

1 for is generalizations that we can take back,
2 not specific labeling and wording of
3 labeling.

4 MR. LEVIN: The second thing is, in
5 some risk management programs, there's an
6 attempt to control the concern about off-label
7 by actually doing it through the distribution,
8 and have you been approached by the sponsor to
9 talk about perhaps targeted distribution as a
10 way of sort of narrowing the opportunities for
11 off-label prescribing?

12 DR. RIEVES: Restricting distribution
13 is on the table as a consideration. We
14 initially issued a non-approval letter on this.
15 One of the suggestions was the consideration of
16 changing the proposed indication actually
17 towards a more restricted patient population,
18 for example, as were the considerations among
19 the many considerations.

20 Our primary concerns relate to the
21 broadness, and we do agree with Dr. Paganini,
22 and our concern here -- there is obviously a

1 substantial concern about off-label use where
2 the risk may be notable also, not only in the
3 postpartum, but the heavy uterine bleeding
4 considerations. So that running theme is
5 among our considerations here.

6 DR. HENNESSY: Dr. Peterson?

7 DR. PETERSON: I think part of the
8 problem here is the people who give iron and
9 take it out are very sensitized to the
10 propensity of the infectious disease and
11 promoting microbial growth, and also very
12 sensitized to cardiovascular effects in
13 enhancement of post-perfusion injury issues.

14 And that raises two questions then
15 as to where the iron is, and the
16 pharmacokinetics as presented only speaks to
17 one compartment. And in serum or plasma, the
18 critical toxicity environment appears to be,
19 at least in the cardiovascular realm,
20 associated with the non-transferrin bound
21 component.

22 So question one would be, were

1 studies of iron partition in plasma done
2 other than what was reported? And two, in
3 tissues, iron has very selective toxicity --

4 DR. HENNESSY: Do you want to let the
5 FDA to respond to that one and then raise part
6 two?

7 DR. PETERSON: Yeah.

8 DR. RIEVES: Those are good questions,
9 and we have -- they're key questions.

10 One of the major challenges here is
11 in the assay technology. The Injectafer
12 interferes with detection of transferrin. So
13 when we say total serum iron as shown in our
14 slide, that includes the iron within the
15 product, within Injectafer, as well as iron
16 bound to transferrin, if you will.

17 Luitpold may have more data -- I'm
18 sure they have tried very rigorously to
19 dissect out the various iron parameters --

20 DR. PETERSON: The issue is not so
21 much when the drug is in the plasma, actually,
22 but then it goes to the macrophage, who are

1 notoriously messy eaters, and that would be when
2 you would expect that the non-transferrin-bound
3 iron would go up, and you'd be more vulnerable
4 to those kinds of effects. So it would be a
5 longer-term study than what at least you look
6 for for drug and blood. And it sounds like
7 those issues weren't considered.

8 The other issue was tissue
9 deposition and distribution, because many
10 tissues -- just for example, the pancreas is
11 very sensitive -- and the beta cells less so
12 and the alpha the delta and the acinar cells.
13 Likewise, where the iron is in the heart
14 regardless of the total amount may be
15 critical depending on how it partitions from
16 the original ligand into tissues.

17 And when the tissue distribution
18 studies were done, were those based on iron
19 measurement and tissue or
20 histological -- because again, they're
21 methodological issues and blood profusion and
22 all that in a given tissue when these things

1 were done. But the data we got was hard to
2 interpret in that regard.

3 DR. HENNESSY: Is that a better
4 question for the sponsor?

5 DR. PETERSON: Or the FDA, whether
6 they got that information, because it wasn't
7 apparent what --

8 DR. HENNESSY: Why don't we let the
9 FDA to take a shot at that, if they would like.
10 If not, remember that one for the sponsor
11 session; okay?

12 DR. JOHN: The sponsor had submitted a
13 study where there was a biodistribution for
14 various organs that was studied using PET
15 imaging technology with one of the iron
16 isotopes. And once again, the problem there is
17 it's a very short-term -- only up to six to
18 eight hours, if I recall correctly -- and major
19 organs were -- I believe it was liver and then
20 bone marrow -- that is where most of the stuff
21 was, but we do not know in the long-term what
22 happens, where it all resides and so forth.

1 DR. HENNESSY: Okay.

2 DR. LU: I remember for that study, I
3 think 100 milligram was used -- for 1000
4 milligram, never studied.

5 DR. HENNESSY: Why don't we do
6 Lockwood, Kramer then Henderson, and then we're
7 probably going to be at lunch?

8 Dr. Lockwood?

9 DR. LOCKWOOD: I'm sort of
10 following-up where Dr. Peterson left off, still
11 trying to come to grips with some mechanism of
12 action that might unify what seem to be
13 disparate mortality events. And the theme in
14 general is that there's alterations perhaps in
15 immune function, and some predisposition to
16 cardiac events of a variety of different
17 iteologies -- coronary vascular disease and
18 arrhythmias, presumably.

19 So is there any data at all either
20 available in literature or known to the FDA
21 or known to the sponsor that either this drug
22 or IV iron therapy in general, for example,

1 alters macrophage function? Does it alter
2 osteoclast function? Is there iron
3 deposition in osteoclast that would alter its
4 ability to be involved in bone metabolism?
5 Do we know anything about clotting changes
6 associated with this drug, or platelet
7 activation changes or lipid changes?

8 In other words, is there one iota
9 of evidence that might be able to provide
10 some biological plausibility to what seems to
11 be a random assortment of mortality events?

12 DR. RIEVES: I think there's a wealth
13 of data on iron metabolism in cells, that sort
14 of thing, both in vitro as well as in animal
15 data. Now, the most striking thing here is we
16 have clinical data of plausibility -- one, of
17 hypophosphatemia -- many anecdotal reports of
18 association of hypophosphatemia with cardiac
19 reactions with cardiomyopathy.

20 Now, the strength of those data is
21 somewhat questionable because they're largely
22 anecdotal selective reports. The

1 plausibility, though -- I think we should
2 perhaps focus on the clinical data as opposed
3 to in vitro or hypothetical aspects of how
4 iron metabolism may alter.

5 I think there's a little question
6 that iron does alter cellular
7 functions -- many aspects of phagocytosis, if
8 you will, and I'm sure some of the
9 hematologists on our panel could elaborate at
10 some length -- on the iron metabolism on a
11 cellular level and the potential toxic
12 effects of iron.

13 But right now, again, we're in the
14 realm of speculation. What we do have
15 though, is a database that shows Grade 3
16 hypophosphatemia and four and perhaps five
17 cardiac deaths where there were no
18 phosphorous levels measured shortly before
19 death. We do not have the data. So in terms
20 of plausibility, that I think is front and
21 center among plausible considerations.

22 DR. HENNESSY: Dr. Kramer?

1 DR. KRAMER: Thanks. I'm Judith
2 Kramer from Duke.

3 I'm still struggling with the
4 fundamental question about whether this is a
5 real signal. I think all the discussions are
6 concerned about which population we expose
7 are predicated on that, and I'm curious,
8 Dr. Suh, about your reaction to Dr. Andrews'
9 presentation, where she cautioned us against
10 the raw accumulation of numbers without
11 considering exposure of the issue of
12 confounding, and if I understood her
13 presentation correctly, the thing that was of
14 most concern was the risk ratio in all
15 controlled studies that included CKD with a
16 risk ratio of three.

17 So could you help us a little bit
18 and tell us, is the fundamental basis of your
19 concern that risk ratio of three, even though
20 it is not specifically significant? Or
21 what's your take on her caution about that
22 whether there really is a signal here?

1 DR. ROBIE-SUH: My comment that there
2 is a signal is that if you look at the data, if
3 you look at the deaths, you've got 10 deaths and
4 versus one on Venofer within this database.

5 I'm a little skeptical of the
6 argument about the length of follow-up. Most
7 of these deaths occurred relatively early,
8 particularly the ones in the controlled
9 studies that -- where we've used most of our
10 comparison. I tend to appreciate the
11 concerns with doing the statistics on this.
12 Our FDA statisticians, though, have done some
13 reasonable assessments of whether this could
14 be statistically meaningful, and they have
15 concluded that it could be.

16 Is it necessarily so? At this
17 point I would have to say that what we have
18 is this observation. We have this
19 observation that the data for which to
20 adequately evaluate it is considerably
21 limited.

22 DR. PAZDUR: Could I add something? I

1 think one of the important things that we have
2 here is we have randomized control data here;
3 okay? Not observational data, but randomized
4 control data, and one of the issues with
5 randomization is obviously, it should take into
6 account factors that you know and factors that
7 you don't know. So these should be randomly
8 balanced.

9 We do have a numerically excess
10 number of deaths in one arm. Why is that?
11 You know, we could speculate as much as we
12 want -- they're there. It is seldom to
13 establish statistical significance with any
14 of these findings because these studies are
15 not powered, obviously, to take a look at
16 where safety findings.

17 But nevertheless, hallmark here
18 folks is we have randomized control trials
19 that show an imbalance in one arm here; okay?
20 Why is that? Bad luck? I don't know.

21 Okay, but it is there. And we
22 can't apply any statistical P value here

1 because it just isn't the purpose of the
2 studies when they were designed here, and
3 that's our concern.

4 DR. KRAMER: Could you clarify that
5 you are mostly concerned about the CKD
6 population, and that contributes to that
7 imbalance in the randomized study?

8 DR. PAZDUR: I think all of the
9 studies -- we presented the excess deaths in
10 this slide, and whenever you have a randomized
11 controlled database compared to the oral iron
12 here, which show an excess death of 0 versus x
13 or 1 versus x, this is bothersome, and you have
14 to give us an explanation for that.

15 And here again, you could
16 hypothesize and really speculate on all of
17 the causes of deaths. But attribution of
18 death and the proximate cause of a death is
19 very, very difficult, and generally the
20 Agency does not go into that realm, and
21 that's why we look at just deaths on one arm
22 compared to deaths on another arm, because

1 nobody is actually there and nobody really
2 notice the proximate cause of that patient's
3 demise.

