

1 studies by stratifying the information on
2 variables that may be confounders. We can
3 stratify the studies, therefore, based on the
4 underlying treatment groups that have
5 different baseline mortality risks, and then
6 develop a pooled estimate of the relative
7 risk across those strata. And we can do this
8 with a Mantel-Haenszel approach, which is a
9 standard method of addressing confounding in
10 which comparisons can be made within studies
11 as well as combined across studies. The
12 uncontrolled studies cannot be considered in
13 the pooled information because there is no
14 comparative information.

15 This table shows the mortality
16 rates expressed as events per 100 person
17 years in three categories of studies: a
18 combination of the postpartum and heavy
19 uterine bleeding control studies, the
20 combination of all other control studies,
21 largely in high-risk populations, and the
22 experience in the uncontrolled studies.

1 This left column displays the
2 mortality rates in the FCM group, and the
3 middle column the rates in the control group.
4 There is only FCM data in the uncontrolled
5 studies.

6 The third column reflects the
7 relative risks comparing FCM to the control
8 groups. The relative risk is ratio measure
9 with relative risk of one representing
10 identical risk in the groups being compared.
11 Within the targeted postpartum and HUB
12 population, the mortality rate for FCM is
13 small, and the treatment group difference is
14 small: .87 per 100 versus zero. The relative
15 risk is infinity, because we're dividing by
16 zero. Nevertheless, we can calculate a
17 confidence interval for that relative risk
18 which has a lower bound of .04.

19 As expected, the population in the
20 other control studies has a higher mortality
21 rate than the postpartum HUB population for
22 both treatment groups. And these rates are

1 consistent with the intrinsic risks and the
2 disease dates as shown earlier.

3 In the comparison across these
4 trials, there is a wide confidence interval
5 around the point estimate of a relative risk
6 of 2.7. We can pool information across these
7 two categories of studies using a
8 Mantel-Haenszel approach. The uncontrolled
9 studies cannot be included because there are
10 no comparative data.

11 The pooled results show that
12 although there is a positive association
13 between FCM exposure and mortality, with a
14 rate ratio of 3.4, the 95 percent confidence
15 interval shows that this rate is consistent
16 with a broad range of preventive as well as
17 positive associations, from .41 to 29.

18 In summary, we've seen that a crude
19 comparison of 10 deaths on FCM to one death
20 on control is not a sound method of comparing
21 the mortality experience across study
22 populations. Appropriate measures must

1 account for differences in individuals and
2 follow-up time.

3 Moreover, we must use methods that
4 take into account the confounding introduced
5 by using populations with different intrinsic
6 mortality risks. We have presented what we
7 believe to be an unbiased approach to the
8 evaluation of these data.

9 The mortality rate in the
10 population of women with heavy uterine
11 bleeding and postpartum anemia is extremely
12 low. The comparative data from the trials in
13 that target population do not by themselves
14 raise concern. The data from the clinical
15 trials across different disease populations
16 provide a signal of a potential increase in
17 mortality rates. They are also consistent
18 with no increase.

19 A study that could definitively
20 detect or rule out small or even modest
21 increases in mortality, when the intrinsic
22 mortality risk is extremely low, would

1 require hundreds of thousands of patients and
2 is simply not feasible.

3 This type of information is almost
4 never available pre-approval, but is often
5 gathered in the post-approval setting through
6 proactive safety monitoring and epidemiologic
7 research.

8 Luitpold has committed to a
9 responsible risk management program to assure
10 appropriate use of this product in patients
11 for whom the clinical benefits outweigh the
12 potential risks. Moreover, they have
13 committed to a large program of a rigorous
14 post-approval epidemiology and safety
15 monitoring.

16 Thank you.

17 DR. MANGIONE: Thank you. Due to time
18 limitations, we're not going to summarize our
19 risk management proposal, but we are prepared to
20 discuss that later.

21 FCM's AE overall safety profile was
22 comparable to that of oral iron. The overall

1 and cardiac safety profile of FCM was not
2 negatively affected by the size of the FCM
3 dose, by the achieved maximum ferritin, or
4 the achieved maximum hemoglobin, supporting
5 that the AE rate is not related to FCM.

6 There's no definitive signal of
7 cardiac toxicity; the cardiac adverse event
8 rate in all the data sets are balanced. The
9 serious adverse event rate for the
10 homogeneous postpartum and HUB target
11 population and the active control data set
12 are balanced.

13 Confirmed cardiovascular serious
14 ischemic event rates are balanced. The small
15 observed difference in the cardiac SAE rates
16 and the oral iron data set is due to the
17 multimorbid non-dialysis dependent chronic
18 kidney disease and inflammatory bowel disease
19 subjects, and is clinically non-interpretable
20 due to the very low event rate.

21 There is no pattern to the cardiac
22 events. There were no similarities in the

1 causes of death, and they were unrelated to
2 the size and timing of the FCM dose. They
3 were unrelated to the magnitude of the
4 hemoglobin increase, and there was no
5 relationship to any known or postulated
6 mechanism associated with any IV iron use.

7 These deaths were related primarily
8 to baseline mortality risks, with the
9 majority occurring in the non-dialysis and
10 hemodialysis-dependent chronic kidney disease
11 population whose annual mortality approaches
12 20 percent.

13 Dr. Goodnough will briefly present
14 an end with clinical perspective.

15 Thank you.

16 DR. GOODNOUGH: Good morning. My name
17 is Tim Goodnough. I'm a hematologist, and I run
18 the transfusion service at the Stanford
19 University. I've had 25 years' experience
20 consulting with obstetricians caring for
21 high-risk postpartum patients and with
22 gynecologists treating women with heavy uterine

1 bleeding. And I'm here to give a few summary
2 comments regarding clinical perspective.

3 This morning, we have seen the
4 efficacy of FCM versus oral iron in two
5 important clinical settings. First, FCM
6 provides a clinically significant increase in
7 hemoglobin response, defined as a hemoglobin
8 increase of greater than or equal to 3 grams
9 per deciliter. It provides a similar benefit
10 when you look at the percentage of responders
11 who attain a hemoglobin of greater than 12,
12 which represents correction of the anemia.
13 In both of these patient populations, FCM is
14 superior to oral iron.

15 This is further illustrated in the
16 HUB studies by the percent of patients
17 achieving hemoglobin of at least 2 grams per
18 deciliter. This is an important clinical
19 increase for these patients, equivalent to
20 the transfusion of two units of blood,
21 allowing for definitive treatment in many
22 women.

1 FCM has an immediate response, even
2 by seven days, over oral iron. And this is
3 further extended over time, heavily favoring
4 FCM so that at the end of the study interval,
5 80 percent of these patients have had their
6 anemia corrected.

7 We see a similar effect in the
8 postpartum trial, in which the percent of
9 patients who achieved a primary endpoint of
10 greater than 12 grams per deciliter was
11 90 percent superior to the oral iron group.
12 What these trials can't show us is the
13 inevitable relapse of oral iron-treated women
14 who still have no iron stores to support
15 ongoing erythropoiesis.

16 This graph illustrates how I think
17 the benefit of FCM is going to have an impact
18 in women's health care. This is a patient
19 from the HUB trial who continued to have
20 blood loss over the course of the study.
21 When you look at the hemoglobin, the solid
22 line, you'll see after administration of FCM

1 on day 0 and 7, there is a trengent (?) rise
2 in the hemoglobin level, which then fell
3 because of continued heavy blood loss. After
4 day 14, however, there was a sustained
5 increase in hemoglobin, from about 7.3 to
6 about 9.3 grams per deciliter.

7 You'll note that the rise in
8 ferritin earlier on reflects the normal
9 trafficking of iron from its intravenous
10 administration into the RE system, where it
11 is stored, and then mobilized into red cells.
12 This is illustrated by the fall in the level
13 of ferritin coincident with the rise in
14 hemoglobin.

15 What this case illustrates is that
16 FCM has substantially improved this woman's
17 anemia in the same way that a transfusion of
18 2 units of blood would have done. Oral iron
19 could not possibly have made this correction
20 in the setting of sustained heavy losses.

21 Furthermore, after day 28, there
22 was no definitive surgical correction, and

1 you can see, because of sustained heavy
2 bleeding, the patient became more profoundly
3 anemic again, with the serum ferritin
4 reflecting continued iron deficiency.

5 In this case, had definitive
6 surgical correction been done at day 28, this
7 case could have been resolved successfully
8 with only the administration of FCM rather
9 than blood transfusion which otherwise would
10 have been necessary to stabilize the patient
11 for the surgical procedure.

12 In these two clinical settings,
13 postpartum hemorrhage and heavy uterine
14 bleeding, oral iron can't replace iron loss
15 in excess of the ability of the GI track to
16 absorb the oral iron. This is the advantage
17 of FCM.

18 Secondly, FCM has safety that is
19 superior to the only other IV iron currently
20 approved in iron deficiency anemia, and that
21 is iron dextran. There will be no
22 requirement for a Black Box Warning with a

1 test dose or a risk of anaphylaxis.

2 Third, we've seen rapid and
3 reliable treatment of iron deficiency anemia
4 in postpartum and heavy uterine bleeding
5 patients, thus making it a viable alternative
6 to blood transfusion.

7 Since the potential clinical
8 benefit from FCM is so direct, the question
9 about its utility and clinical practice
10 clearly comes down to the nature of its
11 risks, and there's nothing that I've seen
12 that convinces me that FCM poses any
13 significant risk to the women who will
14 benefit from it.

15 Thank you.

16 DR. TOKARS: Dr. Hennessy, that
17 concludes our presentation.

18 DR. HENNESSY: Thank you very much.
19 What I'd like to do is move our break to now, so
20 why don't we take 15-minute break which will be
21 until five minutes after 10:00, and then we'll
22 resume with the schedule as published.

1 (Recess)

2 DR. HENNESSY: I have five minutes
3 after now, so we'd like to get started.

4 Dr. Mangione from the sponsor is
5 going to be presenting the risk management
6 plan.

7 DR. MANGIONE: Slide 116, please.

8 Luitpold is committed to work with
9 the FDA to determine the most appropriate
10 risk management program for the introduction
11 of FCM into the marketplace, a program that
12 is tailored to the unique characteristics of
13 IV iron and postulated safety concerns.

