

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT  
ADVISORY COMMITTEE

Silver Spring, Maryland

Friday, February 1, 2008

1 PARTICIPANTS:  
2 DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE  
MEMBERS (VOTING):  
3  
4 RICHARD PLATT, M.D., Chair  
Harvard Medical School  
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6 TERESA WATKINS, Pharm.D., Executive Secretary  
Center for Drug Evaluation and Research  
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16 TIMOTHY S. LESAR, Pharm.D.  
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18 TEMPORARY VOTING MEMBERS:  
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20 MICHAEL LINCOFF, M.D.  
The Cleveland Clinic Foundation  
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22 ROBERT A. HARRINGTON, M.D.  
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24 EMIL P. PAGANINI, M.D.  
The Cleveland Clinical Foundation  
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26 HENRY R. BLACK, M.D.  
New York University School of Medicine  
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28 GARY M. BRITTENHAM, M.D.  
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1 TEMPORARY VOTING MEMBERS (CONT'D);

2 CASSANDRA E. HENDERSON, M.D.  
Our Lady of Mercy Medical Center

3 CHARLES J. LOCKWOOD, M.D.  
4 Yale University School of Medicine

5 GAIL MACIK, M.D.  
6 University of Virginia

7 CHARLES M. PETERSON, M.D., MBA  
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8 HARVEY KLEIN, M.D.  
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9 ARTHUR A. LEVIN, M.P.H.  
10 Consumer Representative

11 JoELLEN CORKERY-DELUCA  
Patient Representative

12 NON-VOTING:

13 D. BRUCE BURLINGTON, M.D.  
14 Industry Representative

15 REEMA BATRA, M.D.  
16 George Washington University School of Medicine

17 CDER PARTICIPANTS AT TABLE (NON-VOTING):

18 RICHARD PAZDUR, M.D.  
Office of Oncology Drug Products

19 DWAIN RIEVES, M.D.  
20 Division of Medical Imaging and Hematology  
Products

21 KATHY ROBIE-SUH, M.D.  
22 Division of Medical Imaging and Hematology  
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1 CDER PARTICIPANTS AT TABLE (NON-VOTING):

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3 Division of Medical Imaging and Hematology  
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4 CHRISTY JOHN, Ph.D.  
5 Office of Pharmacology

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6 MARC TOKARS  
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17 TIM GOODNOUGH, M.D.  
18 Stanford University

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20

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## 1 P R O C E E D I N G S

2 (8:00 a.m.)

3 DR. HENNESSY: Ladies and gentlemen,  
4 I'd like to get started this morning. My name  
5 is Sean Hennessy, and I do pharmacoepidemiology  
6 research at the University of Pennsylvania, and  
7 I have the privilege of being the chair for this  
8 morning's meeting.

9 Before we start the meeting, I need  
10 to read an opening statement.

11 For topics such as those being  
12 discussed at today's meeting, there are often  
13 a variety of opinions, some of which are  
14 quite strongly held. Our goal is that  
15 today's meeting will be a fair and open forum  
16 for discussion of these issues, and that  
17 individuals can express their views without  
18 interruption.

19 Thus, as a gentle reminder,  
20 individuals will be allowed to speak into the  
21 record only if they are recognized by the  
22 chair. We look forward to a productive

1 meeting.

2           In the spirit of the Federal  
3 Advisory Committee Act and the Government in  
4 the Sunshine Act, we ask that the Advisory  
5 Committee members take care that their  
6 conversations about the topic at hand take  
7 place in the open forum of the meeting. We  
8 are aware that members of the media are  
9 anxious to speak with the FDA about these  
10 proceedings. However, FDA will refrain from  
11 discussing the details of this meeting with  
12 the media until its conclusion.

13           A press conference will be held in  
14 the Washingtonian Room immediately following  
15 the meeting today. Also, the committee is  
16 reminded to please refrain from discussing  
17 the meeting topic during break or lunch.

18           Thank you.

19           I'd like to remind everyone to  
20 please silence your cell phones and pagers if  
21 you have not already done so, and I would  
22 like to identify the FDA press contact, Karen

1 Riley, if you're -- Karen Riley's standing  
2 there. Thank you. Okay. Thank you.

3 I'd like to go around the room and  
4 have each of the people sitting at the table  
5 introduce yourselves.

6 We'll start at this end of the  
7 table. Dr. Burlington?

8 DR. BURLINGTON: Bruce Burlington,  
9 industry representative, a guest I guess at this  
10 meeting. I'm retired from the pharmaceutical  
11 industry.

12 MR. LEVIN: Arthur Levin, Center for  
13 Medical Consumers in New York. I am the  
14 temporary consumer representative to this  
15 committee.

16 MS. CORKERY-DeLUCA: JoEllen Deluca,  
17 Spartanburg, South Carolina. I'm the patient  
18 consultant for this committee.

19 DR. MACIK: Dr. Gail Macik. I'm a  
20 hematologist at the University of Virginia,  
21 consultant for the committee.

22 DR. BRITTENHAM: I'm Gary Brittenham,

1 Columbia University, a hematologist, consultant  
2 for the committee.

3 DR. PETERSON: I'm Chuck Peterson.  
4 I'm director of the Division of Blood Diseases  
5 and Resources at the National Heart, Lung, and  
6 Blood Institute.

7 DR. KLEIN: I'm Harvey Klein. I'm  
8 chief of the Department of Transfusion Medicine  
9 at the National Institutes of Health.

10 DR. KRAMER: I'm Judith Kramer from  
11 Duke University, with a background in clinical  
12 trials and working on observational research.

13 DR. LESAR: Timothy Lesar. I'm the  
14 director of Clinical Pharmacy Services, Albany  
15 Medical Center, with expertise in pharmacy.

16 DR. LOCKWOOD: Charlie Lockwood. I'm  
17 the chair of OB-GYN at Yale University, and a  
18 temporary voting member.

19 DR. WATKINS: I'm Teresa Watkins, the  
20 designated federal official for this committee.

21 DR. HENNESSY: Dr. Sander Greenland  
22 will be represented on the phone here once he

1 makes it to the call. He's in Los Angeles where  
2 it's 5:00 in the morning now.

3 He'll be joining us shortly.

4 DR. DAVIS: Hello, I'm Terry Davis,  
5 professor of medicine and pediatrics at  
6 Louisiana State University Health Sciences  
7 Center in Shreveport, and my background is in  
8 health literacy and risk communication.

9 DR. BLACK: I'm Henry Black from New  
10 York University. I'm a cardiologist and a  
11 preventionist.

12 DR. PAGANINI: Emil Paganini, private  
13 nephrologist to Critical Care Nephrology,  
14 recently retired from The Cleveland Clinic.

15 DR. LINCOFF: Michael Lincoff. I'm an  
16 interventional cardiologist at The Cleveland  
17 Clinic, and chairman of our Center for Clinical  
18 Research.

19 DR. HARRINGTON: Bob Harrington. I'm  
20 an interventional cardiologist at Duke and the  
21 director of the Duke Clinical Research  
22 Institute.

1 DR. JOHN: Christy John. I'm clinical  
2 pharmacology reviewer at FDA.

3 DR. LU: I'm Min Lu, medical reviewer  
4 in FDA.

5 DR. ROBIE-SUH: I'm Kathy Robie-Suh.  
6 I'm a medical team leader in the Division of  
7 Medical Imaging and Hematology in CDER.

8 DR. RIEVES: Hi. I'm Dwaine Rieves,  
9 acting director of the Division of Medical  
10 Imaging and Hematology at FDA.

11 DR. PAZDUR: Richard Pazdur, office  
12 director, FDA.

13 DR. HENNESSY: Thank you. I actually  
14 misspoke when I said that there would be a press  
15 conference. There will be no press conference  
16 today.

17 Dr. Watkins will now read the  
18 Conflict of Interest Statement.

19 DR. WATKINS: Thank you.

20 The Food and Drug Administration is  
21 convening today's meeting of the Drug Safety  
22 and Risk Management Committee under the

1 authority of the Federal Advisory Committee  
2 Act of 1972. With the exception of the  
3 industry representative, all members and  
4 consultants are special government employees  
5 or regular federal employees from other  
6 agencies, and are subject to federal conflict  
7 of interest laws and regulations.

8           The following information on the  
9 status of the committee's compliance with  
10 federal ethics and conflict of interest laws  
11 covered by, but not limited to those found in  
12 U.S.C. 208 and 712 of the Federal Food Drug  
13 and Cosmetic Act, is being provided to  
14 participants in today's meeting and to the  
15 public.

16           FDA has determined that members and  
17 consultants of this committee are in  
18 compliance with federal ethics and conflict  
19 of interest laws. Under 18 U.S.C. 208,  
20 Congress has authorized FDA to grant waivers  
21 to special government employees who have  
22 potential financial conflicts when it is

1 determined that the agency's need for a  
2 particular individual's services outweighs  
3 his or her potential conflict of interest.

4 Under 712 of the FD&C Act, Congress  
5 has authorized FDA to grant waivers to  
6 special government employees and regular  
7 government employees with potential financial  
8 conflicts when necessary to afford the  
9 committee essential expertise.

10 Related to the discussion of  
11 today's meeting, members and consultants of  
12 this committee who are special government  
13 employees have been screened for potential  
14 financial conflicts of interest of their own  
15 as well as those imputed to them, including  
16 those of their spouses or minor children, and  
17 for purposes of 18 U.S.C. 208, their  
18 employers.

19 These interests may include  
20 investments, consulting, expert witness  
21 testimony, contracts, grants, CRADAs,  
22 teaching, speaking, writing, patents and

1 royalties and primary employment.

2 Today's agenda involves discussion  
3 of the safety and efficacy of new drug  
4 application NDA 22-054, Injectafer, ferric  
5 carboxymaltose injection used for the  
6 treatment of iron deficiency anemia in  
7 postpartum patients for iron deficiency  
8 anemia in patients with heavy uterine  
9 bleeding.

10 Based on the agenda for today's  
11 meeting and all financial interests reported  
12 by the committee members and consultants,  
13 conflict of interest waivers have been issued  
14 in accordance with 18 U.S.C. 208(b)(3) and  
15 712 of the FD&C Act for Dr. Black and  
16 Dr. Harrington.

17 Dr. Black has been granted these  
18 waivers for being on a competitor's speaker's  
19 bureau on an unrelated issue. Dr. Black  
20 receives less than \$10,001 per year.  
21 Dr. Harrington has been granted these waivers  
22 for being on a competitor's data safety

1 monitoring committee on an unrelated issue.  
2 Dr. Harrington receives less than \$10,001 per  
3 year.

4           The waiver allows these individuals  
5 to participate in today's deliberations.  
6 FDA's reasons for issuing the waivers are  
7 described in the waiver documents which are  
8 posted on FDA's website at  
9 [www.fda.gov/ohrms/dockets/default.htm](http://www.fda.gov/ohrms/dockets/default.htm).  
10 Copies of the waivers may also be obtained by  
11 submitting a written request to the agency's  
12 Freedom of Information Office, Room 630 of  
13 the Parklawn Building.