4 It could be that these are just
5 patients that are high-risk, and there's an
6 insulting feature that comes into play here
7 that causes these deaths -- not that these
8 are the causes of the death here. So this
9 whole area of attribution is a very difficult
10 one to get into.

11 DR. HENNESSY: You had another
12 question, Judy? Okay.

13 DR. KRAMER: I don't know if it's for
14 the sponsor for -- I need some expert who can
15 comment on the concern that the ferritin levels
16 are superphysiologic in terms of what that
17 likely means. There was this implication the
18 FDA presentation was concerned --

19 DR. PAZDUR: I think this was a
20 speculative finding that were putting out there.
21 We are not stating that this is the cause of any
22 of these deaths. It was noted that the ferritin

1 level was there.

2 DR. KRAMER: But wasn't that the basis
3 of the concern, that perhaps this dose is too
4 high? That statement was through our packet and
5 the presentation this morning.

6 DR. RIEVES: In this field, as I'm
7 sure some of the hematologists can elaborate at
8 greater length on, the safety of total dose iron
9 infusion has been debated for many years, using
10 iron dextran, if you will.

11 Some physicians feel very strongly
12 it is safe; other physicians raise questions
13 with that regard. So Injectafer came to the
14 Food and Drug Administration in the context
15 of considerable debate, if you will,
16 regarding the safety of high-dose iron
17 administration.

18 So on the doorstep, if you will,
19 when we see an iron product that comes to us
20 with a dose proposed here of a gram,
21 potentially, as the initial dose, we're going
22 to look very closely at that. Then when we

1 actually go and look at the clinical,
2 randomized clinical data, we see an imbalance
3 in mortality; we see a small imbalance in
4 serious cardiac events; we see a fairly
5 striking incidence of Grade 3
6 hypophosphatemia.

7 We are not looking at the
8 statistical aspects where the data do not
9 prove, if you will, that the product has a
10 mortality disadvantage. Looking at the total
11 picture, though, meaning in the background
12 concern relating to total dose iron infusion
13 that is essentially where we're coming from.
14 We are looking for a broader field
15 perspective on this issue here.

16 DR. HENNESSY: Dr. Henderson will have
17 our last question or two before lunch.

18 DR. HENDERSON: Thank you. I'd like
19 to assure Dr. Harrington as an obstetrician, we
20 probably use more off-label medications than you
21 do. I don't think there's anything that is
22 indicated enough in OB.

1 Because of that -- I have a
2 question for the FDA -- do we know anything
3 about the consequences of using this
4 medication in women who are not -- I'm
5 thinking about healthy reproductive-age women
6 who really have little to no risks to have to
7 be an anemic? It's annoying, but with some
8 nutrition counseling, dietary management and
9 encouragement of taking iron, you can pretty
10 much correct this.

11 So if you limit it and you are
12 targeting healthy reproductive-age women,
13 what happens if they're not iron-deficient,
14 for one? And two, how do you give them a
15 risk-benefit for some medication for a
16 condition that likely is not going to -- not
17 only not kill them but not harm them
18 long-term, and this medication may kill them,
19 albeit unlikely?

20 DR. PAZDUR: I think you hit the
21 question on the head here, and that's what we're
22 going to be discussing here.

1 You know, we have questions even
2 about how do you define intolerances -- such
3 as you stated, you could work with somebody
4 to get them over with, and one of the major
5 concerns could be are people going to just
6 grab this and use it rather than really
7 trying to work with the patient.

8 DR. HENDERSON: For someone who uses a
9 lot of off-label medications, one of the things
10 I find that people are less likely to use it if
11 there's a big consequence.

12 So I'm wondering, do we know, in
13 women who are not iron-deficient but have
14 anemia for other reason, B-12 deficiency,
15 whatever, if we use this medication, what are
16 the potential consequences, and is it easily
17 correctable?

18 DR. RIEVES: The product has been
19 developed almost entirely in iron-deficient
20 anemic patients, so it's used in very mild iron
21 deficiency without anemia --

22 DR. HENNESSY: We're going to adjourn

1 now for lunch.

2 We will reconvene at 1:00 p.m.

3 Panel members are reminded that any lunchtime
4 discussion should not involve any metals
5 containing iron.

6 And we will see you back here at
7 1:00.

8 (Whereupon, at 12:02 p.m., a
9 luncheon recess was taken)

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1 to advise the committee of any financial
2 relationship that you may have with the
3 sponsor, its product, and if known, its
4 direct competitors.

5 "For example, this financial
6 information may include the sponsor's payment
7 of your travel, lodging, or other expenses in
8 connection with your attendance at the
9 meeting. Likewise, FDA encourages you, at
10 the beginning of your statement, to advise
11 the committee if you do not have any such
12 financial relationships. If you choose not
13 to address this issue of financial
14 relationships at the beginning of your
15 statement, it will not preclude you from
16 speaking.

17 "The FDA and this committee place
18 great importance in the open public hearing
19 process. The insights and comments provided
20 can help the Agency and this committee in
21 their consideration of the issues before
22 them. That said, in many instances, and for

1 many topics, there will be a variety of
2 opinions.

3 "One of our goals today is for this
4 open public hearing to be conducted in a fair
5 and open way, where every participant is
6 listened to carefully, and treated with
7 dignity, courtesy and respect. Therefore,
8 please speak only when recognized by the
9 Chair. Thank you for your cooperation," and
10 as a further note, I would ask the speakers
11 to identify themselves by name.

12 You want to get that?

13 DR. WATKINS: Our first speaker is
14 Susan Wysocki, please?

15 MS. WYSOCKI: Yes, thank you. Good
16 afternoon. I'm Susan Wysocki; I'm the president
17 and CEO of the National Association of Nurse
18 Practitioners in Women's Health, as well as
19 being a board-certified women's health nurse
20 practitioner. I'm not being compensated for my
21 time or travel this afternoon.

22 American Regent has provided my

1 organization a grant for a campaign on anemia
2 that includes no branding.

3 As many as one in five women will
4 suffer from excessive blood loss during their
5 reproductive years, especially having a baby.
6 These women are at serious risk for iron
7 deficiency anemia, which can cause
8 debilitating physical and emotional quality
9 of life issues. Of the approximate 4 million
10 women who give birth, about 2 million become
11 iron-deficient; more than 1 million will
12 suffer from postpartum anemia.

13 Despite the high prevalence, iron
14 deficiency anemia tends to go unrecognized,
15 undiagnosed, because many women assume that
16 it's normal to feel tired, weak, irritable,
17 particularly when you've had a new baby. And
18 I don't think it would be any surprise to any
19 woman in this room to know that it's common
20 for women to neglect their own health needs
21 in favor of their family.

22 If, however, untreated, iron

1 deficiency anemia can negatively affect
2 maternal mood, thinking, and behavior of new
3 mothers, which disrupts mother-baby
4 interactions. And I think you've heard a
5 little bit about that today.

6 In fact, infants of mothers who are
7 anemic at 10 weeks postpartum may show
8 evidence of developmental delay. You've
9 heard today also that oral treatments cause
10 GI side effects, and there's a significant
11 concern about the ability to continue with
12 the treatment until someone is well. The
13 other current treatment option, blood
14 transfusion, also comes with risks and
15 difficulties with administering the
16 treatment.

17 While I'm not here to recommend any
18 specific action on any specific product, I do
19 want to make clear that the prevalence and
20 under-diagnosis of postpartum anemia is a
21 serious and growing concern in women's
22 health, and the current treatment options are

1 currently not adequate to correct this
2 problem.

3 Thank you very much.

4 DR. HENNESSY: Thank you.

5 Speaker number 2, please?

6 DR. WATKINS: Ms. Elena Rios.

7 DR. RIOS: I'm Dr. Rios, and I don't
8 have any financial connections with the sponsor,
9 or other pharma companies that deal with these
10 drugs.

11 Dear Chairman and members of the
12 committee, it's an honor to be here to
13 provide comments for your deliberation on the
14 safety of the treatment of Injectafer for
15 iron deficiency anemia with peripartum and
16 postpartum women, and women with intrauterine
17 bleeding.

18 As president and CEO of the
19 National Hispanic Medical Association, I work
20 on behalf of over 36,000 Hispanic physicians
21 in the United States. The mission of the
22 organization is to improve the health of

1 Hispanics and other underserved populations.
2 Our agenda includes expanding access to
3 quality health care, increasing opportunities
4 in medical education, cultural competence and
5 research for Latinos, and we deal with policy
6 development advocacy and education efforts.

7 Iron deficiency and iron deficiency
8 anemia during pregnancy have been
9 longstanding public health issues that have
10 impacted the Latino community. Data from the
11 CDC shows the prevalence of iron deficiency
12 anemia is higher for
13 Mexican-Americans -- 19 percent versus White
14 Americans -- 8 percent. A follow-up '99 to
15 2000 survey from M. Haynes further showed
16 that the prevalence of iron deficiency has
17 had in fact increased to 22 percent among
18 Mexican-Americans.

19 In terms of the postpartum state,
20 for example, 31 percent of Hispanic women
21 suffer from postpartum anemia, a prevalence
22 rate that is 1.6 times higher than that of

1 non-Hispanic whites. This is astounding
2 considering the negative impact this would
3 have on the quality of life for the Hispanic
4 mother and her mother-infant bond, as well as
5 the impact on the family, which is so
6 important to our population, already pushed
7 to the limits by social and economic
8 challenges.

9 The major impact of iron deficiency
10 anemia includes increased morbidity,
11 hospitalizations, depression, decreased
12 cognitive functioning, as was mentioned by
13 the previous speaker. It's important to note
14 also that the overall incidence of anemia
15 ranges in the United States between 3 and
16 6 percent of women in the reproductive stages
17 of their lives.

18 But in comparison, the incidence of
19 anemia among low-income women is roughly
20 21 percent. That leads to higher costs of
21 treatment and hospitalizations in this
22 country. And because of the overall

1 socioeconomic status of this minority
2 population, this disproportionately affects
3 Blacks and Hispanic patients more often than
4 their non-Hispanic White counterparts.
5 Moreover, Hispanics, according to the
6 National Report on Health Disparities
7 released by the U.S. Department of Health and
8 Human Services, are subject to the worst
9 record of access to health care and to
10 quality health care.