14 To be cautious and ensure that no
15 undue safety concerns exist, Dr. Andrews and
16 her pharmacoepidemiology group and Luitpold
17 are designing an approach that will include a
18 targeted product launch focused on those
19 patients with the greatest and most pressing
20 need.

21 This launch will be targeted to a
22 limited group of physicians who are equipped

1 and experienced in the administration of
2 IV iron. Our proposal also includes a
3 comprehensive physician and patient education
4 program, and a special targeted follow-up
5 data collection instrument for deaths,
6 serious adverse events, and serious
7 hypersensitivity reactions.

8 We also plan additional studies, to
9 include a prospective disease registry to
10 quantify the rate and risk factors for deaths
11 and serious adverse events in a large
12 population receiving FCM, and a similar
13 comparison population, and continuation of
14 the two ongoing randomized control trials
15 investigating the safety of FCM versus
16 standard medical care, and evaluations to
17 ensure program goals are met.

18 Luitpold is committed to
19 pharmacovigilance monitoring, to ensure that
20 if risks exist, we can understand and manage
21 this risk as early as possible.

22 The risks, real or imagined, are

1 rare and varied, and therefore cannot be
2 defined in prospective clinical trials. We
3 have details of this proposal which we are
4 prepared to discuss later.

5 Thank you very much.

6 DR. HENNESSY: Thank you very much,
7 Dr. Mangione.

8 So there's now going to be a
9 presentation of an FDA overview of parenteral
10 iron products by Dr. Kathy Robie-Suh.

11 DR. ROBIE-SUH: Good morning. I'm
12 Kathy Robie-Suh. I'm a medical team leader with
13 CDER's Division of Medical Imaging and
14 Hematology Products. The FDA presentation this
15 morning will present the highlights of FDA's
16 review of the new drug application for
17 Injectafer. The main topic today relates to the
18 safety of the product, and our presentation will
19 focus specifically upon this topic. There will
20 be three FDA presenters this morning.

21 First, I will present an overview
22 of approved parenteral iron products. Next,

1 Dr. Christy John of the Office of Clinical
2 Pharmacology will present the major findings
3 from the FDA review of pharmacokinetics and
4 pharmacodynamics for Injectafer. Finally,
5 Dr. Min Lu, primary medical reviewer for this
6 application, will present the FDA evaluation
7 of efficacy and safety for Injectafer.

8 As previously mentioned today,
9 Injectafer is an iron replacement product
10 proposed for intravenous administration as an
11 alternative to oral iron therapy. Oral iron
12 replenishment is generally recognized as the
13 most common and first-line method of iron
14 replenishment for most patients with iron
15 deficiency anemia.

16 However, several parenteral iron
17 replacement products are currently available
18 and approved on the market for certain
19 patients with iron deficiency anemia. In the
20 next few minutes, I will describe these
21 approved parenteral iron replacement
22 products. I will focus on the labeled

1 indications and dosing for these products,
2 and mention the salient aspects of their
3 safety considerations.

4 This slide lists the approved
5 parenteral iron replacement products. All
6 these products consist of iron molecules
7 incorporated into complex carbohydrate
8 structures. The first form of iron dextran
9 was approved in 1968, many years ago. And
10 various versions of the product have been
11 approved over the subsequent years. Examples
12 of iron dextran products include INFED and
13 Dexferrum. About eight years ago, Ferrlecit,
14 sodium ferric gluconate, was approved, and
15 this was followed in 2000 by FDA's approval
16 of Venofer, or iron sucrose.

17 These products all have specific
18 indications and specific dosage regimens.
19 All the products are administered
20 intravenously, and iron dextran is somewhat
21 unique in that it also may be administered as
22 an intramuscular injection.

1 The next few slides highlight each
2 of these products. Iron dextran is approved
3 for the broad indication of the treatment of
4 patients with documented iron deficiency in
5 whom oral administration of iron is
6 unsatisfactory or impossible. The approved
7 dosage regimen importantly includes the
8 recommendation of a test dose due to the risk
9 of hypersensitivity reactions. If this test
10 dose is tolerated, the product is
11 administered as an intravenous injection to a
12 maximum of 100 mgs on any single day.

13 Iron dextran products have been
14 associated with serious hypersensitivity
15 reactions, including fatalities. And this
16 risk is reflected in a boxed warning that
17 appears at the top of the iron dextran
18 product labeling. Highlights of the boxed
19 warning are shown in this next slide.

20 The boxed warning notes that iron
21 dextran carries a risk for anaphylaxis and
22 anaphylactoid reactions which may cause

1 death. The physician is advised to verify
2 the diagnosis, and only use the product when
3 the iron deficiency is not amenable to oral
4 iron administration. Finally, the warning
5 specifies that measures to treat anaphylaxis
6 and anaphylactoid shock must be readily
7 available when iron dextran is administered.

8 Ferrlecit, or iron gluconate, is
9 indicated for treatment of iron deficiency
10 anemia specifically among patients who are
11 receiving hemodialysis and who also are
12 receiving erythropoietin therapy. The
13 recommended maximum dose at each dialysis is
14 125 mg. A test dose is not a component of
15 the treatment regimen. The warning section
16 of the Ferrlecit label does note the risk for
17 serious hypersensitivity reactions, based on
18 the occurrence of these reactions in the
19 post-marketing experience with Ferrlecit.

20 The label for iron sucrose or
21 Venofer carries multiple specific indications
22 for use among patients with chronic kidney

1 disease and iron deficiency, as shown here.
2 These patients consist of those who are
3 receiving hemodialysis or peritoneal
4 dialysis, and also erythropoietin therapy.
5 Venofer is also indicated in patients with
6 chronic kidney disease who are not receiving
7 dialysis.

8 The recommended maximum daily
9 Venofer dose varies with the patient
10 population. The maximum daily dose is 100 mg
11 for patients receiving hemodialysis, 400 mg
12 in patients receiving peritoneal dialysis,
13 and 200 mg in patients with
14 non-dialysis-dependent chronic kidney
15 disease. The dose regimen recommendations
16 for Venofer do not include the use of a test
17 dose. There is no boxed warning for Venofer,
18 although the warning section of the labeling
19 describes a risk for serious for
20 hypersensitivity reactions. These are events
21 that were reported, again, in the
22 post-marketing experience.

1 This slide lists the major safety
2 considerations with all the currently
3 approved parenteral iron products. The top
4 of the list, noted in the first bullet. The
5 most notable risk is for serious
6 hypersensitivity reactions. And these
7 involve anaphylaxis, anaphylactoid reactions;
8 this is especially serious for iron dextran,
9 which have resulted in deaths.

10 The hypersensitivity risks are
11 generally regarded as lower for Venofer and
12 Ferrlecit than for iron dextran. All the
13 parenteral iron products have been associated
14 with less severe but important reactions,
15 most notably consisting of hypotension either
16 during or shortly following infusion of the
17 products.

18 Finally, the clinical development
19 for most of these products culminated in the
20 recommendation that the dosage regimen
21 generally should be limited to a maximum of
22 200 mg of elemental iron in a single

1 administration, with the only exception being
2 the single dose of 400 mg of Venofer among
3 patients receiving parenteral dialysis.

4 The dosing regimen proposed for
5 Injectafer is especially unique when compared
6 to those of the currently approved products,
7 in that a higher single dose administration
8 is being sought.

9 This concludes my presentation on
10 the approved parenteral iron products.

11 Dr. Christy John will now discuss
12 the Injectafer dosage regimen considerations,
13 especially as they relate to clinical
14 pharmacology.

15 Thank you.

16 DR. HENNESSY: Thank you very much.
17 While Dr. John is preparing the presentation, I
18 would ask the sponsor if once the FDA gets done
19 with their presentation, you'd be willing to
20 give us maybe 15 minutes on the risk management
21 plan and your plans for post-marketing studies
22 in a little bit more detail, as you had offered

1 to do with your one of two slides.

2 Thank you.

3 DR. JOHN: Good morning. I will
4 present a summary of major pharmacokinetics and
5 pharmacodynamics findings from the review of
6 Injectafer. First, I will describe the major
7 physicochemical characteristics of and dosing
8 regimen of Injectafer, followed by a short
9 background of iron transport and storage in
10 blood. Then I will describe the pharmacokinetic
11 profiles of ascending Injectafer doses, and its
12 impact on various pharmacodynamic variables. I
13 will conclude with some comments of my clinical
14 pharmacology evaluations.

15 Injectafer is a poly-nucleo complex
16 where iron molecules, shown in red spheres
17 here, are held together via bridging
18 hydroxide and oxide ions, and conjugated to
19 sugar residues, and the molecular weight of
20 Injectafer is 150 kilodalton. The product is
21 proposed for marketing as a solution in two
22 vial sizes, at 2 ml and at 10 ml. The

1 drug product is supplied as a dark brown
2 sterile aqueous isotonic solution. Each
3 milliliter contains 50 mg elemental iron.
4 The drug may be administered as an undiluted
5 intravenous injection, or as an infusion
6 following dilution in 250 ml of saline.

7 The injection or infusion
8 administration is contingent upon the maximum
9 single dose that is to be administered. The
10 proposed single maximum dose of Injectafer,
11 as we have heard this morning, is 1000 mg, or
12 15 mg/kg, which is considerably higher than
13 the approved doses of other iron replacement
14 products.

15 Based upon the total iron deficits
16 and response to the therapy, a maximum of
17 2500 mg may be administered over a period of
18 three weeks, and is contingent, once again,
19 upon total iron deficit. With doses rounded
20 off to 100 mg increments, the single doses of
21 600 to 1000 mg are to be administered as an
22 infusion or intravenous injection for 15

1 minutes. Doses of 500 mg or less, are to be
2 administrated as undiluted injections at a
3 rate of no more than 100 mg/minute.

4 A number of iron binding parameters
5 are important in evaluating Injectafer's
6 clinical pharmacology. The major PK
7 parameter is based on total serum iron
8 concentrations. Transferrin saturation
9 represents the amount of protein-bound iron
10 in the circulation that is the amount readily
11 available for erythropoiesis.

12 Clinically, Transferrin saturation
13 is estimated based upon laboratory measure of
14 total iron binding capacity, known as TIBC,
15 and the measure of serum iron. The
16 measurement of Transferrin saturation is
17 affected when Injectafer is present in the
18 serum, and may provide an unreliable estimate
19 of Transferrin saturation.