14           A copy of this statement will be  
15 available for review at the registration  
16 table during this meeting and will be  
17 included as part of the official transcript.

18           With respect to FDA's invited  
19 industry representative, we would like to  
20 disclose that Dr. Burlington is participating  
21 in this meeting as a non-voting industry  
22 representative acting on behalf of regulated

1 industry.

2 Dr. Burlington's role in this  
3 committee is to represent industry interests  
4 in general and not any one particular  
5 company. Dr. Burlington is self-employed at  
6 D.B. Burlington of Aston, Pennsylvania.

7 We would like to remind members and  
8 consultants that if the discussions involve  
9 any other products or firms not already on  
10 the agenda for which a FDA participant has a  
11 personal or imputed financial interest, the  
12 participants need to exclude themselves from  
13 such involvement, and the exclusion will be  
14 noted for the record.

15 FDA encourages all other  
16 participants to advise the committee of any  
17 financial relationships that they may have  
18 with any other firms at issue.

19 Thank you.

20 DR. HENNESSY: Thank you very much,  
21 and now I'd ask Dr. Dwaine Rieves to give us  
22 some opening remarks from FDA.

1 Thank you.

2 DR. RIEVES: Good morning. We are  
3 here today to discuss Injectafer, a parenteral  
4 iron replacement product currently under FDA  
5 review for marketing consideration. We've  
6 chosen to focus specifically upon the Injectafer  
7 safety data, most notably the mortality results  
8 from the clinical studies, since FDA regards the  
9 efficacy data as robustly demonstrating the  
10 ability of Injectafer to replenish body iron and  
11 to improve hemoglobin concentrations, the  
12 essential clinical benefit expected for this  
13 type of product.

14 Today, our presentations begin with  
15 an overview of iron deficiency anemia by  
16 Dr. Reema Batra from the George Washington  
17 University School of Medicine, who will be  
18 followed by presentations from the  
19 Injectafer-sponsored Luitpold  
20 Pharmaceuticals.

21 Following a break, our FDA review  
22 staff will provide presentations, and after

1 lunch, we will reconvene for the open public  
2 hearing and discussion of questions.

3 On behalf of our review staff, we  
4 thank you for your participation and look  
5 forward to a productive discussion.

6 Dr. Batra?

7 DR. BATRA: Good morning. I was asked  
8 to come and speak today about iron deficiency  
9 anemia. I'm going to do a quick overview about  
10 the physiology of iron and metabolism, as well  
11 as causes of iron deficiency anemia, and I will  
12 conclude with treatment.

13 Okay. So the essential nutrients  
14 for erythropoiesis or the formation of red  
15 blood cells are folic acid, cobalamin or  
16 vitamin B12, and of course iron. The  
17 metabolism of these three nutrients is quite  
18 complex.

19 On the right, I've listed some of  
20 the essential nutrients and enzymes that are  
21 essential for iron's metabolism for  
22 erythropoiesis. The enzyme that's

1 responsible for iron metabolism is  
2 ferrochelatase; its function is in hemoglobin  
3 synthesis. And the source that we get our  
4 iron is meats and in fortification. The  
5 absorption is mostly in the proximal  
6 intestine, and its storage is mainly in  
7 macrophages.

8           The dietary content of iron -- once  
9 again, this is in the right column -- it's  
10 about 20 milligrams of iron, and our daily  
11 absorption range is between 1.0 and 1.5  
12 milligrams, and our storage is about 500 to a  
13 1,000 milligrams.

14           The essential nutrient iron has two  
15 important molecules; one is the hemoglobin,  
16 which -- and myoglobin, both of these have  
17 reversible binding to oxygen. Again, the  
18 enzymes that are responsible are cytochromes  
19 for the heme, the aconitase for the iron  
20 sulfur cluster, and others, including the  
21 ribonucleotide reductase. It also is  
22 involved in immunity, in that there's

1 formation of free radicals to destroy  
2 microbes.

3 Iron can also be potentially toxic.  
4 It's highly reactive with oxygen and can  
5 eventually cause fatal toxicity. Some of the  
6 things that we see with iron overload  
7 situations are cardiomyopathy, liver  
8 cirrhosis and endocrine abnormalities such as  
9 diabetes.

10 Some of the broad themes of iron  
11 metabolism is that the absorption of iron is  
12 highly regulated to prevent excess iron from  
13 being absorbed. And there's also no  
14 physiologic pathway for excreting iron that  
15 exists.

16 Now, body iron compartments differ  
17 in females and males. If you take a 60  
18 kilogram female versus a 70 kilogram female,  
19 you can see just based on looking at the  
20 numbers here that the storage compartments  
21 are different in terms of milligrams. The  
22 total in a female is about 2,500 milligrams,

1 and in a male it's about 3,800 milligrams.

2 In women there is an extra source  
3 of loss from menstruation. Women usually  
4 lose about 0.5 milligrams per day during  
5 menstruation, and therefore, there is a  
6 larger total loss of iron in general, and  
7 iron absorption because of that is increased  
8 in women.

9 So iron absorption is taken from  
10 meats, and it's absorbed better than iron  
11 that's taken from grains. The gastric acid  
12 is an important component in iron absorption,  
13 because the iron needs to be reduced to an  
14 oxidized form that's absorbed. Again, it's  
15 absorbed in the proximal small bowel, and the  
16 absorption increases with patients who have  
17 low iron stores or if they need to form red  
18 blood cells in certain situations. And iron  
19 absorption is inhibited by inflammation and  
20 teas.

21 This is kind of a complicated side  
22 in terms of just metabolism. So the

1 erythroid precursors are in the bone marrow  
2 and they produce hemoglobin, about 18  
3 milligrams of iron per day, and iron is  
4 absorbed from the intestine about 1 milligram  
5 per day.

6           The erythroid precursors that  
7 produce hemoglobin then are broken down  
8 eventually through from the RBCs, the red  
9 blood cells in the spleen, and there are  
10 losses that occur all the time, about 1  
11 milligram or 1.5 milligrams of iron per day.  
12 And these -- once the hemoglobin is broken  
13 down, either it's lost or it's taken in  
14 plasma via transferrin, a protein that brings  
15 it around the body.

16           So iron metabolism, the iron  
17 circulates in the plasma bound to  
18 transferrin, approximately .1 percent of body  
19 iron. It's also stored intracellularly as  
20 ferritin. This is a number that we  
21 hematologists check to see iron stores. And  
22 the serum iron concentration and transferrin

1 saturation reflect iron delivery to the  
2 erythroid precursors. And again, the serum  
3 ferritin concentration reflects the storage  
4 of the macrophages, so this is the number  
5 that we check to see how much a patient has  
6 in terms of their iron storage.

7 Another very complicated slide, but  
8 basically, this is the surface of where the  
9 iron is absorbed in the enterocyte, or in the  
10 small bowel, and this is the complicated  
11 process in which it's absorbed and then into  
12 this plasma here. And this is just an  
13 example of a macrophage that breaks down the  
14 hemoglobin.

15 Another complicated slide, but  
16 basically, iron is transported in plasma via  
17 transferrin protein taken in and then  
18 released again, and then released out into  
19 the system.

20 This is a normal peripheral smear.  
21 Basically, these are red blood cells, and you  
22 can see they're quite abundant in terms of

1 hemoglobin. We call this the "central  
2 pallor." And this is a iron deficiency  
3 smear. The central pallor is quite widened,  
4 and then there's different types of shapes  
5 that you can see of the red blood cells.  
6 Another slide of the iron deficiency anemia.  
7 They sort of look like wedding rings.

8 One more slide.

9 So the causes of iron deficiency  
10 anemia, usually it's chronic blood loss.  
11 Most of the time it's seen in the GI system  
12 from cancers, ulcers, diverticuli, a-v  
13 malformations or hookworms. You can see it  
14 via the genitourinary tract, such as  
15 menorrhagia, uterine bleeding, bladder  
16 cancer. Pulmonary causes can be hemoptysis  
17 or pulmonary hemociderosis, or patients who  
18 are frequent blood donors. So each time a  
19 patient gives blood, about 220 milligrams of  
20 iron is lost with each blood donation.

21 Other causes are dietary  
22 insufficiency, so you see it often with

1 rapidly-growing children or women of  
2 childbearing age. And then another cause  
3 which I've been seeing much more commonly,  
4 just because of gastric bypass surgery  
5 becoming more common, is malabsorption. So  
6 patients who are status post-gastrectomy or  
7 status post-resection of the proximal small  
8 bowel, patients who have Crohn's disease or  
9 celiac disease.

10 Another cause is pregnancy and  
11 lactation. And then finally, hemoglobinuria  
12 due to patients who hemolyze their red blood  
13 cells. And this is seen in patients who have  
14 paroxysmal nocturnal hemoglobinuria or  
15 runner's anemia.

16 Some of the clinical manifestations  
17 of iron deficiency anemia is impaired growth  
18 or psychomotor development, fatigue,  
19 irritability, decreased work productivity,  
20 Pica syndrome, in which patients complain  
21 that they are craving ice chips or eating  
22 dirt; dysphagia, esophageal webs -- that's

1 also known as Plummer-Vinson syndrome or  
2 Patterson-Kelly syndrome; koilonychia,  
3 glossitis and angular stomatitis.

4           The lab findings that we see -- we  
5 check the CBC, and you can see an increase in  
6 the red cell distribution in the platelet  
7 count -- there's a decrease in the MCV, which  
8 is the size of the red blood cells, the MCH,  
9 and MCHC, the concentration of the  
10 hemoglobin, the red blood cells, a decrease  
11 in the red blood cell count and a decrease in  
12 the hemoglobin and hematocrit. Oftentimes  
13 the reticulocyte count is not increased. And  
14 the other test that we can check are the  
15 serum iron level, which would be low,  
16 transferrin saturation, which would be low,  
17 and ferritin, which would be low. You can  
18 see an increase in the TIBC, transferrin, and  
19 transferrin receptor.

20           Another test that we can do is a  
21 bone marrow biopsy, and on the bone marrow  
22 you would see an absent macrophage iron

1 stores, decreased sideroblasts and an  
2 increase in the erythrocyte precursors.

3 Here's an example of a bone marrow  
4 biopsy that has increased iron stains. You  
5 see this, the blue staining? And this is a  
6 bone marrow aspirate which has no iron stains  
7 at all, so no blue staining.

8 So the first thing we do for iron  
9 deficiency anemia is to look for the source  
10 of the blood loss, and the first thing you  
11 want to do is rule out malignancy, especially  
12 in an age-appropriate individual. So you  
13 would send a test for occult blood, and you  
14 have to rule out GI carcinomas, most commonly  
15 colorectal, gastric cancer, esophageal, or  
16 hepatomas. And then of course, genitourinary  
17 endometrial cancer, cervical and bladder  
18 cancer, and then secondly, to correct the  
19 cause of the blood loss.