11 Major factors that account for this
12 include being the largest group without
13 health insurance, poverty, low levels of
14 education and health literacy, lack of
15 knowledge, lack of understanding of healthy
16 lifestyles and treatment regimens, and fear
17 and lack of trust of a health care system
18 which lacks cultural responsiveness and lacks
19 Hispanic physicians and other providers.

20 Current treatment has been found to
21 be inadequate, as was mentioned earlier for
22 the Hispanic population. I'm not going to go

1 into the side effects of iron transfusions,
2 but given the risks associated with blood
3 transfusion, the poor compliance and
4 suboptimal efficacy of oral iron
5 supplementation, women with peripartum anemia
6 are untreated or inadequately treated, which
7 can lead to even worse postpartum health
8 status.

9 We feel the benefits greatly
10 outweigh the possible risks and safety
11 concerns associated with this new treatment
12 option. The Hispanic, the underserved and
13 all peripartum women of the United States
14 deserve another treatment option for iron
15 deficiency anemia.

16 Thank you.

17 DR. WATKINS: Speaker number 3,
18 Jonathan Waters?

19 MR. WATERS: My name is Jon Waters.
20 I'm the president of the Society for the
21 Advancement of Blood Management. The sponsor
22 has provided me gas money to come down here from

1 Pittsburgh, as well is a sponsor of the Society
2 for the Advancement of Blood Management in its
3 annual meeting.

4 My background, I'm chief of
5 anesthesia at Magee Women's Hospital, which
6 is one of the largest women's hospitals in
7 the United States, as well as being in charge
8 of the perioperative blood management system
9 or a program for the health system of the
10 University of Pittsburgh, which encompasses
11 20 hospitals.

12 I served the same role at The
13 Cleveland Clinic here up until 3-1/2 years
14 ago. So I have a fair amount of experience
15 in understanding anemia in women, as well as
16 iron deficiency in the postpartum period.

17 Some of the others have talked
18 about the prevalence of anemia in the
19 postpartum period. This is a slide from some
20 work that Lisa Bodner did. She's an
21 investigator at the University of Pittsburgh,
22 where she looked at the prevalence of anemia

1 in the postpartum period. And if you look at
2 the far-right column here, you'll see that
3 the prevalence, at least in the population
4 that she looked at, which was underprivileged
5 women, ranges from 25 to 30 percent. So it's
6 of high prevalence.

7 We also have obstetrical hemorrhage
8 that leads to iron deficiency anemia as well
9 as iron deficiency. What we're seeing is a
10 growing rate of cesarean sections. In my
11 particular hospital, we have a rate of
12 cesarean section of 29 percent, which
13 actually compares pretty favorably to the
14 national average of 33 percent. And so we're
15 seeing increasing amounts of postpartum
16 hemorrhage leading to these problems of
17 anemia and iron deficiency.

18 I'll just skip through that one.
19 And this was also mentioned before, the
20 functional consequences of iron deficiency
21 and iron deficiency anemia are multiple.
22 Probably the one that's of most note to me is

1 a male, a husband and a father is on the
2 second large line as the mood deviations that
3 take place in women that have iron
4 deficiency. I think it highlights an
5 unspoken problem.

6 Iron supplementation on red cell
7 and red cell parameters is pretty much
8 unquestioned, as is demonstrated by this
9 particular study, where they looked at iron
10 supplementation in non-anemic iron-deficient
11 women, and they showed a significant increase
12 in hemoglobin and ferritin levels in that
13 particular group.

14 The alternative for treatment of
15 iron deficiency anemia has historically been
16 transfusion. Transfusion therapy in most
17 patient populations is done in patients that
18 are within two years of the end of life. For
19 a young women undergoing transfusion at the
20 age of 25, they have 50 years of lifespan in
21 front of them, and so the complications of
22 transfusions are listed here. For the

1 average patient, it doesn't have the same
2 kind of ramifications as it does for that
3 young women with 50 years of lifespan in
4 front of them.

5 And two that I've highlighted in
6 red here I think have become of particular
7 interest most recently. One of them is that
8 of microchimerism, where the bone marrow
9 becomes engrafted by stem cells from a blood
10 transfusion, and leads to lymphocytes that
11 have genetic material that's different than
12 the host.

13 The clinical consequences of this
14 particular microchimerism are not fully
15 elucidated at this point, but there is some
16 indication that it might have an impact on
17 auto-immune disorders, chronic graft versus
18 host disease, blood-borne cancers. There is
19 an increase in the risk of blood-borne
20 cancers in people that have received blood
21 transfusions 20 to 30 years later.

22 Alloantibodies is also a problem,

1 especially at my hospital center, we have one
2 of the most prominent transplantation centers
3 in the United States. Patients that have
4 received blood transfusions have a tendency
5 to develop alloantibodies, making it much
6 more problematic to transfuse them for
7 subsequent need.

8 So a young woman getting transfused
9 with that 50 years of lifetime following is
10 going to be more prone to needing
11 transfusions later in their life.

12 I think that's all I have to say.

13 Thank you.

14 DR. WATKINS: Our next speaker is
15 Francis Hutchins.

16 DR. HUTCHINS: Good afternoon. My
17 name is Dr. Francis Hutchins. I'm adjunct
18 professor of obstetrics and gynecology at Drexel
19 University in Philadelphia.

20 I'd like to speak in a
21 potentially -- let's say a more down-to-earth
22 fashion about this problem. I have had the

1 privilege and pleasure of having a
2 schizophrenic career that started out in
3 perinatal medicine and ended up specializing
4 in uterine fibroids management, et cetera.
5 As a consequence of that, I've had the
6 opportunity to experience both types of
7 issues that people have spoken about here.

8 One of the problems that I
9 encountered early on -- when I was in the
10 faculty at Temple University, one of my
11 interests was adolescent pregnancy. We
12 looked at approximately 4,000 adolescent
13 pregnancies over about a five- or six-year
14 time period. And one of the issues that came
15 out loud and clear was that most of these
16 young women were anemic. And it's sort of
17 interesting. You're talking about anywhere
18 women from 12 to 19 years of age. And it's
19 interesting that that anemia would be that
20 engrained in this minority population, which
21 is predominantly Black, and secondarily
22 Hispanic.

1 So it's a very common disease,
2 starting early on in women -- of
3 disadvantaged minorities -- for want of a
4 better word. It is associated with poor
5 outcome, as we can see in most of the
6 inner-city hospitals, our teaching hospitals,
7 et cetera -- pre-maturity, small for
8 gestational age infants are associated with
9 serious ongoing chronic anemia in pregnancy.

10 It has a substantial impact, as has
11 been noted earlier, on the function and
12 vitality of the individuals who are affected
13 by it, and one of the other issues that one
14 should be aware of is that the number one
15 indication for hysterectomy in this country
16 is uterine fibroids. And the number one
17 symptom that brings women into therapy is
18 anemia or menorrhagia with secondary anemia.
19 And they're more likely to end up with a
20 hysterectomy, and to accept a hysterectomy if
21 they have profound anemia, and the
22 consequences that go along with it.

1 And of course, people are more than
2 happy to recommend that to them when they see
3 that they're anemic and have a rather
4 hopeless view of the outcome of the whole
5 thing.

6 The options for treatment of anemia
7 have been elucidated before, and I'm not
8 going to go through all of them. My major
9 issue that I think I'd like to sensitize the
10 audience to is that we really need to find
11 ways to intervene and correct these anemias.
12 Oral iron therapy is a joke, and I think we
13 need to recognize it as such.

14 If we take a 15-year-old or
15 16-year-old who has a hemoglobin of 8 or 9,
16 and put her on oral iron for the next eight
17 or nine months, the likelihood of her taking
18 that oral therapy and coming into the
19 delivery room with a normal hemoglobin is
20 minimal, and if anything, she tends to become
21 more anemic. In addition, the likelihood of
22 her ending up with a cesarean section is

1 increasing. I applaud those that have only a
2 30 percent cesarean section rate, because in
3 many centers, it's close to 50 percent.

4 So these young women are going to
5 end up in a large percentage of circumstances
6 not only having problems during their
7 pregnancy because of the anemia, but also
8 ending up with transfusion more often than
9 not because they have to undergo a major
10 surgical procedure in order to deliver their
11 babies.

12 So in summary, I'd like to say that
13 the clinical aspect of iron deficiency anemia
14 has been historically and currently is
15 underappreciated. There is a predilection,
16 for the minority population in this country,
17 which is clearly demonstrated in any data
18 that you look at -- the need is great for a
19 safe, effective, and easily-administered
20 therapy.

21 Thank you.

22 DR. WATKINS: Our next speaker is

1 Ralph Rogers.

2 DR. ROGERS: Thanks for allowing me to
3 come and speak to this austere group here in
4 front of me. I'm Ralph Rogers, OB/GYN. I've
5 been in practice for about 29 years. My
6 perspective will be somewhat close to Francis's,
7 but I'm one of the guys that's in the trench and
8 sees these patients every day.

9 As far as a financial disclosure,
10 I'm being paid for my travel arrangements but
11 not for my time or for appearing here. I was
12 going to give a nice slide presentation, but
13 when I looked on Google Image, I couldn't
14 find an appropriate constipation slides, and
15 my wife wouldn't pose. So we're stuck with
16 just me talking.

17 I've been practicing for about 30
18 years in OB/GYN. I've seen the anemia from
19 our patients at our hospital that we have,
20 and I was very interested in seeing some of
21 the numbers the previous speakers have talked
22 about and how close they were to our

1 statistics at our hospital. We're in a
2 suburb of Evansville, Indiana, and I had our
3 information technology department determine
4 our rates of anemia.

5 In 2007, the overall incidence was
6 19.8 percent, approximately 20 percent of
7 approximately 3,400 deliveries we had that
8 year. That was greater when you took that
9 into the Hispanic population, which is
10 approximately 28 percent, and in our Black
11 population, it was as high as 32 percent. So
12 there's a need for an option to treat these
13 patients.