20 The measurement of serum ferritin,
21 however, which is an iron-storage protein, is
22 not affected by the iron molecules from the

1 drug product in the blood. Therefore, the
2 measurement of serum ferritin is the major PD
3 parameter in the clinical pharmacology
4 studies.

5 Injectafer pharmacokinetics and
6 pharmacodynamics were assessed in a dose
7 escalation study of 32 patients with mild
8 iron-deficient anemia. This study used a
9 dose escalation single center randomized
10 double-blind placebo controlled design. The
11 study used doses ranging from 100 mg up to
12 1000 mg, with a total of eight subjects in
13 each dose cohort, six receiving Injectafer
14 and two receiving placebo.

15 This slide represents the total
16 serum iron concentration over time following
17 a single Injectafer dose. The slide shows
18 that there is a dose-dependent increase in
19 total serum iron concentration. The total
20 serum iron concentrations return to baseline
21 by 40 to 60 hours post-dosing.

22 This table shows Injectafer

1 pharmacokinetic parameters of each dose
2 cohort based upon the measurement of total
3 serum iron. Although the Cmax, shown in the
4 first row, for serum iron concentrations
5 increased in dose proportional manner, the
6 area under curve, known as AUC, shows a clear
7 non-linear relationship between dose and
8 exposure. For example, doubling the dose
9 from 500 mg to 1000 mg increased the exposure
10 by 2.7 fold. Similarly, the clearance of
11 serum iron decreased with dose. Serum
12 clearance was reduced by approximately
13 40 percent at 1000 mg dose as compared to 100
14 mg.

15 Moving on to the pharmacodynamic
16 parameters, the major pharmacodynamic
17 parameter measured in dose escalation study
18 serum ferritin is summarized in this table.
19 Shown are the average values, and standard
20 deviations in parentheses. For comparative
21 purposes, normal serum ferritin levels are
22 shown at the bottom of the slide. In

1 general, normal serum ferritin values range
2 between 12 to 300 mg/ml depending upon
3 gender.

4 In this study, the baseline serum
5 ferritin concentrations were low, as shown in
6 the first row, and generally similar in each
7 dose cohort, as reflected in pre-dose serum
8 ferritin measurements. The average maximum
9 serum ferritin concentrations increased
10 progressively with dose. For doses of 500 up
11 to 1000 mg, the average maximum ferritin
12 concentration exceeded the upper bound of
13 normal range. For the dose of 1000 mg, the
14 increase is more than double the upper bound
15 of ferritin concentrations in males, and more
16 than four times the upper bound in females.

17 For all doses, the total serum iron
18 concentrations return to baseline by 48 to 60
19 hours post-dosing. However, the average
20 maximum serum ferritin concentrations for 500
21 mg and higher doses were achieved at 96 hours
22 or later post-dosing. The transferrin

1 saturation another, PD marker, was also
2 measured in the dose escalation study. As
3 shown here in pink, the reported transferrin
4 saturation for 500 mg dose was more than
5 70 percent or baseline persisting up to 60
6 hours after Injectafer administration.
7 However, the sponsor has presented the data
8 that indicates that the assay of transferrin
9 saturation may be affected when Injectafer is
10 present in the blood, especially with 800 and
11 1000 mg doses. Therefore, we are unable to
12 estimate the true extent of transferrin
13 saturation following Injectafer
14 administration.

15 In summary, major pharmacokinetic
16 pharmacodynamic studies show that a total
17 serum iron concentration increased with
18 increasing doses of Injectafer. The
19 incremental increase in exposure was
20 non-linear, and more than the values expected
21 for dose proportionality. The PD marker
22 serum ferritin also increased with increasing

1 doses of Injectafer. The maximum serum
2 ferritin concentrations following 100 mg
3 Injectafer dose was more than twice the upper
4 bound for normal serum ferritin
5 concentration.

6 Also, the study reported increased
7 transferrin saturation with higher Injectafer
8 doses; although these data are reported as
9 unreliable for higher doses due to assay
10 interference by the drug, as mentioned
11 previously. These PK/PD results imply a
12 possibility of iron overload with a dose of
13 1000 mg.

14 The clinicopharmacology data
15 indicated increased levels of serum iron,
16 serum ferritin, and transferrin saturation
17 after escalating Injectafer doses. These
18 data provide evidence that Injectafer
19 replenishes body iron stores and for some
20 doses result in serum ferritin that exceed
21 normal human values. The clinical
22 meaningfulness of high levels of serum

1 ferritin after Injectafer administration are
2 not really known.

3 I thank you for your attention.

4 And now, Dr. Min Lu will present the clinical
5 data.

6 Dr. Lu.

7 DR. HENNESSY: Thank you. Just so
8 people can plan, after Dr. Lu's presentation,
9 the sponsor is going to present on the risk
10 management plan and the plans for post-marketing
11 safety surveillance. And then there will be
12 time for questions from the committee. I would
13 like to start first with questions for the FDA,
14 exhaust this as much as possible, and then go
15 with questions to the sponsor.

16 DR. LU: Good morning. I will
17 summarize the major findings from the Injectafer
18 NDAs that are most pertinent for this
19 discussion. I will restate the proposed
20 indication and briefly provide FDA comments
21 regarding the advocacy results. Most
22 importantly, I will focus upon the safety

1 findings from clinical development of the
2 program. As previously noted, FDA's major
3 safety concern relates to parenteral mortality
4 safety signal within the sponsor's data. This
5 signal is based upon integration and
6 consideration of three major data findings; most
7 notably, the mortality, but also the imbalance
8 in serious adverse event rates, including
9 cardiac event rates and the occurrence of
10 hypophosphatemia.

11 The proposed indication in the
12 original NDA submission in June 2006 was a
13 treatment of iron deficiency anemia in
14 patients having uterine bleeding, postpartum
15 anemia, inflammatory bowel disease, and the
16 inpatient undergoing hemodialysis. FDA
17 completed the review of the original
18 submission and expressed the concerns to the
19 sponsor regarding multiple considerations,
20 but especially the mortality safety signal as
21 well, as concern about a linear data
22 pertaining to repeated cycles of Injectafer

1 administration.

2 In November 2007, during a review
3 of sponsor's response to the initial FDA
4 review findings, the proposed indication was
5 revised to restrict to a treatment of iron
6 deficiency anemia in heavy uterine bleeding
7 in postpartum patients. Conceivably, this
8 narrowed indication may alter concerns
9 regarding risk and the benefits, as well as
10 consideration due to repeated cycle of
11 Injectafer, even with narrowed indication, we
12 will highlight the major findings from the
13 entire clinical development program.

14 In the clinical program, 2080
15 patients were exposed to Injectafer in 14
16 clinical studies. But they used various
17 study designs. Among the 14 trials, eight
18 were multi-center randomized active
19 controlled studies. These eight studies
20 provided the bulk of safety data, and seven
21 of them provided efficacy data. The eight
22 studies consist of six oral iron controlled

1 studies that the user proposed the Injectafer
2 dose regimen of maximum single dose of 1000
3 mg, and the two other studies that used the
4 Venofer placebo controls, and the Injectafer
5 200 mg per dose regimen.

6 It is important to remember that.
7 Injectafer is proposed for use as an
8 alternative to oral iron. Hence, the data
9 from six oral iron controlled studies are
10 especially important for the assessment of
11 efficacy and safety. Four of the six oral
12 iron controlled studies were conducted
13 specifically among patients with heavy
14 uterine bleeding or patient in the postpartum
15 condition.

16 The study population in the 14
17 clinical studies include patients with heavy
18 uterine bleeding, postpartum anemia,
19 inflammatory bowel disease, chronic kidney
20 disease, including non-dialysis and
21 hemodialysis patients, and the patients with
22 multifactor iron-deficient anemia, as well as

1 in patient with chronic heart failure.

2 There are four studies to support
3 the efficacy of Injectafer for the current
4 proposed indication. This includes one study
5 patient with the heavy uterine bleeding, and
6 three studies in postpartum patients. The
7 primary efficacy endpoint was either a change
8 from baseline in hemoglobin or proportion of
9 patients achieving anemia correction.

10 Two studies were designed as
11 superiority trial. And two studies were
12 designed as a non-inferiority trails. All
13 four studies were open labeled and oral iron
14 control trials. The study duration was six
15 weeks in three study, and 12 weeks in one
16 study.

17 In patients having uterine
18 bleeding, study 1VIT-4002/4003 was a
19 compilation of two similar-designed studies
20 of 4002 and 4003. Both studies were
21 terminated early and the results were pooled.
22 The primary efficacy endpoint was a

1 proportion of subjects who achieved increase
2 in hemoglobin more than equal to 2 gm/dl from
3 baseline at any time during the six-week
4 study.

5 In the combined analysis, as shown
6 in the first row of the table, the response
7 rate was 82 percent in the Injectafer group
8 and 62 percent in the oral iron group. The
9 difference in the response rate between the
10 two treatment groups was statistically
11 significant. There were similar results when
12 4002 and 4003 studies were analyzed
13 separately.

14 These slides shows efficacy results
15 from three trials in postpartum patients.
16 The three trials include 1VIT03001,
17 VIT-IV-CL-009, and 1VIT06011.

18 In Study 1VIT03001, the primary
19 efficacy endpoint was a proportion of
20 patients who achieved increase in hemoglobin
21 more than or equal to 2 g/dl from baseline at
22 any time during the six-week study.

1 As shown in the first row, the
2 response rate was similar between Injectafer
3 and oral iron groups. A rate of 96 percent
4 versus 94 percent. In study VIT-IV-CL-009,
5 the primary efficacy endpoint was a change
6 from baseline hemoglobin at the end of 12
7 weeks. Again, the change in mean hemoglobin
8 at week 12 from baseline was similar between
9 the Injectafer and oral iron groups. A mean
10 change of 3.3 g/dl versus 3.2 g/dl.

11 The first two trials were designed
12 as non-inferiority trials. Both studies had
13 met the pre-specified non-inferiority
14 margins. In the third trial, in study
15 1VIT06011, the primary efficacy endpoint with
16 the proportion of the subjects who achieved
17 hemoglobin more than or equal to 12 g/dl at
18 any time during the six-week study. The
19 results show that 91 percent of patients in
20 the Injectafer group as compared to 67
21 percent in the oral iron group, achieved
22 hemoglobin 12 g/dl. During the study, the

1 difference in the response rate was
2 statistically significant.