20 In terms of treatment of iron  
21 deficiency anemia, the general principle is  
22 to remember that the iron absorption occurs

1 at the duodenum and the proximal jejunum, and  
2 if patients are first going to receive oral  
3 therapy, it's important to remember that the  
4 extended release capsules or the  
5 enteric-coated capsules get absorbed at the  
6 lower parts of the GI tract and may not be as  
7 effective as the other types.

8           Also, it's important to remember  
9 that iron salts should not be given with  
10 food, because the salts actually bind the  
11 iron and then impair absorption. Also other  
12 general principles for oral therapy is that  
13 iron should be given two hours before or four  
14 hours after the ingestion of antacids, that  
15 iron is best absorbed as a ferrous salt in a  
16 mildly acidic medium, so to help increase  
17 absorption, one can give it with a tablet of  
18 vitamin C.

19           And then the iron preparation  
20 that's used for the oral iron should be used  
21 based on cost and effectiveness with the most  
22 minimal side effect. The most cheapest is

1 iron sulfate, and that gives a 65 milligram  
2 dose of elemental iron.

3 The GI tract symptoms is directly  
4 related to the amount of elemental iron  
5 that's ingested, and these symptoms may be  
6 seen less in the iron elixir preparation.

7 The most appropriate oral iron  
8 therapy is use of a tablet that contains  
9 ferrous salts, so there's ferrous fumarate,  
10 which has 106 milligrams of elemental iron  
11 per tablet; ferrous sulfate, which is 65  
12 milligrams of elemental iron per tablet; and  
13 ferrous gluconate, which has 28 to 36  
14 milligrams of iron per tablet. And the  
15 recommended daily dose is about 150 to 200  
16 milligrams per day of elemental iron. We  
17 don't have much evidence that one preparation  
18 is better than the other.

19 The side effects of oral iron is  
20 that 10 to 20 percent of patients experience  
21 nausea, constipation, epigastric distress  
22 and/or vomiting. To help alleviate those

1 symptoms, you could give a smaller dose of  
2 elemental iron or switch to an elixir form.

3           You can also slowly increase the  
4 dose from one tablet to three tablets per  
5 day, or take the tablet with meals, and that  
6 actually may decrease the absorption but help  
7 with the side effects.

8           The duration of the treatment of  
9 oral iron depends on the physician, and some  
10 physicians discontinue the treatment when the  
11 hemoglobin level is normal, some may continue  
12 for six months after the hemoglobin level is  
13 normal.

14           In terms of treatment failures,  
15 this is seen when patients have an incorrect  
16 diagnosis, or if they have a pressure of a  
17 coexisting disease. Many patients may have  
18 anemia chronic disease in conjunction with  
19 iron deficiency anemia; many patients are  
20 noncompliant -- you know, it's hard to take a  
21 tablet three times a day. Some patients have  
22 difficulty with absorption, so like I

1 mentioned before, maybe they're taking  
2 antacids or they're taking the enteric-coated  
3 tablets.

4 Many patients are continuing to  
5 bleed or having issues with blood loss, so  
6 the iron loss is still overtaking the amount  
7 ingested, and then some patients have iron  
8 malabsorption issues. They have celiac  
9 disease or H. Pylori.

10 So parenteral iron therapy, the  
11 indications that we use this is when patients  
12 can't tolerate the oral form, you try your  
13 best to do all the manipulations that I had  
14 mentioned in the previous slide; if not, then  
15 you can go to the IV iron.

16 If the patient is continuing to  
17 bleed while they're on oral iron replacement,  
18 it may be better to just start with IV iron.  
19 If patients have inflammatory bowel disease  
20 that's quite active, they won't absorb;  
21 dialysis patients -- and then patients with  
22 advanced malignancy who are anemic.

1           So the available preparations that  
2           are out there right now is iron dextran, also  
3           known as INFED or Dexferrum. This gives  
4           about 50 milligrams of elemental iron per  
5           milliliter, and it can be given either IM or  
6           IV. INFED is a low molecular weight  
7           preparation, whereas Dexferrum is a high  
8           molecular weight preparation. The side  
9           effects, usually seen in about 5 percent of  
10          patients are local reactions, it's probably  
11          low with the IM form, but there is pain,  
12          muscle necrosis, and phlebitis.

13                 And then systemic reactions,  
14          there's anaphylaxis seen in about 1 percent,  
15          fever, urticaria, and sometimes arthritic  
16          flares. The side effects are seen more  
17          commonly with the high molecular weight  
18          preparations.

19                 Another one is ferric  
20          gluconate -- that's Ferrlecit, and that has  
21          12.5 milligrams of elemental iron per  
22          milliliter. And then there's iron sucrose,

1 also known as Venofer, which has 20  
2 milligrams of iron per milliliter.

3 Both of these are used in an IV  
4 formulation. Ferric gluconate has a less  
5 allergic reaction profile versus iron  
6 dextran. In a study in American Journal of  
7 Kidney Disease, there was 3.3 versus 8.7  
8 allergic events per 1 million doses per  
9 year -- that's favoring the ferric gluconate.

10 Iron sucrose also has less side  
11 effects even if there is a prior history of  
12 reaction to the iron dextran. Intramuscular  
13 iron is usually slow in terms of mobilization  
14 and occasionally incomplete; therefore, we  
15 don't usually use it even though it's  
16 available in the iron dextran form.

17 The IV iron is most commonly used  
18 in the dialysis setting, and if ferric  
19 gluconate is used -- they used to do a test  
20 dose, but that's not actually recommended  
21 anymore by the FDA -- they used to do 2 ml of  
22 Ferrlecit, diluted it in 15 milliliters of

1 NS, and then infused over 60 minutes, and if  
2 no reaction was seen, then up to 10 ml were  
3 given in any setting, diluted in about 100  
4 milliliters of normal saline and given over  
5 60 minutes.

6           The calculation that we've used for  
7 IV iron dose is that you have to first  
8 calculate the iron deficit. So if you used  
9 sort of a formula that 1 gram of hemoglobin  
10 is equal to about 3.3 milligrams of elemental  
11 iron, and then you kind of plug it into a 60  
12 kilogram woman who has quite a low  
13 hemoglobin, you can figure out kind of how  
14 much their requirements are going to be, and  
15 then figure out how much they're going to  
16 need over time so that you don't give too  
17 much.

18           I didn't go through that whole  
19 calculation -- it gets a little complicated,  
20 but you can kind of figure out how much a  
21 patient has a deficit, and how much you can  
22 give in the future.

1           So in terms of oral iron therapy,  
2           again, you want to give a dose of 100 to 200  
3           milligrams of elemental iron per day for  
4           adults, much less for children -- 5  
5           milligrams of elemental iron per kilogram per  
6           day for children. Duration, about one to two  
7           months to correct the anemia, and then two to  
8           four additional months to replenish the  
9           stores. And then the side effects again were  
10          mostly GI issues.

11           And the preparations, again, iron  
12          sulfate, carbonyl iron -- I went through this  
13          already. Parenteral iron therapy, I also  
14          went through this, too, so if there's any  
15          questions -- kind of a brief overview, but I  
16          can answer anything now.

17           DR. HENNESSY: Are there any questions  
18          from members of the committee? Well, looks like  
19          you were perfectly clear, Dr. Batra.

20           Thank you very much.

21           DR. BATRA: Okay. Thank you.

22           DR. HENNESSY: I'd like to get the

1 sponsor's presentation started, and I would  
2 first call on Dr. Marc Tokars, who's a senior  
3 director for clinical operations.

4 DR. TOKARS: Good morning. I'm Marc  
5 Tokars, senior director of clinical operations  
6 for Luitpold Pharmaceuticals. Our company,  
7 Luitpold, is better known as American Regent,  
8 and we've been developing IV irons for about 12  
9 years, from 1996, when we developed iron  
10 dextran, our Dexferrum product.

11 Our new product, ferric  
12 carboxymaltose, is a new generation of  
13 intravenous iron. We studied ferric  
14 carboxymaltose in many populations with iron  
15 efficiency anemia, including the otherwise  
16 healthy postpartum and heavy uterine-bleeding  
17 populations, the multi-morbid populations  
18 such as hemodialysis patients, non-dialysis  
19 chronic kidney disease patients, as well as  
20 congestive heart failure and inflammatory  
21 bowel disease patients.

22 The nature of IV iron and the broad

1 range of issues that we will discuss today  
2 calls for multiple levels of expertise.  
3 Therefore, we have asked the following to  
4 present this morning: Dr. Patricia Ford,  
5 Dr. Antoinette Mangione, Dr. James Connor,  
6 Dr. David van Wyck, Dr. Leslie Cooper,  
7 Dr. Elizabeth Andrews, and Dr. Tim Goodnough.

8           The following experts are also  
9 available to answer your questions:

10 Dr. Vincent Dennis, Dr. Robert Foley,  
11 Dr. Louis Grasso (?), Dr. Jeffrey Issacson,  
12 Susan Mathias, and Dr. John Morrison.

13           IV iron products today are mostly  
14 used in patients with chronic kidney disease,  
15 where treatment guidelines are based upon  
16 extensive study of human physiology, iron  
17 metabolism, and clinical experience. The  
18 benefits are well-documented, as are the  
19 safety risks and limitations.

20           However, in the United States, the  
21 limitations of available IV irons have  
22 prevented their use in populations that need

1 iron replacement therapy other than chronic  
2 kidney disease. For example, women in their  
3 reproductive years have unique blood loss  
4 events due to child birth and heavy uterine  
5 bleeding.

6 Ferric carboxymaltose, which we'll  
7 refer to as FCM during this presentation, was  
8 designed to overcome these limitations. To  
9 date, FCM has been approved in 19 countries  
10 in Europe. Our proposed indications are for  
11 the treatment of iron-deficiency anemia in  
12 postpartum patients and patients with heavy  
13 uterine bleeding.

14 These patients by and large can be  
15 characterized as women with symptomatic  
16 anemia whose ongoing blood loss is greater  
17 than the rate of repletion available or  
18 achievable with oral iron, or for those that  
19 need rapid and reliable recovery in  
20 hemoglobin in preparation for surgery.

21 Today, we will briefly summarize  
22 the efficacy data from our postpartum and

1 heavy uterine bleeding patient trials,  
2 followed by a more extensive review of the  
3 safety data from our entire safety database.

4 We've asked multiple independent  
5 experts to comprehensively examine our  
6 database and provide a thorough analysis in  
7 their areas of specialty. And we convened an  
8 independent group of safety experts to review  
9 our database, focusing on cardiac events and  
10 mortality.

11 With these analyses in place, our  
12 presentation is designed to address the  
13 points FDA has asked this committee to  
14 examine. Dose. The 1,000 milligram maximum  
15 single dose is a key parameter in making  
16 treatment practical and reducing barriers to  
17 therapy in these women.

18 Hypophosphatemia, which seems  
19 common to all iron therapies in this  
20 population, and where a reduced lab value is  
21 not expected to have clinical consequences.

22 Cardiac events, which were seen in

1 both the FCM and control populations, but  
2 lacked an identifiable mechanism, and  
3 occurred at such a low rate that  
4 interpretation is impossible. And deaths,  
5 which were adjudicated and found to be  
6 unrelated to FCM.