14 The things that we in general
15 practice see is that when we make a
16 recommendation, whether it's on therapy for
17 hormone replacement, we think that our
18 patients will always be compliant, but when
19 you look at the statistics, it's just not
20 true. We always give ourselves more credit
21 for being a great salesman, saying you need
22 this and it's important for you, it'll do

1 more good than harm. And you know, when you
2 don't get a immediate gratification from
3 something, like -- it's not like you are
4 taking a drug for -- sumatriptan for a
5 migraine headache, you get immediate relief,
6 but when you're told yes, just take this iron
7 pill and you'll better, or take this hormone
8 and your bones won't crumble.

9 So you have a harder time in
10 explaining to these patients. And we do see
11 the effects of it, like the previous speakers
12 have talked. And if you've ever tried to get
13 your patients -- you don't really have to
14 take this iron but you've got to eat a lot of
15 spinach and prunes. They don't have a lot of
16 palette for that.

17 Women have more of a problem with
18 it, because not only have they have been
19 giving part of the blood to their babies
20 during their prenatal course, they're going
21 to lose 1000 ccs or more at the time of
22 delivery, even though obstetrician -- it's

1 500 ccs or less, but it's usually 1000 or
2 more.

3 And so we have a hard job to get
4 these people to take their medications.
5 Constipation, bleeding, interjection,
6 flatulence. I just really look forward to a
7 time -- and hopefully that all the
8 information that's submitted to the FDA will
9 be positive, because this will be a great
10 addition to our ability to treat patients,
11 and then avoid the problem of compliance.

12 And I look forward to having a
13 patient who's had her postpartum hemoglobin
14 the next morning. And if it's again -- the
15 anemia that I quoted was with a level of
16 10 -- hemoglobin of 10 or less in those
17 numbers -- and if I had a patient that had
18 that, I would be able to have 1,000
19 milligrams or so of a medication knowing that
20 her compliance have been met, and there'd be
21 much closer to their treatment goals.

22 Thank you.

1 DR. WATKINS: Our next speaker is Indu
2 Lew.

3 MS. LEW: Good afternoon. My name is
4 Indu Lew. I'm the director of education and
5 research for the Saint Barnabas Health Care
6 System in New Jersey.

7 Thank you. I'm very short as well.
8 So thank you for the committee today for
9 allowing me to present. I'm a speaker on the
10 American Regent speakers' bureau. However,
11 I've not received any honoraria for speaking
12 here today, but they are reimbursing me for
13 my travel expenses.

14 Five years ago, I went in for a
15 C-section for my son being born, and
16 everything was going according to schedule.
17 I've had a C-section before, and I knew what
18 to expect. He was born, everything was going
19 fine. I was joking around with the
20 anesthesiologist and my OB. Twenty minutes
21 later, nobody's speaking to me. Twenty
22 minutes later, my OB is pounding on my uterus

1 as if he is in the gym to get my uterus jump
2 started, because it wasn't contracting and I
3 was bleeding out.

4 Fast-forward about 2-1/2 hours
5 later, my spinal was wearing off, I could
6 feel my feet -- I'm open on the table, and my
7 uterus finally contracted as soon as my
8 husband signed the consent for a
9 hysterectomy. My hemoglobin dropped from
10 about 13-1/2 to 7-1/2 in two hours. I was
11 discharged from the hospital a week later.

12 Now, prior to my delivery, I was
13 working full time, driving an hour and a half
14 one-way to work preparing for joint
15 commission and going to school full time for
16 my doctorate. After discharge, I couldn't do
17 anything when I was home. The fatigue was
18 overwhelming. I would take a shower and I
19 couldn't even dry myself, and my mother had
20 to dry my body.

21 Now, I'm a Type-A personality -- on
22 the go. I couldn't even dry my body after a

1 shower, because my hemoglobin was hovering
2 around 7-1/2 to 8. I couldn't stand for more
3 than an hour without having to take a nap,
4 and I remember it took me about eight weeks
5 to be able to stand for eight hours, and the
6 overwhelming emotional outlet that I had for
7 being able to stand for that eight-hour
8 period of time was huge. My mother quit her
9 job to take care of me.

10 And in that six-month period of
11 time when I was out of work, and I quit my
12 job three times because I thought that I
13 would function again as anybody that could be
14 working. My boss was gracious enough to tell
15 me you know what, call me back next month.
16 Call me back the month after. After six
17 months, I finally went back to work, and my
18 hemoglobin was hovering around 10-1/2.

19 Now I can make it to work all day,
20 round with the physicians in the other health
21 care team, but on my way home, I would have
22 to bring an alarm clock with me and set it

1 for 20 minutes, and take a nap at a strip
2 mall at the side of the road so I could
3 actually get back home and take care of my
4 kids. I can't tell you how overwhelmingly
5 fatigued you are.

6 Now, I'm a pharmacist. I know
7 clinically, I'm going to get better. I know
8 the span to create a red blood cell is about
9 120 days. I know that. I know that this
10 isn't going to last forever. But at that
11 time frame, you cannot do the simple adult
12 daily living things that you and I take for
13 granted, like taking a shower, like cooking a
14 meal, like taking care of your kids. And
15 like I said before, I was Type-A -- on the go
16 all the time.

17 My options for treatment, we've all
18 heard about it. I could have gotten
19 transfused, but I refused. I could
20 have -- ESAs, Erythropoietic Stimulating
21 Agents -- is not an option, because you don't
22 use that for acute blood loss recovery

1 treatment, and it's not indicated. So my
2 other option was oral iron.

3 Health care professionals are the
4 most non-compliant of the group that you'll
5 ever find, and I wasn't about to take
6 anything that I knew was going to wreck my GI
7 system and cause me havoc. So really, I had
8 no alternative. It took me about eight
9 months to get back to where I needed to be.
10 And during that time, I wished I had
11 something that could have expedited this
12 process. It was really, really debilitating.

13 When we look at anemia, we think of
14 fatigue as something that's supposed to
15 happen. You're anemic; you are going to be
16 tired. This is not being tired. You
17 physically can't function when you have that
18 hemoglobin at 8, 9, 10, or 11, and anything
19 that would have expedited that process a lot
20 quicker would have been a lifesaver for me.

21 So I'm kind of presenting it from
22 the patient standpoint and the professional

1 standpoint of how I wish I had an alternative
2 to manage this type of anemia that I was
3 experiencing -- something that I never
4 thought that I would be going through, having
5 my first section go so well.

6 So I'd like to thank the committee
7 today for the opportunity again. What
8 happened to me has left an indelible mark on
9 me personally and professionally.

10 I know I manage my patients a lot
11 differently.

12 Thank you very much.

13 DR. WATKINS: Our final speaker of the
14 day is Phillip Hadley.

15 MR. HADLEY: Ladies and gentlemen,
16 distinguished members of this committee, good
17 afternoon. I appreciate the opportunity you've
18 afforded me to speak briefly about my clinical
19 trial experience as a principal investigator in
20 the use of intravenous ferric carboxymaltose in
21 comparison to standard oral iron therapy in
22 managing postpartum anemia, and anemia due to

1 heavy menstrual bleeding.

2 I have no proprietary interest in
3 the tested product, no equity interest in the
4 sponsor of the study, nor have I been paid,
5 nor has any agreement to pay later for my
6 time here at this meeting. Now, I may be
7 reimbursed for my travel expenses, but of
8 course, it may end up like those rebate forms
9 that I can never seem to hand in.

10 But anyway, I have paid for my
11 hotel accommodations, although all those
12 reservations were made on my behalf. So
13 that's my disclosure.

14 I'm a private practitioner in
15 Decatur, Georgia, and practice OB/GYN. I
16 graduated from med school in '74, and did the
17 residency -- finished in '78. So I've been
18 practicing since that time. Part of that
19 time I spent in the Army. So I retired and
20 came into private practice, and I've been
21 doing that since.

22 I've been conducting clinical

1 research for about the last six years as a
2 sub-investigator and as a principal
3 investigator. I've completed three studies
4 involving ferric carboxymaltose, and I'm
5 currently conducting a fourth one. The
6 patients, randomized at my site, were about
7 evenly split between an IV iron group, 18
8 patients, and the oral iron group, with 16
9 patients.

10 The hemoglobin levels increased in
11 both groups with treatment, but the increase
12 occurred more quickly and was more consistent
13 in the IV iron group as opposed to the oral
14 iron group, where the rise was slower and
15 less predictable.

16 In our study patient population, we
17 noted the occurrence of a drop in the serum
18 phosphate levels in some of the IV iron
19 group, but not in the oral iron group, nor
20 did this decrease occur in the postpartum
21 IV iron group. So on one hand, with the
22 heavy menstrual bleeding patients, we had a

1 decrease, but not with the postpartum ones,
2 even though they were getting the same iron.
3 So I'm not sure what the difference is or
4 whether there's a protective effect with
5 regards to pregnancy or what, but
6 nonetheless, that's what we found. But no
7 patients reported any adverse effects of the
8 low phosphate levels. There were no reports
9 of muscle weakness or difficulty breathing or
10 cardiac problems or any such thing.

11 Compliance was not an issue for the
12 IV iron group. Most of my patients are
13 fairly compliant, but the oral iron group
14 compliance ranged from 80 to 100 percent.

15 Not many of my patients -- it was
16 hoped before they were randomized that they
17 would get the IV group because they don't
18 like taking pills. And they saw the IV iron
19 preparation as being preferable to avoid the
20 extended time for having to take the oral
21 iron. The other thing -- the side effects of
22 constipation, nausea, vomiting, cramping,

1 bloating that occurs oftentimes with the oral
2 iron, they were not wanting to have to deal
3 with.

4 Now, I think that in view of my
5 experience, that this product is valuable for
6 its use.

7 DR. WATKINS: Sir, your time has
8 expired.

9 DR. HENNESSY: Thank you very much.

10 The opening public hearing portion
11 of this meeting has now concluded, and we
12 will no longer take comments from the
13 audience. The committee will now turn its
14 attention to address the task at hand, the
15 careful consideration of the data before the
16 committee, as well as the public comments.