3 The major safety results from the
4 clinical developmental program are
5 highlighted here. As previously noted, three
6 features account for FDA concern about the
7 potential mortality safety signal. Firstly,
8 the hour of safety shows a numerical
9 imbalance in deaths, with a clinical
10 presentation for several of these deaths that
11 suggest cardiac events.

12 Secondly, the database shows a
13 numerical imbalance in serious adverse event
14 rates. And importantly, the serious cardiac
15 event rates. Lastly, hypophosphatemia was
16 relatively commonly associated that was
17 Injectafer administration. And anecdotal
18 reports have suggested that hypophosphatemia
19 may be due to a cardiac dysfunction.

20 The mortality results are
21 summarized here. Overall, there were 10
22 deaths in patients after Injectafer exposure,

1 including five deaths in randomized
2 controlled studies; one death in randomized
3 crossover study, and four deaths in
4 uncontrolled studies. As shown in the second
5 major bullet, there was one death in a
6 patient after Venofer exposure in randomized
7 controlled studies. As shown in the last
8 bullet, no patients died after receiving oral
9 iron in a randomized oral iron-controlled
10 studies.

11 This table summarizes the deaths
12 after Injectafer exposure according to the
13 dose regimen, that those proposed for
14 marketing is 1000 mg maximum single dose of
15 15 mg/kilo maximum, as shown in the first row
16 of the table. Among the 10 deaths after
17 Injectafer exposure, seven deaths occurred in
18 1739 patients in studies that used the
19 proposed 1000 mg maximum single dose regimen.

20 The seven deaths include the four
21 patients with non-dialysis chronic kidney
22 disease, one patient with postpartum anemia,

1 one patient with inflammatory bowel disease
2 and then one patient with multi-factorial
3 iron deficiency anemia.

4 As shown in the last row of the
5 tables, three deaths occurred in 311 patients
6 in studies that used the 200 mg/dose regimen,
7 not proposed for marketing. These three
8 deaths occurred among patients undergoing
9 hemodialysis.

10 As noted previously, only one death
11 was detected in the control group of the
12 randomized controlled clinical studies.
13 Specifically, one death occurred in a patient
14 who had received Venofer. The Venofer
15 consists of 200 mg dose administered twice.
16 The patient was thought to have died of
17 worsening heart failure according to the
18 investigator. In this study, that enrolled
19 patients with congestive heart failure as a
20 baseline.

21 Five of 10 deaths that followed the
22 Injectafer administration occurred among

1 patients who had some evidence of cardiac
2 dysfunction as having impact the deaths,
3 based upon the investigator's statements or
4 other study documents. This slide shows
5 apparent major causes of these five deaths,
6 as mainly reported by citing investigators,
7 along with the number of days between the
8 deaths and the last Injectafer exposure.

9 Major features of event are
10 highlighted in the last column. As shown in
11 the first of three rows and the last row,
12 four patients appeared to die explicitly of
13 cardiac causes. The cardiac cause of death
14 was assessed by citing investigators for
15 these four patients.

16 Specifically, one patient died of
17 cardiac arrest. That occurred in the
18 workplace one day after a single dose of 1000
19 mg of Injectafer. One patient died of
20 pre-partum cardiomyopathy with heart failure.
21 In this case, the patient was found at the
22 home unresponsive and was dead on arrival at

1 the hospital eight days after a single dose
2 of 1000 mg of Injectafer.

3 As noted in the chart below, one
4 patient had acute extensive myocardial
5 infarction four days after a single dose of
6 200 mg of Injectafer, and died nine days
7 after Injectafer exposure. As noted in last
8 row, one patient died of cardio-respiratory
9 arrest suddenly at her home 19 days after
10 last Injectafer injection. This patient had
11 received eight injections of 200 mg
12 Injectafer doses.

13 As noted in the first row, the
14 cause of death in one patient was listed as
15 respiratory failure due to tuberculosis.
16 However, we also notice that the hospital
17 discharge summary states that the patient
18 developed acute cardiac insufficiency and it
19 died on the same day.

20 The next slide summarizes the other
21 five deaths following Injectafer
22 administration. For other five deaths, the

1 causes of deaths include multiple trauma
2 secondary to motor vehicle accident;
3 pneumonia and sepsis; urosepsis and
4 pneumonia; anoxic encephalopathy secondary to
5 GI bleeding, and death due to colon
6 perforation.

7 This slide shows our mortality
8 rate, multi-center randomized controlled
9 studies. For the data pool of all eight
10 studies, there were five deaths in the
11 Injectafer-treated patients and one death in
12 controlled-treated patient. The mortality
13 rate was .4 percent in Injectafer as compared
14 to .1 percent in controlled.

15 For the data pool of six oral
16 iron-controlled studies, there were four
17 deaths in the Injectafer-treated patients and
18 no deaths in oral iron-treated patients. The
19 mortality rate was .4 percent for Injectafer
20 as a compared to zero percent for oral iron.

21 This slide summarizes the major
22 serious adverse event findings in the

1 clinical studies. Within a group of eight
2 multi-center randomized controlled studies,
3 the serious adverse event rates was the same.
4 3.6 percent in the Injectafer and in the
5 controlled groups. However, in the data pool
6 most pertinent to proposed marketing, the
7 oral iron-controlled studies, the serious
8 adverse event rate was numerically high in
9 the Injectafer-treated patients as compared
10 to oral iron-treated patients: a rate of
11 3.2 percent versus 2.5 percent.

12 This slide shows that the imbalance
13 in serious adverse event rate was generally
14 due to imbalance in serious cardiac or
15 infection rates. The small imbalance in
16 cardiac event rates is notable in line for
17 mortality imbalance in the Injectafer
18 program. Within that group of all eight
19 randomized controlled studies, the serious
20 cardiac event rates was 1.1 percent in the
21 Injectafer, was .8 in controlled.

22 As shown at the bottom of the

1 table, within a group of six oral iron
2 controlled randomized studies, there were
3 nine patients with serious cardiac events in
4 the Injectafer group, and three patients in
5 three patients with serious cardiac events in
6 the oral iron group. Specifically, the
7 serious cardiac event rate was .9 percent in
8 Injectafer group versus .4 percent in the
9 oral iron group. The nine Injectafer cases
10 include two fatal cases mentioned earlier,
11 and the seven non-fatal cases.

12 This slide shows the seven
13 non-fatal cardiac events in each patient and
14 the time of event in days after last
15 Injectafer dose. There was one patient with
16 a myocardial infarction and respiratory
17 arrest; three patients with congested heart
18 failure or pulmonary edema; one patient with
19 worsening coronary artery disease; one
20 patient with a serious cardiac event; and one
21 patient with a serious palpitation event.

22 As shown in the middle column, most

1 of these patients participated in studies of
2 patients with chronic kidney disease.
3 However, one subject was in the study of
4 postpartum patients. And the one subject was
5 enrolled in the study of patients with
6 inflammatory bowel disease. As shown in the
7 bottom of the table, there are three patients
8 with cardiac events in oral iron-controlled
9 groups, including two patients with
10 congestive heart failure and one patient with
11 cardiac ischemia.

12 The next few slides summarize the
13 hypophosphatemia findings. This slide
14 highlights are culled from a recently
15 published review of hypophosphatemia, and it
16 typifies the late assessment of the
17 condition. As noted in the publication,
18 hypophosphatemia has been implicated as the
19 cause of rhabdomyolysis, respiratory failure,
20 hemolysis and left ventricular dysfunction.

21 It also states that the high rate
22 of sepsis might result in part from acquired

1 dysfunctions in leukocyte chemotaxis and
2 phagocytosis secondary to hypophosphatemia.
3 The publication provides a recommendation to
4 treat a patient with a severe
5 hypophosphatemia of less than 1 mg/dl in
6 order to avoid potential detrimental
7 consequences of the condition.

8 In the Injectafer clinical studies,
9 there was one subject with heavy uterine
10 bleeding, had a nadir phosphate less 1 mg/dl
11 after Injectafer exposure. This was
12 classified as Grade 4 adverse event, using
13 common terminology criteria. CDC Grade 3
14 hypophosphatemia was common among Injectafer
15 exposure.

16 This slide shows occurrence of CDC
17 Grade 3 hypophosphatemia defined by serum
18 phosphorate between less than 2 mg/dl and 1
19 mg/dl. In two trials, in patients with
20 postpartum anemia, Grade 3 hypophosphatemia
21 occurred among 8 percent of Injectafer
22 patients as compared to zero percent of oral

1 iron patients.

2 In study for patients with heavy
3 uterine bleeding, the instance of Grade 3
4 hypophosphatemia was 17 percent Injectafer
5 patients, as compared to zero percent of oral
6 iron patients. In a crossover study, the
7 incidence of Grade 3 hypophosphatemia was
8 16 percent in the Injectafer group, as
9 compared to 9.9 percent in placebo group.

10 However, about half of placebo
11 patients had received the Injectafer early in
12 the study. In patient with known dialysis or
13 chronic kidney disease, in one controlled
14 study, the incidence of Grade 3
15 hypophosphatemia was 3.8 percent in
16 Injectafer patients, as compared to zero
17 percent in oral iron-controlled patients. In
18 another study of patients with chronic kidney
19 disease, in iron-controlled study, 7 percent
20 of patients had a Grade 3 hypophosphatemia.

21 As highlighted here, phosphate was
22 not a rigorous method in all available

1 studies. However, categorical analysis of
2 available data shows that overall adverse
3 event treated trended toward higher rates
4 with the low phosphate nadir. No similar
5 treatment was found for serious adverse event
6 rates. However, no phosphate values were
7 available after the Injectafer exposure for
8 all five cardiac deaths described early.

9 This slide summarizes our major
10 observations in terms of efficacy.
11 Injectafer has demonstrated efficacy in
12 increasing hemoglobin concentration in
13 clinical studies. However, our major concern
14 is clinical safety. Specifically, the
15 imbalance in mortality. In randomized oral
16 iron-controlled studies, four deaths occurred
17 in 1057 Injectafer patients, while no deaths
18 occurred among the 834 patients receiving
19 oral iron.