7 Dr. Patricia Ford will now begin  
8 with medical need.

9 DR. FORD: Good morning. I'm Dr.  
10 Patricia Ford. I'm an adult  
11 hematologist/oncologist in Philadelphia at  
12 Pennsylvania Hospital. And my experience and  
13 interest with IV iron is based on two components  
14 in my private practice.

15 We have the largest obstetrical  
16 unit at Pennsylvania Hospital, so I see a lot  
17 of women that have anemia associated with  
18 pregnancy and in the postpartum state. And  
19 also, I have a large interest in treating  
20 Jehovah Witnesses who decline blood  
21 transfusion based on religious reasons. So  
22 therefore, I have an expertise in

1 alternatives, which include ESAs and IV iron.

2 IV iron use is well-established in  
3 chronic kidney disease. On the other hand,  
4 iron deficiency anemia in women of  
5 reproductive age is under-recognized and  
6 under-treated. Anemia is a very neglected  
7 area in women's health, especially among  
8 minorities and low-income women.

9 In the United States, 6 million  
10 women of reproductive age are iron-deficient,  
11 which in and of itself can cause symptoms.  
12 Approximately one half of these  
13 iron-deficient women will go on to develop  
14 iron deficiency anemia. The U.S.  
15 Preventative Services Task Force, the CDC,  
16 and the American College of Obstetrics and  
17 Gynecologists have all identified this as an  
18 important U.S. public health issue, and have  
19 developed screening programs for iron  
20 deficiency anemia.

21 The Healthy People 2010 initiative  
22 has identified anemia as one of their key

1 concerns in children and child-bearing women.  
2 Women don't often recognize the signs of iron  
3 deficiency anemia. This can include  
4 shortness of breath, palpitations, ice  
5 craving, cognitive dysfunction, headaches,  
6 dizziness, nervousness, lack of  
7 concentration, forgetfulness, fatigue, sexual  
8 dysfunction, and decreased job performance.

9           They frequently will not bring  
10 these symptoms to the attention of their  
11 physicians, who also may not routinely ask  
12 these questions. That's why no treatment or  
13 inadequate treatment is the norm for many of  
14 these women. At present, there is no safe or  
15 practical alternative to oral iron.

16           Postpartum anemia, defined as a  
17 hemoglobin under 10, has been reported in 5  
18 to 10 percent of women. Approximately  
19 4 percent of women will have iron deficiency  
20 anemia lasting up to 12 months after  
21 delivery. Anemia secondary to heavy uterine  
22 bleeding, defined as hemoglobin under 11, has

1     been reported in approximately 10 to  
2     15 percent of all women sometime during their  
3     lifetime. And among these women, as many as  
4     20 percent develop anemia.

5             Let's look at each of these  
6     populations a bit closer. Postpartum iron  
7     deficiency is a significant health and  
8     socioeconomic issue that disproportionately  
9     affects women under the 130th percentile  
10    poverty, which is the income threshold for  
11    many of our federal aid programs.

12            This data suggests that this  
13    population is four times as likely to have  
14    iron deficiency and iron deficiency anemia in  
15    the first six months postpartum than women  
16    above the federal aid threshold. The  
17    disparity of burden appears to continue at  
18    some level for 24 months after child birth,  
19    perhaps reinforcing for us how difficult it  
20    is to rectify iron deficiency with the  
21    limited tools available. Disproportionate  
22    impact is not limited only to socioeconomic

1 status.

2           This data looks at the prevalence  
3 of postpartum anemia, defined as hemoglobin  
4 under 12 by race. The non-Hispanic white  
5 population in this analysis of low-income  
6 U.S. women experience a 21 percent anemia  
7 rate. Hispanic women also suffered an  
8 increased rate over 30 percent. Non-Hispanic  
9 black women experienced anemia at a rate  
10 double that of the white population, over  
11 43 percent. And the impact of untreated or  
12 under-treated postpartum iron deficiency  
13 anemia is paramount to many issues for both  
14 the mother and the newborn.

15           Among hospitalized U.S. patients  
16 who had pregnancy-related bleeding in 2003,  
17 those with anemia had an 18 percent red blood  
18 cell transfusion rate. Depending on the  
19 severity of blood loss that occurs with  
20 delivery, anemic postpartum patients may  
21 present with increased morbidity that  
22 includes cardiovascular symptoms, dizziness,

1 fatigue, infections, and problems with  
2 lactation.

3           Untreated iron deficiency anemia  
4 can impair maternal cognitive function and  
5 behavior. And this could be very worrisome  
6 in terms of the ability to bond with the  
7 infant. These symptoms contribute to mothers  
8 being less responsive to the needs of their  
9 infants. Infants of mothers with iron  
10 deficiency anemia are developmentally delayed  
11 at 10 weeks. The developmental deficits in  
12 infants of iron-deficient mothers may be  
13 irreversible, or persist long after  
14 correction of maternal iron status.

15           These issues associated with  
16 postpartum anemia retard her capacity to  
17 resume her other usual activities, which  
18 includes returning to the workforce.  
19 Therefore, treatment to restore normal  
20 hemoglobin levels rapidly and reliably is  
21 important.

22           But many women have anemia from

1 blood loss problems not associated with child  
2 birth. These are women who have excessive  
3 menstrual bleeding from other medical  
4 conditions like uterine fibroids that can  
5 lead to surgery.

6           Among U.S. patients hospitalized  
7 due to heavy uterine bleeding in 2003, those  
8 with anemia had a 24 percent red blood cell  
9 transfusion rate. And the biggest predictor  
10 of transfusion risk is the preoperative  
11 hemoglobin.

12           Most surgeons will not accept  
13 patients for surgery until the patient's  
14 hemoglobin has been corrected to at least 9  
15 or 10 grams. So it seems that if women have  
16 symptoms or the inability to get their anemia  
17 resolved, they may choose to undergo more  
18 radical surgical procedures such as  
19 hysterectomy or myomectomy rather than more  
20 conservative options. So it comes as no  
21 surprise to see lower health-related quality  
22 of life data emerge for this patient

1 population.

2 Oral iron is the standard treatment  
3 for iron deficiency anemia. The problem that  
4 limits oral iron effectiveness begins with  
5 noncompliance.

6 Upwards of 40 percent of women will  
7 not complete their prescribed oral iron  
8 treatment because of the significant side  
9 effects. As had been mentioned, it's  
10 predominantly gastrointestinal, and can range  
11 from dyspepsia, nausea, vomiting, to severe  
12 and significant abdominal pain, cramping, and  
13 constipation, which can lead to hemorrhoids.  
14 In order to better tolerate these side  
15 effects, women often take their iron with  
16 food, which decreases the iron absorption by  
17 as much as 40 to 66 percent.

18 Another problem with oral iron is  
19 that there may not be the ability to keep up  
20 with the ongoing blood loss, especially in  
21 those women with heavy uterine bleeding who  
22 may bleed every 14 to 20 days. Before they

1 can complete their therapy with oral iron or  
2 the available IV irons, they are bleeding  
3 again with a subsequent decline in  
4 hemoglobin. It is difficult to keep up with  
5 and replenish their iron stores.

6           Clearly, for this patient  
7 population, a form of directly observed  
8 therapy would be superior to the problems  
9 associated with oral iron, patient education,  
10 and compliance. My nurse spends 20 minutes  
11 with each patient prescribed oral iron, and  
12 it still does not result in satisfactory  
13 compliance.

14           Our current parental therapies are  
15 limited by safety concerns, difficulty in  
16 administration, and labeling restrictions.  
17 At present, only iron dextran has a labeled  
18 indication for the treatment of iron  
19 deficiency anemia outside of the renal  
20 population.

21           It comes with a hypersensitivity  
22 and anaphylactic Black Box Warning, requiring

1 a test dose prior to use. The label also  
2 requires repeated small doses. But many  
3 clinicians choose to give this as a total  
4 dose infusion, which increases the chance of  
5 experiencing adverse events.

6 Our non-dextran IV agents are not  
7 approved for non-renal iron deficiency anemia  
8 but are used off-label. They do not have a  
9 Black Box Warning but have significant side  
10 effects. Examples include hypotension,  
11 especially when the infusion rates are  
12 increased, as well as dizziness, nausea,  
13 arthralgias, and headaches.

14 Beyond these adverse risk events,  
15 there is another significant barrier to  
16 treatment for these women. It lies in the  
17 number of infusions that need to be  
18 administered. For iron dextran, the  
19 approximate number of doses to replenish iron  
20 stores can range from 10 to 20; iron sucrose,  
21 three to five; and ferric gluconate, anywhere  
22 from eight to sixteen.

1           As you can well imagine, this is  
2 quite difficult. If I told any one of us  
3 that you need to now come to my office weekly  
4 for anywhere from three to 20 visits, you  
5 would immediately be confronted with problems  
6 like taking time off from work and/or  
7 arranging and paying for child care. This is  
8 a major barrier to prescribing effective  
9 IV iron therapy.

10           We need a new option both for  
11 patients and for providers. We need a safe  
12 or a safer therapy option. We need an agent  
13 with better and more rapid efficacy than oral  
14 iron. We need directly observed therapy that  
15 assures improved adherence. We need an  
16 IV iron regimen that is easy to  
17 administer -- preferably in one dose. A  
18 decreased number of infusions will impact not  
19 just patient compliance but nursing time and  
20 health care cost.

21           It is my hope as a clinician that  
22 we both increase public awareness of iron

1 deficiency anemia, and that we also meet this  
2 need with a practical labeled option.

3 Thank you.

4 DR. MANGIONE: Good morning. I'm  
5 Dr. Antoinette Mangione, a medical director for  
6 Luitpold Pharmaceuticals. It's been 100 years  
7 since intravenous iron was first administered to  
8 humans. The IV iron breakthrough occurred 55  
9 years ago, when a carbohydrate was first bound  
10 to iron oxide.

11 Current IV iron agents are spheroid  
12 particles with an iron oxyhydroxide core in a  
13 stable ferric state in a carbohydrate shell.  
14 They differ chemically by the type of  
15 carbohydrate and the stability of the iron  
16 carbohydrate complex. These chemical  
17 differences translate into dramatically  
18 different clinical utility and risk.

19 The first generation of these  
20 products was built using dextran as the  
21 carbohydrate. Iron dextran, the first  
22 generation IV iron, is severely limited by

1 the risk of fatal anaphylaxis. Anaphylaxis  
2 risk with iron dextran is labeled in a Black  
3 Box Warning.

4 Furthermore, iron dextran has dose  
5 restrictions of 100 milligrams that commonly  
6 encourages off-label use of total dose  
7 infusions. However, when utilized in  
8 off-label doses of 1 to 2 grams, iron dextran  
9 is associated with a high incidence of  
10 delayed hypersensitivity reactions.

11 Second generation IV irons were  
12 developed to mitigate these risks. The  
13 second generation IV irons reduce  
14 hypersensitivity risk by substituting a  
15 non-dextran carbohydrate. But these second  
16 generation complexes have less stable iron  
17 carbohydrate bonds, which increases the  
18 incidence of dose- and infusion-related  
19 bioactive iron reactions.