17 So where do we go from here? So we
18 had a question or two left for FDA.
19 Hopefully they won't take too long and we can
20 turn our attention to questions to the
21 sponsor.

22 So questions for the sponsor I'd

1 like to divide up into four sections:
2 clinical benefit given to other marketed
3 products; risk; the risk management plan; and
4 the risk-benefit balance.

5 Obviously, we can't spend an
6 inordinate amount of time on any one of those
7 things, and if you do the math, you can see
8 that if all the committee members ask
9 multiple questions for each of those
10 sections, we're never going to get home. So
11 I'd ask you to choose your questions wisely
12 and make them concise clarification points to
13 the degree possible.

14 So Dr. Brittenbaum had a question
15 from before the break for the Agency.

16 DR. WATKINS: Dr. Brittenham, did you
17 still have a question?

18 DR. HENNESSY: Brittenham, I'm sorry.

19 DR. BRITTENHAM: Let me pose it to the
20 sponsor afterwards.

21 DR. HENNESSY: Thanks.

22 Dr. Black?

1 DR. BLACK: I had a question, I think
2 for the Agency, but it may also be for the
3 sponsor. The data that you showed us about the
4 controlled trials had only Venofer as the
5 comparator, and I was wondering what the use of
6 all three IV iron preparations were; how many
7 used dextran and how used the others? And do
8 you have any comparative data using dextran for
9 example?

10 DR. LU: The data we have on the
11 hemodialysis patient and the chronic heart
12 failure patients, they used the Venofer. We
13 don't have any data for other iron injections.

14 DR. BLACK: Do you have any way to
15 estimate what the toxicity would be with the
16 other preparations, and are they more commonly
17 used in the hemodialysis situation than is
18 Venofer?

19 DR. LU: I don't think we have that
20 data.

21 DR. RIEVES: I'm not sure we
22 completely understand the question.

1 There were a few studies compared
2 to Venofer. One in particular that we
3 presented here, where there was the one death
4 in the Venofer study, but in terms of -- and
5 we have to remember also, a number of the
6 studies in the hemodialysis used a different
7 dose regimen. It was the 200
8 milligrams -- multiple times, which is not
9 actually what we're talking about proposed
10 for marketing. So --

11 DR. BLACK: No, I understand that.
12 But we're going to have to make some hopefully
13 intelligent recommendations from data which is
14 not as tight as we'd like. I just wonder what
15 the utility -- what the use of all three of
16 those iron preparations is in that high-risk
17 population? Is it more likely to be Venofer or
18 the others, and if it's the others, what do we
19 know about the mortality rates with those
20 agents?

21 Maybe the sponsor could answer
22 that.

1 DR. HENNESSY: So you're asking about
2 comparative safety data?

3 DR. BLACK: Yes.

4 DR. HENNESSY: I don't think those
5 exist. Is that correct?

6 DR. RIEVES: That's correct; we don't
7 have the full range of products --

8 DR. BLACK: So we'd have to be
9 inferring certain things from that as well.

10 DR. RIEVES: Yes, sir. Unfortunately,
11 there is a great deal of inference, as we've
12 been talking about.

13 DR. BRITTENHAM: Dr. Hennessy, the
14 paper that I referenced earlier -- the Chertow
15 from 2006 does provide comparative experience
16 from the MedWatch database for sucrose gluconate
17 and low- and high-molecular weight iron dextran.
18 These are .6 to 11.3 per million doses
19 administered.

20 There's no direct comparison with
21 the carboxymaltose.

22 DR. BLACK: I don't recall exactly

1 what that said, but could you or anyone give me
2 a breakdown of how many doses are used of each
3 of those three preparations right now?

4 DR. BRITTENHAM: Yes.

5 DR. HENNESSY: So you're asking for
6 comparative safety based on spontaneous reports?

7 DR. BLACK: No. Just what uses it
8 right now.

9 DR. HENNESSY: Does anybody know about
10 the volume of comparative use of the currently
11 available injectable iron products?

12 DR. RIEVES: I don't think we can
13 provide that quantitative information at this
14 point.

15 DR. BLACK: How about qualitative?

16 DR. RIEVES: Again, we're in
17 speculation here.

18 DR. BLACK: Okay.

19 DR. RIEVES: We simply did not track
20 that usage.

21 DR. HENNESSY: Could you do that
22 briefly, please?

1 DR. TOKARS: Most of our -- almost --

2 DR. HENNESSY: Step to a microphone,
3 please.

4 DR. TOKARS: Our company sells
5 iron -- Dextran -- high molecular weight
6 IV iron, iron sucrose -- and iron sucrose.
7 Almost all of our sales are to the nephrology
8 community, within nephrology dialysis centers or
9 nephrologists in general. It's a very small
10 proportion that is sold outside of that.

11 DR. BLACK: What do you sell the most
12 of, and in what proportion?

13 DR. TOKARS: Iron sucrose is the
14 market leader right now. I can't quote
15 percentages, but I believe it's upwards of the
16 high 50s.

17 DR. HENNESSY: Let's turn our
18 attention now to questions for the sponsor,
19 starting out with any questions that people
20 might have about clinical benefit of the
21 products in the context of what's already
22 available.

1 Are there any questions?

2 DR. HARRINGTON: Sir, I have a couple
3 of questions for the sponsor.

4 Although I couldn't find it my
5 briefing work of the FDA or yours, where were
6 these trials conducted? Were those largely
7 conducted in the United States?

8 DR. TOKARS: The trials were split
9 between us and our European partner. The trials
10 that we're talking about for the heavy uterine
11 bleeding and the postpartum patients were
12 conducted largely in the United States. We did
13 have a few sites in Canada, Mexico, and that was
14 it. The postpartum studies that were conducted
15 by Vifor were mostly conducted in Eastern
16 Europe.

17 DR. HARRINGTON: Then my second
18 question says, it's asking about the whole
19 concept of clinical benefit. I accept that the
20 parent hemoglobin status is -- and certainly one
21 of the things that will be asked for is to --

22 Do you have any data in the

1 clinical program of actual clinical outcomes?
2 We've heard from the public speakers -- very
3 importantly, patients and quality of life, et
4 cetera. Did you systematically collect any
5 of that data, quantify it; compare it amongst
6 the groups --

7 DR. TOKARS: We collected quality of
8 life data in both of our postpartum heavy
9 uterine bleeding studies, and I'd ask
10 Ms. Mathias to come up and speak to that data.

11 DR. HENNESSY: And while we're waiting
12 for that, panel members who want to ask a
13 question, Dr. Watkins will note that.

14 MS. MATHIAS: During the HUB as well
15 as postpartum studies, we had an opportunity to
16 look very closely at the quality of life of our
17 patients. Specifically, we had the opportunity
18 using the SF-36, which is a global measure of
19 functioning and well-being at baseline to
20 compare the functioning and well-being versus
21 general population data as well as across other
22 chronic conditions.

1 So if you look, for instance, at
2 the vitality and the physical functioning,
3 you could see in green the general population
4 scoring about this 70-ish, and higher is
5 better, versus the HUB and the postpartum
6 patients are scoring 40 to 45. So there is
7 this quite a large difference that's probably
8 25 points or so in the SF-36 for vitality.

9 Similarly, for physical
10 functioning, you have the general population
11 scoring about 85 or so versus 60 to 65 for
12 the postpartum with anemia and the HUB
13 patients, so --

14 DR. HENNESSY: I'm sorry, I don't mean
15 to interrupt, but are you going to speak to
16 differences between randomized groups in your
17 trials?

18 MS. MATHIAS: Both of these studies
19 for the HUB and the postpartum were randomized
20 studies.

21 DR. HENNESSY: Because what you're
22 showing up there is versus normal population

1 controls, right?

2 MS. MATHIAS: That is correct, so it's
3 versus general population of women aged 25 to 35
4 roughly.

5 DR. HARRINGTON: I'm interested, as I
6 think Dr. Hennessy is getting at, at the
7 treatment-specific issue of comparing the oral
8 iron group versus the IV iron group.

9 MS. MATHIAS: Perfect set-up for my
10 next slide.

11 Now that we're familiar to some
12 extent with the deficit that these patients
13 at baseline had versus the general
14 population, I have in front of me some
15 follow-on data which is looking at the
16 changed scores from baseline to day 42 during
17 treatment of these patients.

18 So again, we're able to get
19 baseline data, day 14 data, day 28 data and
20 day 42 data. So what I have here on this
21 slide is across eight different scales of the
22 SF-36. We have general health, vitality, et

1 cetera. And what we have here are changed
2 scores from baseline, so if you remember, we
3 were talking about vitality and physical
4 functioning on the baseline data, and you
5 could see -- in fact, it's like a
6 reversibility of these deficits and
7 functioning, because these patients'
8 returning to the general population data.

9 So for instance at day 42, the
10 vitality scores have increased by 25, 30
11 points, depending upon which arm you are in.
12 So the grey is the oral iron and the blue is
13 the FCM. So you had statistically
14 significant as well as clinically meaningful
15 improvements in both of these treatments.

16 DR. HARRINGTON: Two follow-up
17 questions here and I'll be quick, is that is
18 this the only study in which you did quality of
19 life measurement, or did you do another study
20 and you're just showing us one example, or are
21 they all consistent with this? And the second
22 is with regard to the methodology, I thought I

1 understood from one of the principal
2 investigators these were not blinded studies.
3 So the patient knows what they're getting. Did
4 the person who's administering SF-36 know what
5 the treatment assignment was?

6 MS. MATHIAS: Thank you for those
7 questions, and I can clarify -- both of these
8 studies -- so we have administered the SF-36 in
9 the HUB studies as well as postpartum studies,
10 and in both of the studies, we did see
11 significant improvement across both arms.
12 However, in the HUB studies, we did find
13 statistical significance between the FCM and the
14 oral iron. In fact, the FCM patients did better
15 in several of the scales of the SF-36.