20 Importantly, these studies are most
21 directly applicable to the proposed market
22 population for the product. However, as 10

1 deaths were observed in Injectafer-exposed
2 subjects, one death in a Venofer-exposed
3 subjects, and no deaths in oral iron-exposed
4 subjects. The other problem is of a
5 mortality safety signal related to a small
6 imbalance in serious adverse events,
7 including cardiac and infection events and
8 the imbalance in occurrence of
9 hypophosphatemia.

10 This slide provides introduction to
11 the questions and the discussion topic for
12 later today. As noted here, we have
13 identified the three major topics for our
14 discussion. Firstly, we request a general
15 discussion of the Injectafer clinical data to
16 assess risk, if any, for mortality.
17 Subsequently, we request the committee to
18 vote upon whether you regard available data
19 as sufficient to support a favorable
20 risk-benefit profile for Injectafer
21 marketing.

22 Finally, if you recommend marketing

1 approval, what are the features of any
2 clinical studies that should be performed as
3 post-marketing commitments? If marketing is
4 not recommended, we request a discussion of
5 important features of any additional clinical
6 studies.

7 I thank you for your attention, and
8 I return the podium to Dr. Hennessy and the
9 Committee.

10 DR. HENNESSY: Thank you very much.
11 At this point, I'd like to thank the Committee
12 for your patience so far. I know that we've
13 been talking at you a lot and you haven't had a
14 chance to have any input; that will change
15 shortly. So now, we're going to have a sponsor
16 presentation on the risk management plan and the
17 plan for post-marketing surveillance.

18 Then we will have questions to the
19 presenters. First, the presenters from the
20 Food and Drug Administration; then the
21 presenters from the sponsor.

22 I'd like to try to keep those as

1 separate as possible, knowing that that won't
2 be completely possible. And for the
3 questions to the sponsor, I'd like to divide
4 those up as much as possible into the
5 following categories, and take them in this
6 order.

7 First, questions about clinical
8 benefit of the drug given the existence of
9 other marketed iron products. The second
10 category would be questions about the risk of
11 the product. The third category would be
12 questions about the risk management program
13 and plans for post-marketing safety
14 surveillance, and then fourth question's
15 about the overall risk-benefit balance of the
16 product given the existence of that risk
17 management plan.

18 So at this point, it looks like
19 Dr. Elizabeth Andrews is going to talk to us
20 about the risk management plan and plans for
21 post-marketing safety surveillance.

22 DR. ANDREWS: Great, thank you.

1 Slide one, please. Well, first of
2 all, I'd like to say that we believe that
3 we've not identified specific safety risks in
4 the population that is intended for this
5 indication -- the population of women with
6 postpartum anemia and heavy uterine
7 bleeding -- and we don't anticipate that we
8 will see an increased risk of serious adverse
9 events. However, we do want to take a
10 reasonable approach to risk management.

11 The serious adverse events that
12 have been seen in the trials don't represent
13 particular kinds of risks that are amenable
14 to management by screening out people with
15 particular high-risk characteristics or
16 taking specific action as has been done for
17 some other products that have risk management
18 programs.

19 So our proposal is for a gradual
20 product rollout to assure that patients who
21 receive treatment are those for whom the
22 benefits will outweigh treatment.

1 Next slide, please. And this is
2 just a schematic showing the general flow of
3 information in the risk management program.
4 We are suggesting that patient selection be
5 a narrower population than the population
6 studied in clinical trial. The rollout would
7 initially be to a smaller group of targeted
8 physicians, supplemented by physician
9 education, patient education. We will have
10 an active program of evaluating the
11 effectiveness of the risk management program.
12 And based on information obtained in that
13 program evaluation, we'll take necessary
14 action to change the program appropriately
15 and continue monitoring -- all the while we
16 are also monitoring safety. And I will go
17 into these different components next.

18 So the goals of the program are to
19 assure the use of FCM in patients who meet
20 the criteria that you saw in your briefing
21 document. So it's a slightly more limited
22 population than in the trials, and the

1 patients for whom we and a number of experts
2 who contributed to the development of these
3 thoughts suggest were the ones who could most
4 benefit from treatment. And we will
5 reinforce that by assuring that providers and
6 patients are well-informed regarding the
7 appropriate use of the product, and then
8 provide quantitative data on safety.

9 So the way we will start out is by
10 making sure that the product is rolled out to
11 a selected group of physicians initially.
12 And the market research that Luitpold has
13 already conducted suggests that the
14 practitioners who are most likely to
15 administer FCM are those who are already
16 administering intravenous irons, and include
17 hematologists, hematologists oncologists,
18 internists practicing in hospitals and fusion
19 centers and clinics that have the appropriate
20 staffing -- patient-monitoring activities to
21 administer FCM safely.

22 We now that they there were a

1 number of ObGyns who participated in the
2 clinical trial program. We are not
3 suggesting that we limit and not allow access
4 to individuals who have already been
5 well-trained. The rollout would be expanded
6 later to ObGyns who could then refer to this
7 initial group of physicians who could
8 administer the product.

9 That rollout will be supported by
10 physician education materials that will be
11 carefully tested in advance. A lot of
12 physician communication. Dosing cards, CME
13 programs, and actually onsite training by a
14 group of clinical support specialists
15 including nurses and pharmacists who already
16 exist and do this kind of work.

17 Luitpold is already familiar with
18 this group of practitioners because they
19 already are in this market and provide this
20 kind of support. So this would be rolled out
21 to a limited group of clinicians initially.

22 And then to assure appropriate

1 patient selection, you saw the criteria
2 before -- the physician education will
3 highlight the need -- the patient selection
4 criteria and the appropriate -- and then
5 there will also be physician education around
6 patient education, be a medication guide and
7 other information targeted for patients,
8 including a brochure that's already been
9 developed, targeted to patients on
10 hypophosphatemia. Describes hypophosphatemia
11 as well as the clinical findings from the
12 study.

13 So the key messages relate to
14 appropriate patient selection, dosing
15 precautions, non-adverse reactions, and the
16 importance of reporting to the company any
17 serious adverse experiences. The key
18 messages for patients relate to patient
19 selection, risks and benefits, and awareness
20 of the signs and symptoms of potential
21 adverse events and actions they should take,
22 like seeking -- contacting their physicians.

1 So as we evaluate the program, the
2 evaluation program -- we'll attempt to
3 compare the objectives of the program with
4 actual practice. It will start with
5 evaluating the utilization patterns among
6 physicians, through provider studies that
7 look at -- and here we anticipate -- I should
8 have said earlier -- this is still a program
9 that is still very much in development, so we
10 certainly welcome the committee input here.

11 We can look through existing market
12 research kinds of databases to see who's
13 actually using the products by specialty,
14 geographic location, clinic setting, and can
15 compare the actual use against the target
16 utilization that was guided by the risk
17 management program. Likewise, we can look at
18 the patient characteristics through using
19 existing electronic medical databases or
20 perhaps surveys to compare the patient
21 characteristics that are intended with the
22 people who actually receive the product.

1 And then on a regular basis, the
2 company would evaluate the information coming
3 from that evaluation and decide if there is
4 evidence of non-compliance. If there is,
5 then what's the root cause of that? Is it
6 because of insufficient education or
7 misunderstanding of educational materials?
8 And then they can take action to further
9 reinforce the appropriate use.

10 We also anticipate that there would
11 be an evaluation of the educational
12 effectiveness. So in addition to the
13 utilization studies, there would be some
14 surveys -- slide RN 15, please.

15 And these are fairly routine
16 methods of evaluating whether their
17 physicians understand the messages that are
18 intended by the educational materials, as
19 well as patient surveys relating to the
20 knowledge regarding patient selection risks
21 and benefits, and early signs of adverse
22 events and what action they should take. So

1 we hope that in the development of the
2 education materials and then in the actual
3 use, we can make sure that people are
4 understanding the messages.

5 On to the safety evaluation.
6 That will have a couple of different
7 components. First of all, there are
8 post-approval safety standards studies that
9 are either planned or ongoing. And
10 Dr. Mangione has already mentioned
11 post-approval randomized trials. And I'll
12 spend a few minutes talking about the
13 proposed patient registry.

14 And then there's the potential for
15 long-term monitoring using electronic records
16 such as electronic medical records,
17 databases. But of course, a fundamental part
18 of the risk management program is enhanced
19 pharmacovigilance, because events that occur
20 rarely are most likely to be detected first
21 through the spontaneous reporting data set.

22 So the company will be developing

1 follow-up forms for events of special
2 interest to make sure that if calls come in
3 about those events, there can be immediate
4 follow-up asking the specific questions that
5 will help get at a better understanding of
6 the sequence of events and the clinical
7 aspects of the events.

8 So now I'd like to talk about this
9 patient registry. The objectives of this
10 cohort study, I prefer to call it, are to
11 monitor for the occurrence of previously
12 unidentified serious events associated with
13 the use of FCM, and then to
14 monitor -- evaluate frequency of risk factors
15 for events of special interest. And again,
16 this is a study that's still in development,
17 has not been discussed with Food and Drug
18 Administration. So we're in the preliminary
19 stages and welcome input. So we've
20 identified some of the types of events that
21 we'd like to monitor for including serious
22 cardiac events, serious cases of

1 hypersensitivity, cutaneous disorders not
2 seen in the randomized trial, that we will
3 make sure that we can evaluate, detect these
4 events that if they occur at a frequency of
5 one out of a thousand or greater.

6 So the design of the study is -- we
7 have a cohort study of new users, not
8 including anyone who has previously used FCM.
9 And there would be a comparison group of
10 similar patients not receiving FCM, and this
11 is perhaps the most challenging part, because
12 we would anticipate that people get FCM for a
13 reason, and those reasons might make them
14 very different from people not receiving FCM.

15 So we're considering several
16 different possible comparison groups.
17 Concurrent comparison group in the centers
18 that are administering FCM, a concurrent
19 comparison group in centers that have similar
20 patients but who are not using FCM, and
21 perhaps a historical cohort in the same
22 centers that are using FCM.

1 So the outcomes would be the events
2 of special interest that I noted before and
3 any serious events. The follow-up would be
4 between 30 and 45 days after the last dose.
5 And we anticipate we'd be able to follow-up
6 all of the patients. But in the event that
7 we're unable to track all patients, then we
8 could link with vital records to identify any
9 deaths in patients who were not available for
10 a follow-up.