20 We tried with our lead product,  
21 iron sucrose, to administer higher doses.  
22 But they lead to severe sudden symptomatic

1 hypotension. Similar results are reported  
2 with ferric gluconate. The significant  
3 single dose limitation of these products  
4 render them impractical for most outpatient  
5 and acute therapy outside of hemodialysis  
6 where the patients are seen two to three  
7 times a week.

8 FCM was developed to overcome the  
9 limitations of current therapy. The  
10 carbohydrate in FCM is not a dextran. Yet it  
11 is a stable iron carbohydrate complex like  
12 iron dextran that produces slow release from  
13 the complex, and slow delivery of the iron to  
14 endogenous iron binding sites. Consequently,  
15 FCM allows for administration of large doses  
16 over a short time period, with minimal risk  
17 of bioactive iron reactions, without the  
18 dextran risk of life-threatening  
19 hypersensitivity reactions.

20 Selection of the FCM maximum dose  
21 of 15 milligrams per kilogram up to 1,000  
22 milligrams is supported by the chemistry of

1 the product just mentioned. And it's also  
2 supported by the preclinical program, where  
3 FCM's maximum acute lethal dose was five  
4 times greater than that of iron sucrose.

5 In vitro studies of FCM showed no  
6 dialyzable free iron and no participation in  
7 direct donation to transferrin, which may  
8 correlate with bioactive iron risk.  
9 Pharmacokinetic studies following 1,000  
10 milligrams demonstrated that the majority of  
11 the iron in the drug complex was out of the  
12 serum in 72 hours, with no accumulation with  
13 weekly dosing.

14 It's important to note that the  
15 percent transferrin saturation and unbound  
16 iron binding capacity are both calculations  
17 of serum iron, and are not valid while the  
18 IV iron complex is in the serum.  
19 Consequently, early TSAT, transferrin  
20 saturation measurements, are not useful for  
21 dose selection. Transferrin saturation was  
22 normal by day 7. In the heavy uterine

1 bleeding trials, lower TSAT values were seen  
2 after FCM dosing than after oral iron.

3 The selection of the maximum dose  
4 is also confirmed by the lack of any  
5 dose-related safety findings in the FCM  
6 clinical development program. The FCM  
7 development program is the largest  
8 prospectively enrolled IV iron program  
9 reviewed by the agency.

10 Our program consists of 12  
11 multi-center clinical trials involving over  
12 3,000 patients with over 2,000 FCM-treated  
13 patients, including 700 postpartum, 352 heavy  
14 uterine bleeding, 528 chronic kidney disease,  
15 and 201 inflammatory bowel disease patients.

16 Over 5,200 individual doses of FCM  
17 had been prospectively studied. Over 1,700  
18 patients had received the maximum single dose  
19 of 15 milligrams per kilogram up to 1,000  
20 milligrams. We have studied over 1,700 women  
21 in the indications we're seeking today.

22 In our slides, you will postpartum

1 and heavy uterine bleeding abbreviated as PP  
2 and HUB respectively. We enrolled postpartum  
3 women for studies. Three of them are  
4 randomized trails comparing FCM to oral iron.  
5 One study, VIT-09, was conducted by our  
6 development partner in Europe.

7 Today, we are presenting the  
8 efficacy results from the studies Luitpold  
9 conducted. These are highlighted in yellow  
10 on this slide. Postpartum patients were also  
11 enrolled in the VIT-06 study: a large,  
12 short-term, placebo-controlled, randomized,  
13 blinded crossover safety study focusing on  
14 acute events. We have two studies that  
15 enrolled heavy uterine bleeding patients, one  
16 randomized trial comparing oral iron to FCM,  
17 and the same crossover safety trial just  
18 mentioned.

19 In addition, we have studied  
20 approximately 1,400 patients in other  
21 indications, many of which represent very ill  
22 and multi-morbid populations. Fifty percent

1 of these 1,400 patients are  
2 non-dialysis-dependent or  
3 hemodialysis-dependent chronic kidney disease  
4 patients. A long-term repeat cycle 44-week  
5 safety study was also conducted in the  
6 non-dialysis chronic kidney disease  
7 population. This is the first of its kind in  
8 IV iron development.

9 Our women's health clinical program  
10 conducted two postpartum and one heavy  
11 uterine bleeding -- randomized, open-labeled,  
12 multi-center studies. The patients were  
13 anemic, defined as a hemoglobin less than  
14 equal to 10 in postpartum, and less than or  
15 equal to 11 in heavy uterine bleeding, and  
16 iron deficient, generally defined as a  
17 transferrin saturation of less than equal to  
18 25 percent and a ferritin less than equal to  
19 100, with no other known etiology for their  
20 anemia other than iron deficiency.

21 The patients were randomized to  
22 either oral iron at full therapeutic doses of

1 195 milligrams of elemental iron a day that  
2 was given on an empty stomach for six weeks,  
3 or FCM, where the total iron replacement dose  
4 was calculated using a modification of the  
5 Ganzoni formula that's been used for iron  
6 dextrans for over 50 years.

7           The calculation is based on the  
8 patient's weight, hemoglobin, and iron  
9 indices. FCM is given as 15 milligrams per  
10 kilogram up to a maximum of 1,000 milligrams  
11 of iron as FCM over 15 minutes on day 0, with  
12 repeat doses weekly, up to a maximum total  
13 calculated dose of 2,500 milligrams.

14           Demographics and baseline  
15 characteristics were comparable in both  
16 treatment arms and all three trials. Of note  
17 is that the populations are markedly iron  
18 deficient. HUB patients had mean ferritins  
19 of 6 and transferrin saturations of  
20 5 percent, despite the fact that greater than  
21 70 percent reported oral iron use.

22           All the results we will present

1 today are for the modified intend to treat  
2 population as specified in our protocols.  
3 Similar results are achieved in the intend to  
4 treat and the evaluable populations. A  
5 significantly greater percentage of  
6 FCM-treated patients than oral iron patients  
7 and the postpartum and HUB studies reached a  
8 hemoglobin greater than 12, the lower limit  
9 of normal range.

10 This plot provides a summary of the  
11 between arm differences illustrated with  
12 their means and their 95 percent confidence  
13 intervals for the percent of patients  
14 achieving a hemoglobin greater than 12. For  
15 example, as seen in the top line in the  
16 postpartum VIT-11 study, 25 percent more  
17 FCM-treated patients achieved a hemoglobin  
18 greater than 12 with a 95 percent confidence  
19 interval of 15 to 34 percent.

20 Please note the consistency of the  
21 95 percent confidence intervals across the  
22 studies.

1 Superiority of FCM over oral iron  
2 was also observed using the criterion of an  
3 increase in hemoglobin from baseline of  
4 greater than equal to 3 grams per deciliter,  
5 or greater than equal to 2 grams per  
6 deciliter, as summarized here.

7 The next figures put the results  
8 into a time context and a central measure due  
9 to acute patient need for early and reliable  
10 hemoglobin correction. This figure  
11 illustrates in postpartum patients the  
12 proportion achieving the primary endpoint, a  
13 hemoglobin greater than 12 according to  
14 treatment assignment at different time  
15 points.

16 FCM produced a hemoglobin greater  
17 than 12 earlier than oral iron. Significant  
18 differences were reached by day 14 versus  
19 oral iron, and continued at each visit. A  
20 similar pattern was seen for achieving the  
21 endpoint of a greater than equal to 3 gram  
22 increase.

1                   When evaluating the FCM efficacy  
2 data, it's important to note two things; one,  
3 that oral iron adherence in these studies was  
4 impressive, with adherence to six weeks of  
5 three times a day oral iron at full  
6 therapeutic doses reaching over 96 percent in  
7 the VIT-11 postpartum study, and 90 percent  
8 in the heavy uterine bleeding study, a level  
9 that's dramatically different than what is  
10 commonly observed and reported in clinical  
11 practice.

12                   Secondly, by day 7, FCM treatment  
13 was completed in 92 percent of the postpartum  
14 and HUB patients, while the women in oral  
15 iron arm study required three times a day  
16 treatment for five more weeks.

17                   We saw an even earlier benefit in  
18 the HUB study. This figure illustrates a  
19 similar rapid response to FCM in HUB  
20 patients, with significant and earlier  
21 differences by day 7. FCM also demonstrated  
22 that it was more effective than oral iron in

1     correcting iron depletion by replenishing  
2     iron stores.

3             Persistence of efficacy of IDA  
4     depends upon replenished iron stores. In all  
5     studies, one course of FCM replenished iron  
6     stores, as defined by ferritin level, while  
7     six weeks of oral iron at full therapeutic  
8     doses did not. Looking at the iron stores in  
9     the HUB population at week 6, we see a change  
10    from baseline of 175 nanograms per ml for  
11    ferritin following FCM versus 17 nanograms  
12    per ml following oral iron. Larger iron  
13    stores at week 6 predicts for persistence of  
14    effect. The storage effect was even greater  
15    in postpartum women.

16            Turning to safety, the main reason  
17    we're here today -- we found that the FCM  
18    safety profile is comparable to that of oral  
19    iron. We conducted five controlled studies  
20    in postpartum and heavy uterine bleeding that  
21    provide solid comparative data. We will also  
22    present safety across all indications in the

1 entire program whether or not it is  
2 controlled, to aid in understanding of FCM's  
3 safety and tolerability.

4           Accordingly, the safety database  
5 goes beyond the otherwise healthy postpartum  
6 and heavy uterine bleeding populations and  
7 includes high-risk hemodialysis patients,  
8 non-dialysis-dependent chronic kidney disease  
9 patients, as well as congestive heart failure  
10 and inflammatory bowel disease patients.

11           We will also review potential  
12 predictors of adverse events prior to our  
13 consideration of safety topics of interest.

14           Let's begin with the target data,  
15 target population, the 1,720 treated  
16 postpartum and heavy uterine bleeding  
17 patients. You have the more detailed safety  
18 tables in the briefing document.

19           This table summarizes all related  
20 and unrelated adverse events where there was  
21 a greater than 2 percent difference in AE  
22 rates in the SOC or preferred terms. The

1 first two columns summarize direct  
2 comparisons of FCM to oral iron from the four  
3 oral iron control trials, where the overall  
4 incidence of adverse events were comparable.

5 Notable differences were for the  
6 high incidence of GI events with oral iron,  
7 most notably constipation and nausea, and for  
8 administration site reactions, phosphate  
9 decreases, and skin disorders with FCM. The  
10 last two columns provide direct comparisons  
11 of FCM to placebo obtained in a crossover  
12 blinded safety trial. The only other notable  
13 difference was the higher incidence of  
14 headache with FCM.

15 Adverse events resulting in  
16 discontinuation of study drug included  
17 primarily GI events for oral iron, and skin  
18 reactions for FCM. The overall incidence of  
19 discontinuations was comparable between the  
20 two arms. This table summarizes serious  
21 adverse events occurring in greater than one  
22 patient. All serious adverse events were

1 considered unrelated to study drug, with a  
2 comparable overall SAE rate between the two  
3 arms of 1.7 versus 1.6 percent.