16 In the postpartum patients,
17 however, there was highly significant
18 improvement over time for both treatment
19 groups, the FCM and the oral iron. However,
20 there was no difference between treatment
21 groups. And the quality of life was a
22 non-ranked secondary endpoint in this

1 quality. So it was pretty much for
2 descriptive purposes. And specific to the
3 blinding, it is my understanding that it was
4 an open-label study; however, the
5 questionnaires were self-administered by the
6 patient.

7 DR. HENNESSY: Just a couple more.

8 Dr. Black?

9 DR. BLACK: I think we should talk
10 about the phosphate issue a little bit, and I
11 think there was a somewhat glib statement made
12 early that all you had to do was have a little
13 milk when you were starting or something, a
14 little more meat. Do you have any evidence that
15 that's going to prevent anything?

16 Did you try that?

17 DR. TOKARS: Dr. Dennis, would you
18 come up and respond to this question please?

19 DR. DENNIS: Thank you. I'm Vincent
20 Dennis. I have a 30-year history of research
21 and scholarly interest in phosphate. I'm a
22 nephrologist.

1 I do need to clarify the issue with
2 regard to phosphate, and the first thing that
3 I need to clarify is there is a tremendous
4 difference between hypophosphatemia and
5 phosphate depletion.

6 For instance, rhabdomyolysis can be
7 a complication of phosphate depletion, not of
8 hypophosphatemia per se. So many of the
9 reviews that you read, including the one that
10 was included in your briefing document, smear
11 the lines of demarcation between
12 hypophosphatemia and phosphate depletion.
13 Phosphate depletion in man takes weeks to
14 months to unfold, and typically, it requires
15 not only dietary restriction, but also some
16 phosphate binder.

17 The second point is that the
18 clinical significance of hypophosphatemia
19 depends on the clinical context in which it
20 occurs. If we see hypophosphatemia in an
21 intensive care unit setting, in a coronary
22 care unit setting, it may be a marker of some

1 other risk-enhancing situation that would be
2 significant.

3 When we see transient
4 hypophosphatemia that is lacking in any
5 association with adverse effects that is
6 self-correcting, then I agree with one of the
7 summary statements in the review that again
8 was in your briefing document, that we know
9 of no clinical consequences for moderate
10 hypophosphatemia that is defined as the range
11 of a serum phosphate between one and the
12 lower limits of normal.

13 Our knowledge of the regulation of
14 serum phosphate has led us to conclude that
15 it's much more sophisticated than we once
16 thought. We're in the era of what we call
17 phosphatonins. These are low molecular
18 weight proteins or glycoproteins that
19 regulate serum phosphate level on an hourly
20 basis, on a daily basis. They respond to
21 changes in dietary phosphate. They change in
22 a circadian rhythm.

1 The regulation of serum phosphate
2 is a very fluid state. It may be a marker of
3 risk states, but in the benign setting in
4 which it occurred here, there were no
5 associated consequences.

6 DR. HENNESSY: Thank you.
7 Dr. Paganini, and to remind people, we're on
8 questions about clinical benefit.

9 DR. PAGANINI: So you want me to hold
10 off, because I have a safety question. You want
11 to wait for that?

12 DR. HENNESSY: If it's a safety
13 question, please hold off.

14 Dr. Lincoff? Yours was a safety
15 question as well?

16 DR. LINCOFF: Yes.

17 DR. HENNESSY: Dr. Burlington?

18 DR. BURLINGTON: In the FDA analysis,
19 they presented that the pooled results of the
20 two randomized studies postpartum had
21 significant results, but the individual studies
22 did not, and then I guess one of the other

1 studies also seemed to have a significant
2 difference in favor of the product in question.

3 So I wanted to ask the sponsor,
4 were they projecting or anticipating that
5 they would be labeling or promoting this
6 product as superior to oral iron replacement?

7 DR. TOKARS: Our pivotal studies
8 showed statistically significant clinically
9 meaningful increases in hemoglobin, and it was
10 proved in our HUB study -- the combined analysis
11 as well as the individual analysis -- and in the
12 postpartum studies. We would anticipate that
13 our labeling would reflect those results.

14 DR. HENNESSY: Dr. Kramer?

15 DR. KRAMER: I'd just like to push a
16 little more on Dr. Harrington's question, since
17 someone from the audience spoke about the
18 importance of the avoiding transfusions, I need
19 to understand whether or not the company has
20 studied transfusion rate in a comparative way in
21 the studies.

22 DR. TOKARS: Transfusion rates was not

1 an endpoint on our studies, unfortunately.

2 DR. KRAMER: Was it collected? It
3 wasn't collected at all?

4 DR. TOKARS: No, it wasn't. It was
5 collected -- Dr. Mangione could speak to that.

6 DR. MANGIONE: Yes, it was collected.
7 It was an endpoint that was measured. The
8 transition rate was low.

9 One of the exclusion criteria in
10 the trials was an anticipated need for a
11 blood transfusion, so that pre-selected that
12 subgroup.

13 DR. HENNESSY: Dr. Klein?

14 DR. KLEIN: Let me just make one
15 comment, because this did come up during the
16 public period.

17 I know of no credible textbook or
18 no credible publication that advocates giving
19 transfusions to correct iron deficiency
20 anemia. Not a very effective way to deliver
21 iron. There were a few emergency situations
22 in which it is done.

1 DR. HENNESSY: Thank you.

2 Dr. Greenland, did you have any questions to the
3 sponsor about effectiveness and clinical
4 benefit?

5 Dr. Greenland, are you on the
6 phone?

7 So now why don't we move to the
8 question of risk?

9 Dr. Paganini, you had a risk
10 question, I believe; right? And we will put
11 Dr. Lincoff on the list as well.

12 DR. PAGANINI: One of the issues that
13 we saw was some of the folks were associated
14 with some rather significant infections, which
15 led to mortality, especially in this subgroup of
16 population where infection is a big potential.

17 Do you have any data on maximum
18 ferritin levels that were given either
19 immediately after giving the drug or beyond,
20 and other issues -- PMN migration, anything
21 with free iron generation -- anything with
22 TNF-alpha or any of the other inflammatory

1 agents in response to such a large dose?

2 DR. TOKARS: Dr. Mangione, can you
3 speak to our data?

4 DR. MANGIONE: Yes, I can begin by
5 addressing your question about ferritin levels.

6 We specifically looked at the
7 incidence of the relationship between the
8 maximum ferritin level that was achieved in
9 the study and the specific incidence of
10 infection.

11 Slide on, please? This particular
12 slide is from our oral iron control data set,
13 and it includes postpartum anemia, heavy
14 uterine bleeding, non-dialysis
15 dependent-chronic kidney disease, and
16 inflammatory bowel disease.

17 On the left, you can see the
18 relationship between the maximum ferritin
19 achieved in the study and the incidence of
20 adverse events, and there was no particular
21 pattern seen. And in fact, the incidence of
22 serious adverse events, which this table

1 summarized, was lowest for that group that
2 achieved a maximum ferritin of greater than
3 800.

4 DR. HENNESSY: Dr. Lincoff?

5 DR. LINCOFF: I was wondering if you
6 could expand upon the designs of -- the ongoing
7 randomized studies sound fairly large and how
8 you're adjudicating, or what's your endpoint
9 assessment as for the safety endpoints in the
10 population? It's described briefly in your
11 management plan here.

12 DR. MANGIONE: Yes, yes. There are
13 two studies. One is a study particularly in the
14 indications we're seeking for postpartum anemia
15 and heavy uterine bleeding, and the patients are
16 being randomized to FCM versus standard medical
17 care. It's anticipated at this point that we'll
18 be enrolling 1,000 patients in that.

19 The primary endpoints of safety
20 endpoint, and includes the specifically the
21 incidence of serious adverse events, which
22 will be analyzed thoroughly.

1 The second study is in the chronic
2 kidney disease population -- the
3 non-dialysis-dependent chronic kidney disease
4 population, which will receive the maximum
5 dose, potentially, of up to 1,000 milligrams
6 and the hemodialysis population, which will
7 receive the dose of 200, and those were being
8 analyzed similarly.

9 DR. LINCOFF: Can I ask a question?
10 And in relation to the point that Dr. Harrington
11 brought up, it was striking to me that in the
12 randomized studies -- in the non-peripartum or
13 menstrual bleeding groups, where most of the
14 deaths were, four of the five were outside of
15 the U.S.

16 Now, I don't recall if you told us
17 what the proportion of patients in those
18 studies that were actually enrolled outside
19 of the U.S., so that may just be
20 proportional, or I wonder if it's not
21 proportional.

22 So in connection with that if you

1 could answer that, and also of these ongoing
2 studies, where they're being performed, and
3 where do you anticipate most of the
4 enrollment would be carried out?

5 DR. MANGIONE: Yes. Three of the
6 deaths were in hemodialysis patients. It was 3
7 out of 311 hemodialysis-treated patients. All
8 the hemodialysis studies were conducted in
9 Eastern Europe. The non-dialysis-dependent
10 studies, there were two of them. There was the
11 one randomized control trial, and the one open
12 label 44-week trial. Both of those were
13 conducted in the United States.

14 The inflammatory bowel disease
15 study was conducted in Eastern Europe. There
16 were three postpartum studies, randomized
17 trials; one of those was conducted primarily
18 in Eastern Europe. The two that were run
19 primarily by us, a small percentage, I
20 believe, less than 10 percent, included
21 Mexico, very few Canada, and thirdly, heavy
22 uterine bleeding study was totally conducted

1 in the United States, with a small
2 percentage, 5 to 10 percent in Mexico, and --

3 DR. LINCOFF: For your ongoing
4 trial -- the new trials are being --

5 DR. MANGIONE: All in the United
6 States.

7 DR. HENNESSY: Thank you.

8 Dr. Lockwood.

9 DR. LOCKWOOD: I have a couple of
10 questions that relate to the differences in the
11 rates of hypophosphatemia between the heavy
12 uterine bleeding and the postpartum anemic
13 patients, and I'm trying to understand why there
14 would be such a discrepancy in occurrence -- in
15 one case, it was 8.8 percent; the other case, it
16 was 70-something percent.