11 So in terms of sample size
12 considerations, we anticipate that the number
13 of FCM users to be monitored would be 3000.
14 And what this does is it gives us the ability
15 to detect events that occur one out of a
16 thousand, or if there are no serious adverse
17 events of a particular type, we can conclude
18 with 95 percent confidence that the absolute
19 risk of that event is one out of a thousand
20 or less.

21 This sample size and power curve
22 also shows the ability to detect increased

1 relative risks with the sample size, and you
2 can see that with 6000 patients, 3000 in each
3 group, we'd have about 82 percent power to
4 detect a relative risk of three.

5 We also gave serious consideration
6 to the design of a study that could help rule
7 out an increase in mortality risk, which I
8 mentioned earlier. If we assume that the
9 baseline mortality rate in the patient
10 population is similar to the rate in the
11 general population of women of childbearing
12 age, that rate is pretty low.

13 And so if we design a study with
14 the intent of assuring that the 95 percent
15 confidence interval upper limit is less than
16 two, would require, we estimate, 320,000
17 women, half in each arm, which is probably
18 quite a few more than will be receiving
19 treatment for many years.

20 So we did not consider that that
21 design was at all feasible.

22 So I think that's all on that.

1 DR. HENNESSY: Thank you very much,
2 Dr. Andrews.

3 So at this time, we're actually
4 going to open up the floor for questions from
5 the committee, first to the Food and Drug
6 Administration.

7 And I think that we could try to do
8 this by putting your microphone light on, and
9 if we start getting too much feedback, we can
10 try a different method. But for now, let's
11 try that. Put your microphone on if --

12 And we'll start with Ms. DeLuca?

13 MS. CORKERY-DeLUCA: Yes.

14 This would be a question for
15 Dr. Suh.

16 Talking about the different groups
17 that you had listed, do you have any idea of
18 the hardship of somebody that's -- that most
19 of those patients coming into the hospital
20 are coming in IBD or coming in an horrible
21 condition, how they can possibly take those
22 horse-sized tablets? Iron tablets are not

1 like prednisone. They're not small; they're
2 gigantic.

3 I recognize it's been the first
4 line of defense, but I think part of the
5 failure for people to not follow what they
6 should, their obligation to their doctors'
7 orders are because they just experience
8 failure early on in being to swallow enough
9 pills and then give up. And --

10 DR. HENNESSY: Did you want to let the
11 FDA respond to that, and you're welcome to ask a
12 follow-up if you have that.

13 DR. ROBIE-SUH: I think you're asking
14 about the difficulty of complying with oral
15 iron therapy? Certainly that has been and
16 continues to be an issue with the use of oral
17 iron. It requires a bit of dedication to comply
18 very well with an oral iron regimen. But it can
19 be done. I think in a couple of the studies
20 that were done as non-inferiority studies, that
21 was shown.

22 But in actual clinical practice,

1 the compliance there certainly varies
2 considerably.

3 MS. CORKERY-DeLUCA: Your chart was so
4 low, and I think if you're looking at the IBDS
5 or the chronic kidney disease, you're looking at
6 people that not just compliance is low, it's the
7 inability to take the pill is impossible.

8 DR. ROBIE-SUH: Certainly people who
9 are unable to take oral iron -- those are the
10 populations for whom currently the parenteral
11 iron preparations are used.

12 MS. CORKERY-DeLUCA: How successful is
13 that, particularly with the postpartum as well
14 as with the -- because I would assume that the
15 postpartum and the women with a heavy uterine
16 bleeding are pretty disabled themselves. So I'm
17 trying to gauge how possible it is to get enough
18 iron to survive and to do well and thrive, yet
19 not to have it pool in some organ?

20 DR. ROBIE-SUH: Maybe I could address
21 this a little bit to talk about the differences
22 between the approved products. They have

1 different labeled indications. But I guess I
2 probably should point out that it's not because
3 the newer products failed under other clinical
4 settings. The labeling of the newer products
5 reflects the restricted clinical settings in
6 which those products were studied. I think in
7 current practice, the hemodialysis setting is
8 the most common setting where parenteral iron
9 products are used now.

10 MS. CORKERY-DeLUCA: Thank you.

11 DR. HENNESSY: Dr. Macik, did you have
12 a question?

13 DR. ROBIE-SUH: And their utility
14 there is certainly very well-established.

15 DR. HENNESSY: Dr. Macik, did you have
16 your light on?

17 Dr. Brittenham?

18 DR. BRITTENHAM: Yes, I'd like to ask
19 a couple of inter-related questions. The first
20 has to do with what's -- this is probably for
21 Dr. Lu -- what's the size of the population that
22 we're discussing? What's the total number of

1 doses or patients per year that would be treated
2 with this product if it were approved? We
3 certainly can't know for sure, but some
4 estimate.

5 DR. LU: I think based on sponsor's
6 data, they mentioned about 10 percent of
7 postpartum women will have iron deficiency
8 anemia -- based on sponsor's earlier data. Also
9 mentioned, 10 to 15 percent heavy uterine
10 bleeding patient will need the iron
11 replenishment.

12 DR. BRITTENHAM: But do we have any
13 idea how many this is? Is it a hundred, a
14 hundred thousand, a million?

15 DR. LU: I think it's --

16 DR. RIEVES: This is Dwaine Rieves.
17 Those are good questions, and I'm sure
18 especially with the risk management plan that
19 has this targeted marketing rollout, some of
20 those considerations -- I wonder if Luitpold
21 actually could give more-specific numbers.

22 As you have noted, the sample size

1 estimated -- and these are very rough
2 estimates -- is very large, potentially. But
3 in terms of the numbers, I suspect Luitpold
4 could plug some of the -- perhaps more exact
5 numbers.

6 DR. HENNESSY: And just to clarify,
7 this would be numbers of what?

8 DR. RIEVES: The potential market
9 population, I think.

10 DR. BRITTENHAM: The number of doses
11 per year to be administered. Or number of
12 patients per year, just how many --

13 DR. HENNESSY: Sure. Why don't we
14 invite the sponsor to help us out with that if
15 they have that information.

16 DR. ANDREWS: I think the numbers that
17 you gave are absolutely accurate, in about 10 to
18 15 percentage of women. But I believe the
19 question wanted a little bit more in terms of
20 number of patients or infusions.

21 So if we estimate that somewhere
22 between 20 to 40 percent of women will fail

1 an attempted oral iron therapy, we could be
2 looking at a population of about 520,000 to
3 840,000 women with anemia due to heavy
4 uterine bleeding that may require treatment
5 options other than oral iron.

6 DR. HENNESSY: And that's per year?

7 DR. ANDREWS: Yes.

8 DR. HENNESSY: Did you have a
9 follow-up question?

10 DR. BRITTENHAM: Yes, I do. To put
11 perspective on this, if I interpret it
12 correctly, there's a paper by Chertow et al from
13 2006 that went through the MedWatch database and
14 explained that there were approximately 30
15 million doses of IV iron that had been
16 administered, about 10 million a year.

17 One question is, this estimate of
18 half a million to a million women a year,
19 does that envision the FCM replacing oral
20 iron, or is it to be used only in patients
21 after they fail oral iron?

22 DR. RIEVES: The question before the

1 committee is whether this product is safe and
2 effective as an alternative first-line treatment
3 for iron deficiency anemia in this patient
4 population.

5 DR. BRITTENHAM: So that it could be
6 advocated or promoted as a first-line treatment.

7 DR. RIEVES: That is correct. If the
8 proposed indication is for first-line treatment,
9 and it could be marketed specifically for that
10 first-line treatment.

11 DR. BRITTENHAM: This is really for
12 the FDA, because this is data from the MedWatch
13 program -- just to give me perspective on the
14 magnitude of these risks is the motivation
15 behind the question, because in the same
16 article, they identified the level of the risk
17 per million doses of -- identified from the FDA
18 MedWatch database as being .6 for sucrose, .9
19 for gluconate; for low-molecular weight iron
20 3.3, and for high-molecular weight iron 11.3,
21 per million.

22 And if I understand this, we've had

1 10 deaths in 2,000 people. Is that a fair
2 statement of the --

3 DR. RIEVES: That is a general
4 characterization of the data -- that correlates
5 with our concern, and the question we'll forward
6 it to the committee --

7 DR. HENNESSY: Right.

8 DR. BRITTENHAM: One final question
9 is, is there a concern or -- how would the risk
10 of off-label use; that is, if you have half
11 million to a million women for whom this is
12 approved, but the total number of doses of 10
13 million a year are being used mostly for
14 hemodialysis patients, is there a risk that if
15 we approve this for the stated indication, that
16 there will be off-label use for the much more
17 common indication?

18 DR. RIEVES: Your question is very
19 pertinent from a regulatory standpoint. We have
20 asked ourselves that also. And one would think
21 that physiologically -- why is there any reason
22 this product would not work in other situations

1 of iron deficiency anemia?

2 And we've not come to a medical
3 reason as to why it should not work. So your
4 point about off-label use is very pertinent
5 to the considerations.

6 DR. HENNESSY: Dr. Davis and
7 Dr. Harrington -- oh, there's another response
8 from the Agency.

9 DR. ROBIE-SUH: Just one additional
10 comment about the MedWatch -- this is from our
11 Office of Drug Safety folks -- with
12 post-marketing reports, spontaneous reports,
13 there's little danger in trying to
14 calculate -- even when you know doses that have
15 been distributed, you'll have to be a little
16 careful about calculating actual rates of
17 events, because the reports are spontaneous, and
18 we're not sure of denominators or numerators.

19 DR. BRITTENHAM: Right, but there's a
20 big difference between 10 per 2,000 and almost
21 11 per million.

22 DR. ROBIE-SUH: Quite certainly.

1 DR. HENNESSY: Dr. Davis and
2 Dr. Harrington. Then we'll see whether
3 Dr. Greenland on the phone has any questions.

4 DR. DAVIS: I don't know whom these
5 are for, maybe Dwaine or Dr. Suh. These have to
6 do with risk and safety.

7 First of all, as a curiosity, I
8 have three questions. Are there any
9 contraindications either for individuals or
10 for other drugs or supplements in having this
11 injection?

12 DR. RIEVES: With respect to proposed
13 contraindications? I'm trying to remember if
14 Luitpold has actually proposed any
15 contraindications. Usually, known
16 hypersensitivity is a contraindication.

17 Just off the bat in terms of the
18 issues identified here, I don't recall any
19 contraindications from the proposed labeling.
20 But again, our labeling development is very,
21 very contingent upon this committee's
22 conclusions here.