4           SAEs occurring in greater than one  
5 patient included two cases of uterine  
6 hemorrhage in the FCM group, and two cases of  
7 endometritis and pelvic abscess in the oral  
8 iron group. There was one death that  
9 occurred in the women's health program due to  
10 peripartum cardiomyopathy, and was judged to  
11 be unrelated to FCM. This case will be  
12 discussed later.

13           We also saw quite clearly in our  
14 trials that FCM as well as oral iron had a  
15 common effect on lowering phosphate,  
16 especially in the non-renal population.  
17 Decrease in serum phosphate after FCM  
18 administration was frequent, with 8 percent  
19 of postpartum and 70 percent of heavy uterine  
20 bleeding patients reaching a nadir phosphate  
21 of less than 2 milligrams per deciliter. The  
22 effect was transient, with a slow onset, with

1 nadirs in heavy uterine bleeding patients  
2 occurring at a median of 15 days and  
3 recovering at a median of 18 days later.

4           The decreases in phosphate were not  
5 associated with any adverse events. There  
6 were no adverse events due to symptoms of low  
7 phosphate, and no patient discontinued  
8 therapy secondary to low phosphate. We found  
9 that the magnitude of phosphate decreased  
10 after FCM treatment was directly related to  
11 baseline phosphate for both the IV and oral  
12 iron populations. This scatter plot  
13 illustrates this finding in the HUB patients.

14           The largest decrease in phosphate  
15 was seen in the patients with the highest  
16 baseline phosphate for both FCM and oral  
17 iron. The magnitude of the decrease was  
18 greater following FCM, and no patient fell  
19 below .9 milligrams per deciliter. Phosphate  
20 experts, represented today by Dr. Vincent  
21 Dennis, reviewed the clinical data, and  
22 concluded that multiple processes may be

1 responsible, and that the finding of  
2 hypophosphatemia is interesting but not  
3 clinically meaningful.

4           The experts know that phosphate is  
5 a nutrient. And although ionic, phosphate is  
6 not an ion involved in action potentials.  
7 Also, transient hypophosphatemia is not  
8 equivalent to phosphate depletion.

9           The experts recommend that patients  
10 with clinical evidence of malnutrition,  
11 alcoholism, or other risks for  
12 hypophosphatemia have serum phosphate  
13 concentrations measured on the day of FCM  
14 infusion, and if low, receive instructions to  
15 take milk or phosphate supplements for one to  
16 two weeks.

17           The next slides summarize data from  
18 the integrated oral iron trials, integrating  
19 inflammatory bowel disease and recently  
20 completed high-risk non-dialysis chronic  
21 kidney disease population with the low-risk  
22 postpartum and HUB patients.

1                   The pattern for all related and  
2                   unrelated adverse events is similar to that  
3                   seen in postpartum and the HUB populations.  
4                   The overall cardiac event rate is not listed  
5                   in this table, as the rates were comparable:  
6                   1.3 percent for FCM versus 1.1 percent  
7                   following oral iron. Adverse events  
8                   resulting in discontinuation was higher for  
9                   oral iron than FCM. The reasons for  
10                  discontinuation parallel those seen in the  
11                  postpartum and HUB populations.

12                  This table summarizes serious  
13                  adverse events occurring in greater than one  
14                  patient. All SAEs were considered unrelated  
15                  to study drug, with an overall SAE rate  
16                  between the two arms of 3.2 versus  
17                  2.5 percent. SAEs occurring in greater than  
18                  one patient included two cases of congestive  
19                  heart failure in both treatment arms; two  
20                  cases of coronary artery disease, sepsis, and  
21                  uterine hemorrhage in the FCM arm; and two  
22                  cases of GI hemorrhage, pelvic abscess, and

1 chronic renal failure in the oral iron arm.  
2 We will discuss the cardiac events later in  
3 this presentation.

4           It's both difficult and essential  
5 to keep the comparison groups clear and  
6 appropriate for our safety examinations. As  
7 an example, FDA clarified that there is no  
8 imbalance in the overall SAE rate in the  
9 largest data set, the all active control  
10 trials. When looking at the control data in  
11 its entirety, the overall SAE rate was  
12 identical -- 3.6 percent for FCM versus  
13 3.6 percent for the control group.

14           We also found that the overall  
15 safety profile of FCM was not negatively  
16 affected by higher FCM doses and higher  
17 post-baseline ferritin and hemoglobin levels.  
18 This figure summarizes adverse events and  
19 serious adverse events by the size of the  
20 maximum single dose for the oral iron control  
21 trials. There was no relationship to the  
22 overall incidence of adverse events and dose

1 and no pattern seen.

2 This figure summarizes adverse  
3 events and serious adverse events by the size  
4 of the total FCM dose for this data set. And  
5 again, there was no dose relationship.

6 FDA raised the issue that transient  
7 ferritin increase, an indirect measure of  
8 stored iron observed post-FCM treatment, may  
9 have contributed to adverse events. We  
10 investigated this and found no relationship  
11 between the maximum ferritin achieved and the  
12 incidence of adverse events and serious  
13 adverse events.

14 We found that the overall rate of  
15 SAEs was higher for the group achieving a  
16 suboptimal maximum hemoglobin, defined as  
17 less than equal to 12, for both the FCM and  
18 the oral iron treatment arms. This  
19 presumably reflects the increased disease  
20 burden that suboptimal hemoglobin correction  
21 reflects for these patients.

22 Next, we'll turn our attention to

1 selected safety topics of interest. I will  
2 discuss cardiac safety; Dr. Connor, oxidative  
3 stress; Dr. Cooper, cardiac serious adverse  
4 event cases; and Dr. Van Wyck, non-cardiac  
5 safety and mortality; and Dr. Andrews,  
6 mortality epidemiology.

7           This slide summarizes the cardiac  
8 serious adverse event rate for the different  
9 data sets. In the target postpartum and HUB  
10 population, there were two cardiac SAEs in  
11 the FCM-treated arm versus one in the oral  
12 iron group, and none in the  
13 placebo-controlled safety studies.

14           In the oral iron control trials,  
15 the rate is .9 percent for FCM versus  
16 .4 percent for oral iron. In the active  
17 control data set, the cardiac SAE rate is  
18 1.1 percent for FCM versus .8 percent for  
19 controls. We found that the cardiac safety  
20 profile of FCM was not negatively affected by  
21 higher FCM doses and higher post-dosing  
22 ferritin and hemoglobin levels and

1 hypophosphatemia. These findings support  
2 that the cardiac AE and SAE rates is not  
3 FCM-related.

4 We found no dose relationship  
5 between FCM and cardiac AEs for all the oral  
6 iron and multi-center trials. The highest AE  
7 rate were reported in the lowest single dose  
8 category of less than or equal to 799  
9 milligrams, represented in the slide on the  
10 left.

11 There was also a trend towards an  
12 actual higher adverse event rate in the  
13 lowest total dose category, of 0 to 1,000  
14 milligrams. There was no relationship seen  
15 between maximum achieved ferritin and cardiac  
16 adverse event rate. The cardiac adverse  
17 event rate was highest in those patients that  
18 achieved the lowest hemoglobin category.

19 This figure summarizes the cardiac  
20 adverse event rate, which includes serious  
21 adverse events by the lowest phosphate  
22 achieved post-dosing. As seen on the far

1 left, all the cardiac adverse events occurred  
2 in the patient group who did not become  
3 hypophosphatemic. The confirmed serious  
4 cardiovascular ischemic event rates in the  
5 oral iron control trials was low, with a  
6 comparable rate between the FCM and oral iron  
7 groups of .3 percent versus .4 percent.

8           Due to the observed mortality  
9 imbalance, we asked external independent  
10 clinical pharmacology and epidemiology safety  
11 experts last year to conduct an evaluation of  
12 our entire raw database completed as of  
13 January 2007, and to particularly focus on  
14 cardiovascular events. They prospectively  
15 defined cardiovascular events, and concluded  
16 that there were no safety difference in  
17 cardiovascular events in the studies  
18 analyzed.

19           The FDA raised the concern that  
20 high serum ferritin concentration has been  
21 hypothesized in some publications to be  
22 related to oxidative stress and

1 cardiovascular disease. While most iron  
2 experts do not believe this to be true, we  
3 went back to the lab to investigate evidence  
4 of oxidative stress with FCM.

5 Dr. Connor, an iron biologist, will  
6 summarize the data from these recently  
7 completed studies.

8 DR. CONNOR: Thank you. Good morning,  
9 I'm Dr. James Connor, from Penn State  
10 University, where I hold the titles of  
11 university distinguished professor and vice  
12 chairman of neurosurgery.

13 I've edited two academic books on  
14 metals and oxidative damage, and I'm here  
15 today to share with you and take this  
16 opportunity to highlight the findings of our  
17 pre-clinical studies which were performed to  
18 address the possibility that intravenous iron  
19 compounds could be associated with oxidative  
20 stress.

21 In the first slide, you see the two  
22 models that we have used to interrogate the

1 questions before us. One was an in vivo  
2 model using rats that received 40 milligrams  
3 per kilogram of intravenous FCM injections  
4 weekly for four weeks, and a cell culture  
5 model in which we used two cells, a human  
6 kidney cell line and rat renal cortical  
7 homogenates.

8           The first set of data I would like  
9 to show you is the concentration of TBARs.  
10 TBAR stands for thiobarbituric acid-reactive  
11 species. The studies come from the liver,  
12 heart, and kidney following IV iron  
13 injections for the four weeks.

14           You can see that the amount of  
15 lipid oxidative stress which are measured as  
16 TBARs is no different following FCM treatment  
17 than saline exposure. You can also see that  
18 the iron gluconate induces a significant  
19 increase in TBARs, and this is used and shown  
20 here as a positive control for the study.

21           Consistent with the evidence that  
22 there is no lipid damage following IV iron,

1 we show on the next slide that glutathione  
2 peroxidase, an enzyme that catalyzes the  
3 reaction between glutathione and hydrogen  
4 peroxide to remove potentially harmful  
5 peroxide, is unaffected by FCM.

6           So these data are showing you that  
7 a major antioxidant pathway is again  
8 unaffected by the FCM exposure. The previous  
9 two slides were examples of the data that we  
10 have which point to the absence of oxidative  
11 stress in an in vivo model, but we wanted to  
12 push the system little more and determine  
13 what would happen if we placed the iron  
14 compounds directly on the cells and let the  
15 cells expose directly to these iron compounds  
16 for 48 hours. This model allows us to  
17 examine the potential mechanisms of action of  
18 iron compounds and their cellular response.  
19 We examine both the human cell line and renal  
20 cortical homogenate preparation.

21           In the next slide, you can see that  
22 there's no change in LDH release, a marker of

1 cell membrane integrity, with increasing  
2 concentrations of FCM, whereas iron dextran  
3 is associated with significant loss of  
4 membrane integrity, and this loss of membrane  
5 integrity is usually indicative of cell  
6 death.

