not as restricted outside of the requirements to follow hemoglobin, but you do find that individuals can't always afford it. So it's going to vary, and it's going to vary very much on Medicare rules and the other rules across the country.

I do find, though, when people start dialysis, they're iron deficient because unless you have a program to give them intravenous iron, they don't tend to either tolerate or absorb oral iron very well. That's part of that hepcidin effect as they get chronic kidney. That would be an interesting question, but that is a population that
I find is typically truly iron deficient.

DR. ARMSTRONG: So that's a little different than this population because they had to be iron replete here. Would that be a population where you could say do a randomized trial and look and see who ends up needing iron and who doesn't?

DR. CHAWLA: You could, but my concern would be that the residual renal function issue and patients who first come on dialysis affects all these issues. And generally speaking, after you're on dialysis six months, your residual renal function goes to zero. So in order to compare apples to apples and actually ascertaining your residual renal function in dialysis patients is logistically impossible. I would never ask anyone to go through that. That's nearly impossible.

So I think that from a pragmatic standpoint, although that was an interesting population to study, I don't think you would be able to accomplish it without dealing with that important confounder. I think that because of the safety set, what we're really looking at is to broaden the
safety set. I think we should ask them to do it in
the continued population for which they've shown
expertise, for which they continue to conduct the
study, and then answer this important question,
among others.

DR. ARMSTRONG: Does anybody else on the
panel have any suggestions? Does this provide you
guys with some information that's helpful?

DR. LIEBMANN: Let me just ask, then, to the
FDA, because we've heard this concern about you
can't do a randomized trial, comparing it against
IV iron. Is that your position?

DR. FARRELL: No. You could do a randomized
trial against IV iron. There would be no
restrictions.

DR. LIEBMANN: One of the things that has
bothered me with a lot of this discussion is our
end points, or laboratory endpoints. For the most
part, I don't care about laboratory endpoints. I
care about is a patient alive or dead, how does the
patient feel, how is the patient doing. And I
think that one of the virtues of a randomized trial
with what is currently the standard of care, which is IV iron, would be you will get those clinical endpoints, which right now we don't have.

DR. ARMSTRONG: So just to summarize for question 2, I think we are in agreement that there needs to be another study done to document efficacy in terms of reducing ESA requirement or assessing impact on ESA requirement, and we've heard a few things.

DR. FARRELL: Right. And for this kind of a claim, we'd usually require two adequate and well-controlled trials.

DR. ARMSTRONG: I'm also -- just because of the variation in the ESA use, if you looked at this study at the halfway point, you actually would have gotten exactly -- the opposite response.

With regard to question 1, I think, as you've heard from most of us, we would certainly think it was worthwhile to do a well designed trial to try and look at whatever is the standard of care, whether it's got FDA approval or not, compare to this and see if there's an improved outcome.
Dr. Friedman?

DR. FRIED: I agree you want hard endpoints, but I actually think it's less of an efficacy than as a safety because I'm not convinced -- despite the hemoglobin, I think the ESA trials have told us that you can't look at that hemoglobin and say, well, the nadir hemoglobin, or the hematocrit, the old USRDS could say 30 to 33 or 11 to 12. That essentially achieves hemoglobin because in dialysis, we are trying to hit a target, and what you're getting are people who are at the target or below the target, and that's the problem.

I think that if you're very anemic, you don't feel so well. But I think really what you're getting at is do I think -- if you're going to be talking about comparing this to IV iron, then really what you're asking is -- you're giving iron in both cases, really, is one safer than the other. So the endpoints I don't think should be -- on that case, you might do efficacy with ESA dosing, but really what you're asking is, if we believe that intravenous iron causes an increased risk of
oxidative stress and cardiovascular events, and infection, that's what your endpoints would be, not whether or not you decrease mortality by giving intravenous iron.

DR. CHAWLA: I agree with that point. And I would point out that the pragmatic design head to head will not answer the ESA question because you won't get ESA -- because there's iron on both sides. Those are two separate issues.

DR. ARMSTRONG: We've been talking a little bit back and forth between question 1 and question 2. That's why I've been trying to keep --

DR. CHAWLA: But I just want to point out that I agree that the issue -- these patients do need iron, period. I think all of us, at least in nephrology, we all agree with this. They all need iron. It's important. They lose it as a part of dialysis. They need it.

The question is can we do it -- what's the safest way to do this. And this appears to be an encouraging approach, but we need, in my opinion, a larger safety set.
Adjournment

DR. ARMSTRONG: We're not going to vote on question 2. We've had some discussion on it, and hopefully it's helpful for everybody in the room. So at this point, unless there are any other issues to bring up, we will now adjourn.

Panel members, please remember to drop off your name badge at the registration table on your way out so that they can be recycled. Thank you everybody.

(Whereupon, at 4:58 p.m., the afternoon session was adjourned.)