1 DR. HENNESSY: Why don't we ask the
2 sponsor to address the question about
3 contraindications?

4 DR. TOKARS: Currently, the three
5 contraindications are for patients that have a
6 known hypersensitivity to ferric carboxymaltose,
7 or evidence of iron overload, or anemia not
8 related to iron deficiency.

9 DR. DAVIS: These are just background
10 contextual -- what do you all know of these
11 infusion centers? Who does the infusion? How
12 closely are they hooked up to the prescribing
13 physician? Do they receive the risk management
14 education in the infusion centers?

15 DR. RIEVES: The concept of delivering
16 Injectafer solely in infusion centers is not a
17 topic that we've addressed with the company,
18 this approach. Because in essence, what we're
19 talking about in this aspect of marketing is
20 almost a form of a restricted distribution
21 program, if you will.

22 We appreciate the concern, because

1 many in our oncology office actually do have
2 important infusion-related risks to them, as
3 you have seen -- actual infusion-related risk
4 here -- not especially novel with respect to
5 the very acute-type reactions to the product
6 either during or just within a few minutes
7 after its administration.

8 Conceptually what we envision is
9 that especially for in the situation of
10 postpartum women, the need, as we all know,
11 is for a very simple single dose of iron to
12 replace the iron deficit, which conceivably
13 would be administered shortly before going
14 home from the hospital with a new baby.

15 That is what we envision as one of
16 the considerations for delivery of the
17 product.

18 DR. HENNESSY: Do you want to hold on
19 to that question and ask that again at the
20 sponsor session?

21 DR. DAVIS: Can I ask one more?

22 DR. HENNESSY: Sure.

1 DR. DAVIS: This is just a background
2 about what you all have learned in general. I
3 know we haven't voted on this yet. But about
4 black boxes, about their efficacy in
5 decision-making for physicians or patients.

6 You think Black Box Warnings are
7 helpful or --

8 DR. RIEVES: This is an opinion. We'd
9 like to think they are useful. There have been
10 more and more. Safety has been a major focus of
11 FDA concern over the last couple of years in
12 particular. But we do try to reserve the use of
13 boxed warnings for the most essential safety
14 information and considerations. We like to
15 think -- of the entire label, physicians and
16 prescribers do pay attention to those boxed
17 warnings.

18 DR. HENNESSY: Dr. Harrington?

19 DR. HARRINGTON: I too have a series
20 of questions -- they're just trying to put for
21 me the balance of the risk and the benefit here.

22 If maybe Dr. Suh or Dr. Rieves

1 could clarify for me -- the basis of approval
2 for all of the previous iron products as well
3 as what the agreement is with this sponsor is
4 strictly related to a change in hemoglobin.

5 Is that correct?

6 DR. RIEVES: That is correct. An
7 increase in hemoglobin -- correction; of
8 anemia -- most products used in the treatment
9 of --

10 DR. HARRINGTON: I just want to
11 clarify that that there's been no requirement
12 for measuring quality of life improvement,
13 avoidance of transfusion, et cetera?

14 DR. RIEVES: That has not been a
15 requirement. We're looking at somewhat of a
16 minimal expectation here for employing anemia
17 treatment drug.

18 DR. HARRINGTON: My second question is
19 for Dr. Lu is that you nicely presented to us a
20 look at the mortality and the cardiac events,
21 and you presented them separately.

22 Given the infrequency, did you do

1 any analysis where you combined these in a
2 composite of death plus the serious cardiac
3 events? I can add them up, but I'm just
4 curious if you did any formal analysis.

5 DR. LU: I think that table -- we have
6 one slide, "Serious Adverse Events."

7 The oral iron control trials
8 .9 percent versus .4 percent -- oral
9 control -- all randomized trials is 1.1
10 compared with .8, that's included as and also
11 cardiac events.

12 DR. HARRINGTON: The cardiac event?

13 DR. LU: Yes.

14 DR. HARRINGTON: My next question, I
15 think the sponsor said that -- and I remember
16 reading in one of the documents that the drug
17 has been approved for use in 19 countries,
18 though if I remember right, it's actually only
19 being used in one.

20 Does FDA have access to any of to
21 EMEA post-marketing experience with this
22 drug?

1 DR. RIEVES: We can obtain access to
2 this. And correct me, Luitpold, if I'm
3 misspeaking. The indication approved in EMEA is
4 different from the indication proposed for
5 marketing here in the United States. And again,
6 if I read the documents correctly, it's not
7 approved for first-line treatment in Europe.

8 Is that correct? And as I
9 understand, the product launch apparently has
10 only been in one country so far.

11 DR. HARRINGTON: That's correct.

12 DR. RIEVES: So we have very --

13 DR. HARRINGTON: So very little
14 ex-U.S. experience?

15 And then I want to follow-up on
16 something that Dr. Brittenham had asked which
17 I think is important. These are in fact
18 relatively narrow populations, though
19 Dr. Ford I think suggests that its
20 potentially a big population overall.

21 What's the history of the
22 prescribing of these drugs by these types of

1 physicians? I'm an interventional
2 cardiologist and we're an off-label group of
3 people.

4 What's the experience with this
5 group of physicians? Are these off-label
6 physicians or are these physicians who are
7 going to stick to what the indication is?

8 DR. RIEVES: I think we're getting
9 into opinions here, and I'm sure all of us have
10 different opinions.

11 DR. HARRINGTON: Most of this is, so
12 that's good.

13 DR. RIEVES: So given the proposed
14 indication -- and I think there's no question,
15 and we -- the FDA supports the need for a
16 simple, effective and safe product that can be
17 administered to treat iron deficiency anemia,
18 especially in the postpartum situation where
19 there may only be a need for one or two
20 injections here.

21 We anticipate, much as everyone
22 here I think reasonably could anticipate,

1 this would, because of the convenience
2 factor, have a substantial market population.
3 And it gets into some of the deliberations of
4 how to construct a label.

5 For example, if we had a boxed
6 warning for mortality, though, on a product
7 that was supposedly marketed as safe as an
8 alternative to oral iron, one would have to
9 question the logic in that approach, I think.
10 So we're somewhat in a conundrum here of how
11 to move forward with the proposed indication.

12 We don't have a simple answer to
13 that question.

14 DR. ROBIE-SUH: If I could comment as
15 well, since we've admitted these are opinions.

16 As Dr. Rieves said, we worked very
17 hard to try to make sure we have accurate,
18 informative labeling. But once a product is
19 approved and put out on the market, we don't
20 really regulate the practice of medicine
21 other than when very bad things happen -- of
22 course, they come back and we deal with

1 those.

2 But in terms of overseeing the
3 individual use of products by physicians,
4 that's not something the Agency is charged
5 with.

6 DR. HENNESSY: Dr. Greenland, welcome.
7 Can you hear us okay?

8 DR. GREENLAND: I've been on for about
9 an hour, I don't know if you've noticed? I hear
10 the speakers okay and I hear you. Most of the
11 rest, I'm not able to make out what's being
12 said.

13 DR. HENNESSY: We'll see what we can
14 do about getting you to hear us better. So you
15 can hear me and you can hear other people when
16 they talk into the microphone directly, it
17 sounds like?

18 DR. GREENLAND: I hear the speakers
19 doing the presentations, and most of the rest is
20 too muffled to make out.

21 DR. HENNESSY: Did you have any
22 questions for the FDA?

1 DR. GREENLAND: I'm new to this. And
2 I had a general comment, a question that I'm not
3 sure where it would fit in, especially as I
4 can't get oriented because I can't hear what
5 else is going on.

6 DR. HENNESSY: You want to try it now?

7 DR. GREENLAND: My impression, based
8 on looking at the materials and hearing the
9 presentations and what little I can make out
10 elsewhere was that the primary concern here was
11 the mortality, and that -- the central issue
12 here about whether the approval could take place
13 with contraindications for particular patients
14 that might have cardiac risk factors?

15 DR. HENNESSY: I'm not sure if that
16 was -- I mean, that was one way of framing the
17 question. I'm not going to endorse that framing
18 of the question, nor am I going to disagree with
19 it.

20 Does anybody at the Agency want to
21 take a stab at that?

22 DR. RIEVES: That's going to be a part

1 of our subsequent discussions. So we will cover
2 that topic.

3 DR. HENNESSY: It seems like there's a
4 limit to the number of microphones that are on.
5 So remember to turn yours off when you're done
6 speaking.

7 We'll go to Dr. Burlington.

8 DR. BURLINGTON: I have two related
9 questions for Dr. John and Dr. Lu.

10 It appeared from the
11 pharmacokinetic data that was presented that
12 almost all the events of interest that we've
13 been exploring this morning and discussing
14 occurred sometime after the drug was cleared
15 from the bloodstream. And that at least
16 suggests to me that we need to be looking at
17 secondary mechanisms to account for the
18 events.

19 And I'd like you to comment on
20 that. But let me ask my question of Dr. Lu
21 first.

22 You presented information from the

1 Nature of Clinical Practice Review of 2006
2 about hypophosphatemia. And in that, there
3 were multiple mechanisms or manifestations of
4 Hypophosphatemia presented -- rhabdomyolysis,
5 respiratory failure, hemolysis, LV
6 dysfunction and infection.

7 I guess we have a case of
8 respiratory failure, we have a couple of
9 cases of LV dysfunction, and we certainly
10 have some infections. Was there any evidence
11 of rhabdomyolysis, or any evidence of
12 hemolysis in this study population?

13 DR. LU: I'm not aware of any report
14 about that, if the sponsor has some -- any
15 detailed data.

16 DR. BURLINGTON: Dr. John, what about
17 the relation between blood serum levels and
18 these events we're talking about?

19 DR. JOHN: You're absolutely right.
20 The serum ferritin -- the total serum iron
21 concentration has come down to the baseline
22 level by about 60 to 48 hours. However, when we

1 look at the transfer in saturation in serum
2 ferritin -- transfer in saturations levels are
3 high, up to 70 percent after subtracting
4 baseline up to 72 hours post-injection. And
5 serum ferritin levels, the maximum that we've
6 seen that was reported to us by sponsor, I see
7 that 96 hours and -- 120 hours.