7           The clinically relevant  
8 concentration in this study is between .2 and  
9 .4 mg/ml concentrations, representing the  
10 maximum clinical dose of 1000 milligrams. We  
11 can conclude from these data that directly  
12 exposing cells to maximum clinical dose of  
13 FCM does not compromise the cell.

14           In the next slide, a similar study  
15 was performed, this time using the renal  
16 cortical homogenates, and once again the  
17 outcome is the same. There's no release of  
18 LDH in the presence of FCM, indicating that  
19 direct exposure of the iron compounds to the  
20 cells does not cause cell damage.

21           So in conclusion, there's no  
22 evidence of oxidative stress in liver, heart,

1 or kidney following four weeks of iron  
2 compound exposure, and I point out that we  
3 also have histological data that the  
4 stainable iron that we've seen following  
5 these injections is found in macrophages that  
6 were looked at in the heart and not in the  
7 cardiomyocytes, which is again indicative  
8 that the organs and the cells were handling  
9 the iron effectively. There's no evidence of  
10 cell damage in our cell culture studies as  
11 well. And this includes using the clinically  
12 relevant maximal dose.

13 So the data suggests that the  
14 elevated ferritin in serum in the human  
15 studies is associated with change in body  
16 iron stores and not an inflammatory response  
17 to liver damage.

18 Thank you.

19 DR. COOPER: Good morning. I'm Leslie  
20 Cooper from the Mayo Clinic. I have an interest  
21 in myocarditis and cardiomyopathy. I was asked  
22 to speak today about the cardiac serious adverse

1 events and mortality cases.

2           The first slide illustrates three  
3 cases of cardiovascular death that were  
4 observed in the FCM treated groups. The  
5 first is a woman with postpartum anemia who  
6 died of peripartum cardiomyopathy. The  
7 second is a man with inflammatory bowel  
8 disease and anemia on that basis. He died of  
9 a cardiac arrest. The third case is that of  
10 a man on hemodialysis who had an acute  
11 myocardial infarction following treatment.  
12 Fourth case, a patient with heart failure,  
13 enrolled in a separate clinical trial, died  
14 of heart failure.

15           This slide illustrates the timeline  
16 of the first case. She was a 27-year-old  
17 African-American woman, who six days prior to  
18 therapy had an uncomplicated vaginal  
19 delivery. Her hemoglobin was 7.9 on the day  
20 of treatment, when she received 1000  
21 milligrams of FCM.

22           We have no data for the subsequent

1 week, but she was found unresponsive on  
2 day 8, and an autopsy revealed a non-ischemic  
3 dilated cardiomyopathy. The diagnosis of  
4 peripartum cardiomyopathy was made.

5           The first question is did she  
6 indeed have peripartum cardiomyopathy? The  
7 data supporting this conclusion are that she  
8 had three risk factors: her ethnicity, her  
9 high parity, and her weight. And two of  
10 these risk factors, ethnicity and high  
11 parity, are associated with the fatal  
12 outcome. At autopsy, a number of important  
13 disorders were excluded. She had neither  
14 coronary artery disease nor coronary  
15 thrombosis. There was no pulmonary embolism.  
16 She had no congenital and no valvular heart  
17 disease. The walls of her heart were of  
18 normal thickness, although her heart, the  
19 left ventricle and right ventricle were  
20 dilated.

21           Importantly, there was no  
22 histological evidence of a hypersensitivity

1 reaction either in the heart or in other  
2 organs. And finally, there was no evidence  
3 of a toxic myocarditis, such as could be seen  
4 if this was an idiosyncratic or dose-related  
5 toxic effect of the drug.

6 To conclude, the diagnosis is  
7 consistent with peripartum cardiomyopathy.

8 The second question, could FCM have  
9 caused PPCM in this case. The mechanism of  
10 PPCM is not known, and so we can't link  
11 mechanistically FCM to PPCM. However, the  
12 characteristic findings of iron overload in  
13 the chronic setting, namely thickened walls  
14 that would suggest a restrictive  
15 cardiomyopathy, were not present.

16 Chronically, iron overload  
17 cardiomyopathy can evolve into a dilated  
18 cardiomyopathy, but that takes time, and this  
19 was an acute presentation. This was too  
20 early for hypophosphatemia, as we have  
21 already heard, and importantly, in the  
22 pre-clinical toxicity studies in the dog and

1 the rat, there was no evidence of a cardiac  
2 toxicity signal, there was specifically no  
3 uptake of iron within the cardiomyocytes,  
4 either in this case or in the animal models.

5 The second case is that of the man  
6 who was 56 years old and had ulcerative  
7 colitis. He had documented aortic stenosis  
8 of unknown severity, mitral regurgitation and  
9 recent angina. Twelve days prior to therapy,  
10 his hemoglobin was 5.5. On the day he was  
11 treated, day 0, his hemoglobin had dropped to  
12 4.8. He did not receive a transfusion. He  
13 was treated with FCM of 1000 milligrams, and  
14 the subsequent day had a witnessed cardiac  
15 arrest, likely due to severe ischemia in the  
16 setting of aortic stenosis.

17 The third case is that of a  
18 58-year-old man who was on hemodialysis. He  
19 had diabetes and hypertension. Seven days  
20 prior to therapy, his hemoglobin was 11. On  
21 the day of treatment, his hemoglobin had  
22 dropped to 9.3. He received only 200

1 milligrams of FCM, and that day, it was noted  
2 that he had significant blood loss in his  
3 hemodialysis tubing. Five days later, he had  
4 a hemoglobin of 7.8 when he presented with an  
5 acute ST-segment elevation anterolateral  
6 myocardial infarction. At that time, or I  
7 should say over the next four days, he  
8 developed heart failure and died four days  
9 following hospital presentation. He did not  
10 have an echocardiogram or an attempted  
11 coronary revascularization during that  
12 hospitalization.

13           Now, this slide illustrates the  
14 cardiac serious adverse events in the  
15 postpartum and heavy uterine bleeding  
16 studies. The first, that of heart failure,  
17 was already covered in my discussion of the  
18 postpartum case.

19           The second case of congestive heart  
20 failure occurred in the control group. And  
21 the third case we will now discuss was that  
22 of a woman with mitral valve prolapse. She

1 was 38 years old, had a normal delivery, and  
2 it was noted at the time of her enrollment  
3 that she had preeclampsia, which was  
4 associated with hypertension, dyspnea, and  
5 upper and lower extremity pitting edema. On  
6 the day of treatment, she received only 400  
7 milligrams of a scheduled 1000 milligram dose  
8 because she lost IV access, and the degree of  
9 edema was too great to get new IV access.

10 Three days following therapy, she  
11 was admitted to a hospital with peripheral  
12 edema and worsening dyspnea. She was  
13 transfused, given diuretics, and dismissed.  
14 An echocardiogram, which led to this  
15 categorization of SAE, showed 3+ mitral  
16 insufficiency on a scale of 0 to 4, and as  
17 far as we know, the SAE result without  
18 consequence.

19 This slide shows the other SAEs in  
20 the non PP/HUB cohort. The first one, the  
21 man who died with inflammatory bowel disease,  
22 we've already discussed. I only have two

1 comments on this slide; one, the case of  
2 palpitations had no EKG documentation, and  
3 resolved in one day without treatment.

4 The final one, the tachycardia  
5 case, was in a man with inflammatory bowel  
6 disease whose hemoglobin was 6.6 at that  
7 time. His heart rate was 126. His heart  
8 rate documented at the time of study entry  
9 before therapy was 120.

10 The final two slides that I'm going  
11 to show are actually not from this data set  
12 but are from two recent publications relevant  
13 to IV iron and heart failure. The first was  
14 published six weeks ago in the Journal of the  
15 American College of Cardiology, and in this  
16 population, the study of 40 patients with  
17 heart failure and chronic kidney disease  
18 associated with anemia, IV iron was given in  
19 a randomized placebo-controlled fashion.

20 The leftmost pair of lines  
21 demonstrates what you would expect, an  
22 improvement in hemoglobin. The next over

1 shows an increase in injection fraction,  
2 which was significant associated with the  
3 treatment. There was a decrease in proBNP  
4 which is a biomarker of wall stress and a  
5 decrease in C-reactive protein, which is an  
6 inflammatory marker. These are non-specific,  
7 but suggest a salutary effect of IV iron in  
8 the small population. Adverse events for  
9 balance between the groups.

10           The final slide is that of a second  
11 paper published two weeks ago, also in the  
12 Journal of the American College of  
13 Cardiology. This, an even smaller study of  
14 34 patients, showed a significant improvement  
15 in New York Heart Association functional  
16 class and in peak oxygen consumption  
17 following intravenous iron in patients with  
18 heart failure and iron deficiency.

19           To summarize my presentation, I  
20 believe that there were alternate and  
21 plausible explanations for the few cardiac  
22 serious adverse events that I've presented.

1 Some of these, such as the man with  
2 tachycardia, may have been related to  
3 pre-existing or other conditions.

4 There was a different mechanism of  
5 action -- more than one mechanism of action  
6 for the death cases, and indeed from other  
7 data, there may even be a benefit of IV iron  
8 in anemic patients with heart failure.

9 Thank you.

10 DR. VAN WYCK: Good morning. I'm  
11 David Van Wyck from the University of Arizona.  
12 I'm a nephrologist. My interest is in anemia  
13 and iron disorders in patients with kidney  
14 disease.

15 To frame the discussion of adverse  
16 events and mortality, the non-cardiac adverse  
17 events and mortality in patients in the  
18 controlled and uncontrolled trials, consider  
19 the time course of the changes in iron  
20 disposition and the hemoglobin in the  
21 patients who received FCM.

22 As you can see from this slide, the

1 ferritin rises abruptly after administration  
2 of the first, and then second dose on day 0  
3 and day 7, 92 percent of the patients in the  
4 heavy uterine bleeding trial received only  
5 two doses. The ferritin rose, and then as  
6 the hemoglobin began to rise, there was a  
7 reciprocal decrease in the ferritin following  
8 the mean into -- to the normal range by  
9 day 28, and well into the normal  
10 range -- lower by day 42. The entire mean  
11 delta hemoglobin was greater than 3 grams per  
12 deciliter over that period of time.

13 So what we're seeing is the uptake  
14 of iron carbohydrate into the  
15 reticuloendothelial system, that is increase  
16 in stores manifested by a rise in serum  
17 ferritin, then the transfer of iron from  
18 stores to hemoglobin, manifested by a  
19 reciprocal decrease in ferritin and a rise in  
20 hemoglobin. This is the expected result  
21 after IV iron administration.

22 The timing then that we should be

1     considering is over the first -- during the  
2     administration of iron, during and shortly  
3     after the administration of IV iron and  
4     within the first two weeks, when there are  
5     rapid changes in internal iron disposition.

6             Let us consider then hypotension.  
7     We saw seven events in six subjects, none of  
8     them clinically significant.  What about  
9     allergies?  Potential allergic reactions were  
10    gleaned from the entire database, over 5,200  
11    doses, there was no anaphylaxis, there was no  
12    serious allergic reaction, and there were 13  
13    urticarial events, most mild, and resolved  
14    within two hours.