17 And so my questions are, do you
18 have any information that sheds any light as
19 to why there is such a differential
20 occurrence? And secondly, can you tell me a
21 little bit more about the heavy uterine
22 bleeding patients? Were they on, for

1 example, long-term progestin-only
2 contraceptives, were they on estrogen, were
3 they on a hormonal regimen that could affect
4 bone metabolism, availability of phosphorus
5 et cetera?

6 That's the question.

7 DR. TOKARS: Dr. Mangione?

8 DR. MANGIONE: Yes, if I may have the
9 slide about baseline characteristics and
10 postpartum and heavy uterine bleeding.

11 There was one thing that was
12 striking about the difference between the
13 postpartum and heavy uterine bleeding
14 population, is that the heavy uterine
15 bleeding population was by and large more
16 anemic and more iron-deficient.

17 Slide on, please? If you look at
18 the mean TSAT values for the FCM And oral
19 iron for heavy uterine bleeding on the far
20 right side versus what we saw in the first
21 and second column, the transferrin
22 saturations were almost double in the

1 postpartum population. The ferritins were
2 significantly lower, approximating seven in
3 heavy uterine bleeding population, but higher
4 in the postpartum population.

5 Secondly, what we saw is that the
6 degree of erythropoiesis was greater in the
7 heavy uterine bleeding population than it was
8 in the postpartum overall, and whether or not
9 that's a contributing factor, it's not
10 totally clear.

11 DR. LOCKWOOD: Erythropoiesis after
12 the therapy begins?

13 DR. MANGIONE: That's correct.

14 DR. LOCKWOOD: And were there big age
15 differences? I assume there were, but do you
16 know what they were offhand, the age of the
17 women?

18 DR. MANGIONE: The mean age
19 approximately was in the low range of 23 to 25
20 for postpartum population, and the mean 30s, 35
21 for a heavy uterine bleeding population.

22 DR. LOCKWOOD: Do you know about

1 approximately how many of the heavy uterine
2 bleeding patients were on Provera or some kind
3 of long-acting progesterone?

4 DR. MANGIONE: We did capture that
5 information, and I can't give you exact numbers.
6 We did require that the treatment was held
7 stable during the course of the trial and prior
8 to enrollment.

9 So there was at least balance, but
10 I don't know the exact numbers, I'm sorry.

11 DR. HENNESSY: Dr. Brittenham?

12 DR. BRITTENHAM: Yes, I'd like to
13 pose questions about the short- and long-term
14 effects of the treatment of the ferric
15 carboxymaltose on iron metabolism, and how these
16 might underlie the observations.

17 But I'd like to begin by saying as
18 a hematologist -- and I think any
19 hematologist certainly appreciates that
20 current therapy for iron deficiency is
21 unsatisfactory. Indeed every woman with
22 postpartum anemia represents a failure of

1 iron therapy or supplementation. They
2 shouldn't be anemic or iron-deficient at that
3 point.

4 At the same time, with the product
5 you're proposing not only a new pharmacologic
6 entity to be used, but a new kind to
7 treatment, to use a total dose infusion.
8 That's the particular advantage that you
9 portray for it. And I have to say that we
10 have no previous systematic experience, and I
11 think the studies the company has done are
12 the largest set of information that's
13 available about this.

14 So although total dose infusion is
15 recommended by some and practiced by some,
16 information about it has never been
17 satisfactorily collected in advance. We're
18 looking for any uncommon events, and so
19 single individuals are unlikely to have an
20 indication of such events.

21 Specifically what I'd like to ask
22 about is whether there is any further

1 information about the short-term effects of
2 infusions on what's on circulating iron in
3 this -- within the systemic circulation?
4 Normally, all iron is bound to transferrin as
5 it circulates. With the ferric
6 carboxymaltose, the iron within it seems,
7 from -- to be bound within this and not
8 interacting, but when the iron is taken up by
9 macrophages, it's very promptly recycled and
10 going out into the circulation.

11 So have you determined whether or
12 not it produces a non-transferrin,
13 non-carboxymaltose bound fraction? If so,
14 then you could imagine that that would in
15 circumstances produce oxidative -- could
16 produce oxidative stress, or a whole variety
17 of complications that might link some of
18 these observations. So have you specifically
19 in the studies determined whether or not
20 there's non-transferrin-bound,
21 non-carboxymaltose-bound circulating iron?

22 DR. TOKARS: Dr. Van Wyck will talk to

1 some his research.

2 DR. VAN WYCK: I couldn't agree with
3 Dr. Brittenham more that the introduction of the
4 science package for FCM has brought science and
5 knowledge -- facts -- to a area which has not
6 been regulated and has had, despite use for over
7 40 to 50 years, really very little science
8 behind it. If I may, I'm going to take your
9 points one at a time. First, about the
10 possibility of free iron in the preparation,
11 free or labile iron --

12 DR. BRITTENHAM: Not in the
13 preparation. Let us accept for the moment that
14 the preparation itself doesn't contain it, the
15 part you inject doesn't contain free iron. What
16 I'm concerned about is iron recycled -- after
17 it's given, that the iron recycled by
18 macrophages exceeds the transferrin's binding
19 capacity.

20 DR. VAN WYCK: Correct, correct. J2
21 first, please? Slide on? In this method, we
22 asked the proximate question, which is, is there

1 iron that passes directly from the agent to
2 transferrin? We examined that question by
3 removing the agent from the serum, adding agent
4 to serum, and then removing it by passing it
5 through an alumina column. That removes the
6 agent, and then we can measure whether the
7 transferrin-bound iron by the standard
8 transferrin saturation test, serum iron test,
9 changed. It did not. It did not change.

10 So that's step one.

11 DR. TOKARS: But that's not the
12 question. The question is not if you add the
13 compound to serum, does it transfer? It's that
14 when you inject it into a patient and the
15 patient's macrophages recycle that iron, there's
16 a limit on how much iron the macrophage can
17 retain. Is it putting iron out into systemic
18 circulation that's not transferrin-bound?

19 DR. VAN WYCK: Slide on? I think this
20 will take several slides, if you will abide.

21 Slide on, please.

22 DR. TOKARS: I think it's a very

1 important question.

2 DR. VAN WYCK: A very important
3 question. Dr. John and Dr. Rieves referred to
4 interference of the agent in the determination
5 of the serum iron level, and demonstrated this
6 slide, which is the yellow slide. Let me just
7 simply that by showing -- slide on?

8 The serum iron determination over
9 the first 24 to 48 hours was done in the
10 presence of circulating agent. So this
11 determination is erroneously elevated by the
12 presence of circulating agent. You are in an
13 unbound iron-binding capacity, or apparent
14 unbound iron-binding capacity increases late,
15 as you would expect.

16 Now, TS2, please?

17 This perhaps then gets to your
18 question. If we have excluded the
19 possibility that agent is interfering with
20 the serum iron determination at day 7, 14, 28
21 and 42, then what you can see here on the top
22 line is oral iron transferrin saturation, and

1 the change in -- there's another slide I
2 believe on the change in the serum iron. But
3 in short, serum iron levels increase more
4 after oral iron then after FCM. And that's
5 because these patients are continuously in a
6 oral iron challenge test. They remained for
7 42 days iron-deficient. They had -- the
8 highest TSAT at day 42 in the oral iron
9 treatment group was 91.

10 The highest in the FCM-treated
11 group was 45. This seems to be working as we
12 would expect for an intravenous iron agent
13 that's taken up by macrophages. Here's that
14 slide with the delta iron and time after
15 treatment.

16 So does that answer your question?

17 DR. TOKARS: I'm afraid not.

18 DR. HENNESSY: Can you try to make it
19 so that he can answer it quickly? We need to
20 try to move on.

21 DR. BRITTENHAM: It's a critical
22 question. Is there non-transferrin,

1 non-carboxymaltose iron circulated? And that's
2 possible to measure. But I don't believe that
3 the methodology that they used in these studies
4 measures it. And I think it is the critical
5 question for the possibility of short-term
6 toxicity.

7 DR. HENNESSY: Can you answer that
8 question?

9 DR. TOKARS: I think Dr. Connor might
10 be able to shed some light on this.

11 DR. CONNOR: From the preclinical
12 animal data, we don't have those exact
13 measurements of what's the free iron. But the
14 outcome of what you are worried about is the
15 oxidative stress measurements. And there, we
16 have two bits of data that I think can address
17 that. One is that we did see sustainable iron
18 going into the macrophages, which is -- as you
19 said, that the direction that the iron would go.
20 And then the iron, if it's released from there,
21 the increase in serum ferritin that we see
22 indicates that it is, then we see the same thing

1 in the animals and we don't see an increase in
2 oxidative stress in kidney, liver or heart that
3 we looked at. So I think that addresses the
4 outcome part of your question.

5 DR. BRITTENHAM: I don't have any
6 hesitation about giving the product to healthy
7 rats. But the difficulty is that in patients
8 with infection or inflammation, you may to have
9 the same results. And the other is that rats
10 can excrete iron in a way that humans cannot.

11 DR. HENNESSY: I'll allow a follow-up
12 to this, and then we'll go to Dr. Harrington.

13 DR. VAN WYCK: Because infection came
14 up, and Dr. Paganini's question was not answered
15 in that respect, then I think perhaps we should
16 review the specific infectious cases, if that
17 would be helpful.

18 DR. HENNESSY: You mean the
19 individual --

20 DR. VAN WYCK: No. No.

21 DR. HENNESSY: A clarification of
22 that?

1 SPEAKER: Yes.

2 DR. HENNESSY: Okay.

3 DR. LOCKWOOD: How would it be
4 measured? With MSPAC? What are you getting at?
5 What is the requirement for measuring free iron
6 availability?

7 DR. BRITTENHAM: Non-transferrin-bound
8 iron -- there are well-worked-out procedures in
9 patients with transfusional iron overload for
10 measuring specifically that fraction. And I see
11 no reason why they couldn't be applied in these
12 sorts of studies.