8 DR. HENNESSY: Dr. Macik?

9 DR. MACIK: A couple of questions.
10 First, I'd like to start with Dr. John, and one
11 implication that I perceived from your
12 presentation was a reference to how high the
13 ferritin levels were, and these were out of the
14 normal range.

15 And so I was wondering, were you
16 implying that being out of the normal range
17 would be equivalent to a clinical problem or
18 just noting that they were higher?

19 DR. JOHN: We really don't know the
20 clinical consequences. All we're saying is we
21 noticed that levels were fairly high as compared
22 to the normal healthy volunteers.

1 DR. MACIK: The question I guess that
2 I would pull out of that also is that I got a
3 strong feeling -- the implication that would
4 bad; we really don't know that.

5 We know that in other
6 situations -- and I could defer to others
7 that know even more -- that we don't see
8 clinical problems with high ferritins until
9 they're much higher than what was obtained in
10 the study -- if you are going to use a
11 ferritin level alone -- whether that's really
12 a good marker.

13 DR. JOHN: We don't know that for sure
14 clinically.

15 DR. MACIK: Another question -- and
16 actually prompted a bit by an earlier question.

17 I'm a treating hematologist,
18 frequently use intravenous heparin -- I'm
19 sorry, heparin, too, but iron. And one of
20 the reality checks here is that we frequently
21 have a need for an intravenous product. Now,
22 I will see a selected group of

1 people -- typically those who had already
2 tried oral iron by their primary care
3 physicians, then get referred to me for
4 additional work-up.

5 I would be very interested in your
6 own collection of data, how often the package
7 insert dosing schedule for iron dextran is
8 actually followed, because I cannot remember
9 a time that I've used 100 milligrams of IV.

10 And so I guess one of the concerns
11 that I would raise to the FDA is do you
12 have -- there are statements that well, we do
13 have other products you can use to try to
14 avoid off-label use of this product -- but I
15 think it would be a real challenge in those
16 of us already using higher levels of IV iron
17 not to look at a product that appears much
18 safer than the current product.

19 And so have you any feedback? Do
20 you have an idea of how much off-label use of
21 higher doses of IV iron -- to put this in a
22 question form, Dr. Suh.

1 DR. ROBIE-SUH: We have no database at
2 the Agency that assesses off-label use. What we
3 can do is look at the post-marketing reports of
4 adverse events that quite often are rather
5 incomplete. Occasionally, there is dosing
6 information there regarding how a product was
7 used.

8 But it's certainly not anything
9 that could be used with any degree of
10 quantitative authority, if you will, to
11 estimate. That might be something that
12 actually more an epidemiologic type of
13 evaluation or something could be done by
14 people in practice.

15 DR. HENNESSY: Dr. Klein?

16 DR. KLEIN: I'm going to confine
17 myself to factual questions rather than asking
18 your opinions, but they're important ones.

19 Do you have any additional data,
20 except for what you showed us and what we've
21 seen today -- either from European studies
22 that haven't been given to us or data that

1 you consider proprietary -- that gives a
2 signal that we should be concerned about with
3 this specific drug?

4 DR. RIEVES: No, sir. We have
5 presented all the data that we have here in
6 terms of relevance. There are no other data
7 that we've been supplied with that impact --

8 DR. KLEIN: As sort of a follow-up to
9 Dr. Harrington's question, are there European
10 studies, are there European data aside from the
11 German post-marketing data that are available?

12 DR. RIEVES: It has not been supplied
13 to us. We are not aware of other data.

14 DR. KLEIN: My second question is
15 somewhat related, and that is, are you concerned
16 about a class effect? Do you have data that
17 we're not are privy to right now from other
18 injectable iron preparations that suggest that
19 there may be a class effect from injectable iron
20 preparations?

21 DR. RIEVES: That is a lingering
22 question for some of the other -- the parenteral

1 iron products. The parenteral iron products
2 have very specific indications -- especially
3 with respect to iron dextran, where iron dextran
4 is more of a second-line treatment -- and that
5 question has been I think in this field for
6 many, many years.

7 But right now, we cannot come to
8 conclusions with respect to comparisons
9 between these parenteral iron products and
10 oral iron, primarily just because they've
11 largely been developed -- not for the patient
12 population who would otherwise be treated
13 with oral iron, they were more second-line.

14 DR. KLEIN: So even with the millions
15 of reports or millions of uses a year, you don't
16 have reports that would suggest there's a class
17 effect that we should be concerned about?

18 DR. RIEVES: It's so difficult since
19 we don't have comparators, if you will, to come
20 to conclusions in that, and oftentimes the
21 background rate of deaths -- it's so high, it's
22 very difficult to dissect out from the

1 epidemiologic uncontrolled data.

2 DR. KLEIN: And finally, I'm assuming
3 that if there's a problem, it is going to be a
4 problem -- that is secondary processing and not
5 primary -- but just to make me feel a little bit
6 more comfortable, I'm assuming that the
7 structure you showed us and when you analyze
8 what's in the bottle, it's very homogeneous and
9 no other additional little --

10 DR. JOHN: That's correct.

11 DR. KLEIN: Thank you.

12 DR. HENNESSY: Dr. Black?

13 DR. BLACK: Thanks very much. I have
14 a question. This is also primarily an
15 opinion -- coming from the same off-label
16 community that Dr. Harrington comes from. And
17 we have to assess a risk-benefit, and I'm also
18 making the assumption that this will be used
19 extensively in hemodialysis settings and other
20 settings rather than what the label says.

21 So I just wonder, if you've a),
22 done any analysis of how many transfusions

1 might be avoided, how many doses of
2 erythropoietin might be avoided, in that kind
3 of population?

4 And then one specific question: I
5 think the number we got was a .87 increase in
6 mortality based on that one case really. How
7 many deaths would that mean if it's used in
8 postpartum, or used in high uterine bleeding?

9 DR. HENNESSY: Has anybody at the
10 Agency crunched those numbers?

11 DR. RIEVES: We're in the realm of
12 speculation again.

13 DR. HENNESSY: Exactly.

14 DR. RIEVES: No, we have not gone to
15 the length of speculating. Again, those are
16 very good questions. But candidly, we do not
17 have the databases to address them. The source
18 database is simply not there. We can only
19 speculate, and I think that the tone of the
20 questions -- we all appreciate the potential for
21 off-label use here -- is very substantial -- and
22 as well as the market patient population there.

1 But in terms of quantitative answers to these
2 type questions, we do not have those answers.

3 DR. BLACK: Just a couple of other
4 things. I can imagine that the urgency for
5 someone who just delivered an infant, to make
6 sure that her hematocrit is reasonably good
7 during the early newborn's phase is a little
8 different than someone who has heavy uterine
9 bleeding on a somewhat chronic basis who might
10 be able to try oral medicine and only uses it
11 if it failed as opposed to someone who was going to
12 leave the delivery suite, get her injection and
13 then go home.

14 I can imagine that that's probably
15 going to become a common practice if this
16 becomes safe. So I don't know if we have
17 enough information about how those two
18 separate populations might respond.

19 DR. HENNESSY: Was there a question in
20 there?

21 DR. BLACK: Yes. Would you be willing
22 to consider analyzing this separately, or

1 possibly having a label where you only gave this
2 to people with heavy uterine bleeding who had
3 failed oral therapy, as opposed to people who
4 are postpartum, where there's a certain amount
5 of urgency to get that treated during those
6 first few months?

7 I think there was a compelling case
8 made in what we got about the importance of a
9 recently delivered mother being as on her
10 game as she can during those early weeks of
11 the newborn's life.

12 DR. HENNESSY: For the Agency, can you
13 crystallize that question? I'm not sure I'm
14 getting it.

15 DR. BLACK: We're all clearly
16 speculating.

17 But could there be a different
18 label for heavy uterine bleeding as opposed
19 to postpartum?

20 DR. RIEVES: Multiple options are on
21 the table for discussion. We're going
22 to -- that's actually along the lines of one of

1 our key questions to the committee.

2 If the proposed indication does not
3 have an acceptable risk-benefit, then what
4 about another indication. We actually
5 outlined that in the questions.

6 DR. HENNESSY: Dr. Paganini?

7 DR. PAGANINI: My question for the
8 FDA. The vast majority of deaths were
9 CKD-related or CKD-generated or CKD-associated
10 patients, the company has pulled that from their
11 proposal and asked that the drug be used only in
12 the postpartum, in heavy uterine bleeding group,
13 where the mortality statistics tend to be a
14 little bit less onerous.

15 But again, going with the off-label
16 issue that we're all struggling with, when
17 and if this drug is used in the peritoneal
18 dialysis population where one of their
19 associated placebos, Venofer, was used at
20 higher dose to avoid folks having to come
21 back and getting multiple IV iron injections
22 in the home dialysis population, specifically

1 PD -- this drug would obviously be targeted
2 in that area, even albeit off-label.

3 So is it appropriate for us to not
4 consider, although we're considering
5 obviously in the mortality -- CKD mortality
6 data, but in the proposed labeling target a
7 population that has a very low mortality?
8 Shouldn't we especially, from the thought
9 process of off-label indications for iron
10 deficiency, look at all mortality and decide
11 based on all mortality as opposed to a
12 subgroup of those that have less of a
13 problem?

14 DR. ROBIE-SUH: Let me just comment,
15 if I can. You are quite right. Well, one way
16 we look at is that we have this signal of
17 mortality that lends itself to limited
18 statistical analysis and inference and so forth,
19 but nevertheless, mortality is a very important
20 finding.

21 We certainly agree with you in
22 looking at the cases that many of the deaths

1 were CKD patients for whom illness is a
2 lot -- who have a lot more underlying illness
3 than these otherwise healthy patients in the
4 heavy uterine bleeding and postpartum
5 populations which are being targeted for the
6 product approval.

7 DR. HENNESSY: Mr. Levin?

8 MR. LEVIN: Just a few things for
9 clarification. One, I've been at for so long
10 that my sequencing maybe off. But I don't find
11 anywhere even a -- that we've been supplied with
12 proposed labeling. Normally, wouldn't we have
13 some skeleton of what labeling might look like,
14 or not.

15 DR. PAZDUR: Basically, we would take
16 your recommendations and then discuss labeling
17 internally. Generally, we do not discuss the
18 details of labeling. We could discuss
19 generalities as far as labeling, but specific
20 detailing and negotiations of exact terminology,
21 et cetera, we really do after these meetings.

22 So here again, what we're asking