15            Three adverse events were reported  
16    as hypersensitivity.  These were poorly  
17    characterized, but there were no changes in  
18    vital signs and no treatment was indicated or  
19    was given for these cases.  There were 32  
20    non-urticarial-related rashes, mostly  
21    flushing and macular-papular.

22            Next, we should consider bioactive

1 iron reactions during acute administration of  
2 IV iron. We looked through the comprehensive  
3 database for possible preferred terms which  
4 would describe the classic bioactive iron  
5 reaction of pain, nausea, vomiting, diarrhea,  
6 or hypotension.

7           And from those, we found the  
8 following -- only dizziness and nausea were  
9 increased numerically over those in the  
10 placebo control trials. This was in the  
11 placebo controlled crossover trial within 24  
12 hours of administration of either placebo or  
13 FCM. So this was the head-to-head comparison  
14 for potential bioactive iron reactions.

15           What about infection? Infection  
16 rates in the oral iron control trials were no  
17 different than those in the FCM treatment  
18 arm. And the iron sucrose control trials  
19 were no different in iron sucrose and FCM,  
20 and they were no different in the crossover  
21 trial with placebo.

22           Next, the death cases were

1 adjudicated by a panel of independent  
2 external experts, including Judith Jones and  
3 Stefan Russmann, clinical pharmacologists of  
4 the Degge Group, and safety  
5 experts -- Dr. Cooper, who you have been  
6 introduced to, Dr. Nancy Phillips, a  
7 pathologist at St. Louis University,  
8 Dr. Robert Foley, a nephrologist and  
9 epidemiologist and deputy director of the  
10 USRDS, and myself.

11           The conclusion of the panel was  
12 that no deaths were related to FCM. There  
13 were six deaths in controlled trials, five  
14 after FCM, one in an iron sucrose treatment  
15 arm, one in women's health indication, and  
16 three in CKD.

17           In the uncontrolled trials, there  
18 were five deaths, two in hemodialysis, two in  
19 non-dialysis CKD, and one in a patient with  
20 iron deficiency anemia. When we look at  
21 these 10 deaths in aggregate, there was no  
22 relationship between the size of the last

1 dose and the death -- from as low as 100  
2 milligrams to as high as 1000 milligrams,  
3 with several doses in between. Similarly,  
4 there was no relationship between death and  
5 the elapsed time between the last dose and  
6 death -- varying from one day to nearly 100  
7 days.

8           Next, there was no relationship  
9 between the known or potential phosphate  
10 levels and death -- either the value was  
11 known and it was not low, the subject was a  
12 hemodialysis patient where the phosphate  
13 changes were not seen, or the death occurred  
14 too early for a phosphate decline to be a  
15 factor.

16           Similarly, the causes of death  
17 varied. You have heard of the  
18 cardiac-related, the first three cases in the  
19 controlled trials. Let me discuss for you  
20 the other two deaths in the control trials,  
21 individually one at a time.

22           This patient is a 76-year-old man

1 with a chronic kidney disease, urinary tract  
2 infections in the past, peptic ulcer disease,  
3 hypertension. He received FCM, 1000  
4 milligrams for anemia and iron deficiency,  
5 and two subsequent doses.

6 On day 42, after the first  
7 administration of FCM, he ran a stop sign;  
8 the car was hit from the side in the  
9 intersection, he died, and the passenger in  
10 the vehicle also died. This was a fatal  
11 motor vehicle accident.

12 This is an 85-year-old man with  
13 CKD, coronary artery disease, heart failure,  
14 hypertension, atrial fibrillation, prostate  
15 cancer refractory to radio therapy and  
16 hormonal ablation. He suffered MRSA  
17 urosepsis secondary to bladder outlet  
18 obstruction.

19 As his GFR declined during the  
20 hospital and it became apparent that he would  
21 need dialysis, his advanced directives were  
22 invoked; his advanced directives precluded

1 dialysis. So given medical futility, life  
2 support was withdrawn and he was referred to  
3 hospice. This was a death by choice and was  
4 due to MRSA urosepsis.

5           One other death occurred in the  
6 controlled trial. This is in an iron sucrose  
7 arm. A 72-year-old woman with non-dialysis  
8 CKD and a Class 4 heart failure, died at home  
9 on day 18 after receiving two doses of iron  
10 sucrose, 200 milligrams. This is a death  
11 from congestive heart failure in a  
12 hemodialysis patient. These are all the  
13 deaths in the controlled trials we have  
14 covered between Dr. Cooper and I. We have  
15 complete summaries of the deaths from the  
16 uncontrolled trials, and I'll just touch on  
17 them briefly here.

18           A 54-year-old hemodialysis patient  
19 with Class 3 congestive heart failure and  
20 poorly controlled hypertension received doses  
21 of FCM on hemodialysis for anemia. She died  
22 at home. The death was judged to be

1 secondary to her congestive heart failure.  
2 This was a death in an uncontrolled patient  
3 from heart failure on hemodialysis.

4 This was a 59-year-old female  
5 hemodialysis patient with active  
6 tuberculosis, chronic lung disease, chronic  
7 heart disease, chronic persistent hepatitis.  
8 She suffered progressive respiratory failure  
9 secondary to tuberculosis pneumonia after  
10 receiving a course of FCM for anemia and  
11 hemodialysis. This was a death from  
12 pulmonary tuberculosis.

13 Finally, the third case is a  
14 48-year-old female with recurrent infections,  
15 depression, seizures, a gastric bypass for  
16 morbid obesity. She suffered bacteremic  
17 aeromonas pneumonia with  
18 neutropenia -- shock. She died in the  
19 emergency room from overwhelming aeromonas  
20 pneumonia. In retrospect, she had been in  
21 the placebo control trial, a blinded trial,  
22 she received placebo on day minus 8. She was

1 given levofloxacin and fluconazole on day  
2 minus 3 by another physician for a urinary  
3 tract infection and URI -- vaginitis  
4 respectively. She then received FCM on  
5 day 0.

6 Day 4, she received an otic  
7 solution of antibiotics, and on day 25,  
8 amoxicillin and clavulanate for another  
9 suspected urinary tract infection and URI.  
10 When she was admitted to the emergency room,  
11 her white count was 1.7; she had 28 percent  
12 sags or bands. Together, this is a  
13 neutropenic death in bacteremic aeromonas  
14 pneumonia.

15 An 86-year-old man with CKD  
16 diverticulosis and diverticulitis in the  
17 past, and a previous history of a hepatic  
18 abscess, suffered abdominal sepsis from what  
19 was found to be a laparotomy -- a perforated  
20 colon. This was a death from colonic  
21 perforation, day 182, after receiving a first  
22 dose of FCM.

1                   And the final death in the  
2                   uncontrolled trials is a patient who  
3                   underwent laparotomy for a mesenteric  
4                   adenopathy that had been identified prior to  
5                   the trial. After day 154 of the trial, she  
6                   suffered a massive GI bleed in the  
7                   perioperative setting, anoxic encephalopathy,  
8                   and life support was subsequently withdrawn  
9                   on day 189. This was a massive GI bleeding  
10                  after exploratory laparotomy.

11                  In conclusion, none of the deaths  
12                  were judged related to FCM by the panel of  
13                  experts. No relationship was found between  
14                  the maximum or initial FCM dose size, maximum  
15                  hemoglobin, ferritin, or phosphate nadir. No  
16                  death was consistent with known IV iron  
17                  effect, no hypotension, not allergic  
18                  reaction, not bioactive iron reaction. And  
19                  there was no apparent clustering or pattern  
20                  or safety signal.

21                  Thank you.

22                  DR. ANDREWS: Good morning. I'm

1 Elizabeth Andrews, an epidemiologist at the  
2 Research Triangle Institute. Over the past 25  
3 years, I've been conducting epidemiologic  
4 studies of drug safety, and over the last eight  
5 years, I've participated in the development and  
6 evaluation of risk management programs.

7 Today, I would like to present some  
8 considerations regarding the evaluation and  
9 interpretation of the mortality data. I do  
10 not think that today's discussion will focus  
11 on a comparison of deaths by simple counts  
12 and proportions. However, such comparisons  
13 were presented in the briefing document and  
14 therefore require some comment. The crude  
15 count of deaths in the FCM and control groups  
16 suggest a larger treatment group difference  
17 than actually exists. This misperception  
18 results from two factors: imbalances in the  
19 numbers in follow-up as well as confounding.

20 There were over twice as many  
21 subjects and twice as much follow-up time in  
22 the FCM group than in the control -- in this

1 comparison that was made in the entire safety  
2 database that included the uncontrolled  
3 studies. Some differences still remain  
4 within the comparative studies.

5 The appropriate measure for  
6 comparison purposes, therefore, is a rate  
7 which is expressed as a number of events over  
8 a denominator of person time, rather than  
9 counts or proportions of patients.

10 It is also important to include in  
11 the denominator of proportion only those  
12 individuals who have the opportunity to be in  
13 the numerator. Therefore, in the evaluation  
14 of the crossover trial in which all events  
15 that occurred after the 7-day per treatment  
16 evaluation period were counted as  
17 FCM-exposed, we must consider that study to  
18 be an uncontrolled study of FCM for mortality  
19 purposes.

20 It is not appropriate to include  
21 the total number of patients who received  
22 both FCM and placebo in the denominator of

1 the placebo group, because it erroneously  
2 inflates the denominator of the placebo group  
3 by a large number of patients who are not  
4 eligible to be included in the numerator.

5 In addition, there is confounding  
6 in these crude comparisons as a result of  
7 including the uncontrolled studies. The  
8 uncontrolled studies included populations at  
9 higher intrinsic mortality risks than the  
10 target postpartum HUB population.

11 You can see from this table that  
12 the baseline or the expected mortality rates  
13 vary substantially across patient populations  
14 included in the development program.  
15 Mortality rates in the women with HUB were  
16 not readily available, but are likely similar  
17 to the overall very low mortality rates in  
18 women of childbearing age which are shown  
19 here.

20 The estimates of mortality in the  
21 chronic kidney disease population shown here  
22 is actually on the low side compared with

1 some more recently published studies,  
2 including a study using the Kaiser Permanente  
3 experience in chronic kidney disease.

4           You can see from these mortality  
5 differences why combining data from the  
6 experience of high-risk populations on FCM  
7 without a control group confound the  
8 association between FCM and mortality when  
9 using a crude comparison across all studies.

10           Some experts have suggested that  
11 it's not appropriate to compare the outcome  
12 experience in a low-risk population with the  
13 outcome experience in a high-risk population.  
14 However, in the evaluation of drug safety, we  
15 generally try to develop insights from the  
16 total body of information available to us on  
17 the use of a product, controlling for sources  
18 where -- and confounding through careful  
19 analytic approaches -- and acknowledging the  
20 imperfections of these approaches.

21           A fairly straightforward approach  
22 is to assess the data from comparative