13 DR. HENNESSY: Dr. Harrington?

14 DR. HARRINGTON: My question is for
15 Dr. Cooper. You showed us some data that was
16 recently published looking at the relationship
17 between correction of anemia and improvement in
18 LB function. But I want to go to the same place
19 that Dr. Brittenham I think is going. On the
20 clinical side, is there any data that, following
21 the acute injection of FCM, that we know
22 anything about sort of the clinical parameters

1 of oxidative stress? Do we have ECOs (?) in
2 these patients? Does LB function change? Do we
3 have things like brachia form reactivity? Does
4 that change in the early hours of receiving it?
5 Not three weeks later, when anemia has also been
6 corrected.

7 DR. COOPER: Of course, both of the
8 studies I alluded to that were just published
9 did not use FCM. As far as I know, in the
10 clinical development program, ECOs were not
11 performed. EKGs were normal in a small
12 sub-study but there are measures of oxidative
13 stress systemically in the animal data. But not
14 in human data.

15 DR. HARRINGTON: This is not my area,
16 oxidative stress in animals, but in the animal
17 data, if I understood the methodology, these
18 were chronic studies where the cells were
19 exposed over a period of several weeks. I'm
20 interested in what happens in that first day or
21 two. We don't have that data.

22 DR. COOPER: No, there's no brachial

1 arm reactivity and ethelial cell function
2 surrogates, nitrous oxide and prostacyclin.

3 That's as far as I know.

4 DR. HENNESSY: We'll go to Dr. Klein.
5 Dr. Greenland, have you joined us?

6 DR. GREENLAND: Yes, I'm here.

7 DR. HENNESSY: After Dr. Klein, we'll
8 give you the opportunity to ask any questions
9 about risk, if you have any.

10 DR. GREENLAND: Okay.

11 DR. HENNESSY: Dr. Klein.

12 DR. KLEIN: I want to get back to the
13 hypophosphatemia question, and again, I want to
14 make clear that I'm not particularly concerned
15 about absolute phosphate levels, not concerned
16 about depletion. But I don't understand the
17 mechanism -- and perhaps someone here does,
18 because if the mechanism may simply be pointing
19 out to us that there's something we don't
20 understand that's happening. It may be a
21 signal. I'm not concerned that the phosphate
22 levels get so low that there are going to be

1 cardiac toxicity. That may or may not be the
2 case. But could this be a signal? Or is this
3 just something that happens with excessive
4 erythropoiesis. And I'm frankly not always
5 convinced that that's the case.

6 Do you have anything about the
7 mechanism?

8 DR. TOKARS: Dr. Dennis can speak to
9 that.

10 DR. DENNIS: Yes. Thank you very
11 much. Of course, obviously, clinical trials can
12 only be hypothesis-generating. But let me make
13 a couple of observations about the
14 hypophosphatemia which I think is absolutely
15 fascinating and is apt to be telling us a lot
16 about what is going on.

17 Slide, please. Slide on, please.
18 You saw this presentation from Dr. Mangione.
19 And this is what happens with phosphate, that
20 with baseline levels that were lower in the
21 HUB group than in the postpartum group at 3.6
22 versus 4.2, there's a nadir, as it's reported

1 here, that occurs at about 14 days, and after
2 an initial approximately 18 days, it returns
3 towards normal as you see here.

4 Slide on, please. Slide on. Thank
5 you. Now, this is what is going on with the
6 total population in the controlled trials for
7 the postpartum patients in the blue dots and
8 the HUB patients in the open circles. And
9 you can see that what this slide compares is
10 the baseline phosphate to the nadir
11 phosphate. Some of this is regression around
12 the mean, but the data are striking, that
13 essentially all points are below the line of
14 identification. The HUB population comes in
15 with a lower phosphate and goes down a little
16 bit lower. But basically, that's the same
17 trend. It is almost a universal observation.

18 The time course of the observation
19 is that it kicks in probably about 24 hours
20 to seven days. It is not immediate. And
21 again, the rest of the time course is there.
22 We know from additional studies it's not

1 associated with any major leak of phosphate
2 in the kidney. There is a slight reduction
3 in total phosphate re-absorption by the
4 kidney that's still within the normal range.
5 It is about a five percent change from
6 92 percent re-absorption to 86 percent
7 re-absorption.

8 There's no change in serum calcium
9 magnesium and there's no correlation with
10 profile. Now, the interesting thing to me is
11 this follows the evolution of the processing
12 of iron, as you see from the ferritin. It's
13 almost a mirror image. As the ferritin is
14 rising, the phosphate is falling. I come
15 back to the central issue. We know that the
16 regulation of serum phosphate is much more
17 sophisticated, much more complex than we used
18 to think.

19 And the way we came to know this
20 was from genomic studies in individuals who
21 have genetic defects in phosphate
22 conservation -- lifelong hypophosphatemia.

1 And what do they develop? They develop
2 osteomalacia. They develop bone disease.
3 They don't die of coronaries and they don't
4 die of dialysis. They die of deficient
5 phosphate.

6 So my hypothesis, which I can only
7 bring as totally speculative, is that there
8 is some activation of one of the so-called
9 phosphatonins that we identified from genomic
10 studies of those who have x-linked and
11 autosomal dominant hypophosphatemia, the most
12 notable of which is fibroblast growth factor
13 23. And in all probability, there's some
14 alteration in the activity in that substance
15 that leads to these changes.

16 DR. KLEIN: Do you think that could be
17 a signal of cell toxicity coming at that point
18 in time, or is it totally out of the realm of
19 possibility?

20 DR. DENNIS: I've struggled with what
21 term I would use for this. I think it is
22 basically physiologic, probably worst case,

1 patho-physiologic. I think it tracks with iron
2 trafficking -- I think when this information
3 comes into the public domain, I'm well-aware of
4 a number of investigators who will measure the
5 appropriate phosphatonins and undoubtedly
6 elucidate the mechanism.

7 DR. HENNESSY: Doctor --

8 DR. DENNIS: It is without
9 consequence.

10 DR. HENNESSY: Dr. Greenland, we're
11 asking questions about risk, or on the flip
12 side, safety.

13 Do you have any question that you
14 want to ask of the sponsor?

15 DR. GREENLAND: Well, this -- not so
16 clear on the materials that I received and what
17 little I have gotten out of this so far is how
18 narrowly the product can be prescribed given the
19 risk factors that appear to be present in the
20 cases that have been reported here?

21 DR. HENNESSY: Could you repeat that?
22 I wasn't clear on what that question was.

1 DR. GREENLAND: What I'm not clear on
2 is to what extent can this leading -- the panel
3 recommend approval for -- restrictive based on
4 the observation that are the cause of concern
5 here? In particular, the deaths, for example.
6 That is for example, restricting by indication
7 cardiovascular problems that were present in
8 this --

9 DR. HENNESSY: Are you on a speaker
10 phone or do you have a hand-held set? Because
11 we're having --

12 DR. GREENLAND: Handheld.

13 DR. HENNESSY: Okay. Because we're
14 having a lot of trouble hearing you.

15 DR. GREENLAND: I'm having trouble
16 hearing you, too. But --

17 DR. HENNESSY: I'm not sure how to
18 handle this. So can you try it slowly one more
19 time, Sander?

20 DR. GREENLAND: Okay. Once again, to
21 what extent can the approval (inaudible)
22 Reflect the risk factors that are present and

1 the adverse reports of concern in the trial data
2 that have been presented as showing a signal for
3 problems, such as the mortality risk?

4 DR. HENNESSY: Right. So let me try
5 to put that in my own words and see if it is the
6 same thing. So I think you are speaking to risk
7 management. Can the risk management plan, if
8 the drug is approved, would the risk management
9 plan manage the apparent risks that are showing
10 up in the trials. Is that your question?

11 DR. GREENLAND: I think that's close
12 enough.

13 DR. HENNESSY: You want to take a stab
14 at that one?

15 DR. TOKARS: Dr. Andrews, could you
16 speak to that?

17 DR. ANDREWS: Well, to actively manage
18 a risk, you generally need to have a specific
19 risk that you know how to manage or that can be
20 managed. And in terms of the causes of death
21 that were seen in the controlled studies, which
22 I believe is the only legitimate comparison,

1 because the uncontrolled experiences had no
2 controls and they were in populations with an
3 expected mortality that was exactly what was
4 observed or even higher.

5 The pattern in the deaths from the
6 controlled studies really do not indicate a
7 clustering or commonality that would suggest
8 any mechanism for managing that risk
9 post-approval through screening of patients
10 with respect to response rate, et cetera. So
11 therefore, the conservative approach to a
12 risk management plan in the absence of a
13 specific risk to manage would be to restrict
14 the patient population and make sure that
15 there's a very deliberate phased rollout so
16 the drug is being used appropriately by
17 clinicians who are well-trained and will
18 agree to carefully monitor patients and
19 report any adverse events so we could get
20 some better data on what is currently an
21 uncertain signal.

22 DR. HENNESSY: We're up to

1 Dr. Paganini. We're still doing safety or risk,
2 and when we have gotten the risk questions,
3 we'll turn to the risk management plan.

4 DR. PAGANINI: My question on the free
5 iron was answered.

6 DR. HENNESSY: Dr. Lesar.

7 DR. LESAR: Yes. Back to the
8 phosphate again. Just one question, and this
9 has to do with -- we can have relative risks
10 between iron products, and whether or not
11 there's data on other intravenous iron products
12 and the rate or degree of hypophosphatemia that
13 may give us some insight into either
14 similarities or differences between these
15 agents.

16 DR. TOKARS: Dr. Dennis.

17 DR. DENNIS: First of all, I'm not
18 aware of any other association, except for a
19 fascinating experiment that was done in nature
20 by physicians in Japan. It was with a product
21 called saccharated (?) iron. And there was an
22 epidemic of osteomalacia. It turns out that by

1 tracking prescriptions, physicians noted that
2 the number of prescriptions for intravenous iron
3 almost exceeded the population of Japan.

4 And so in the Endocrinology Journal
5 of 1993, Sato reported ten patients that came
6 to his attention. These were people who
7 presented with osteomalacia, and they had
8 received up to daily high-dose intravenous
9 saccharated iron for years. And he admitted
10 that this was totally a bizarre
11 practice -- a totally bizarre practice.

12 And they presented with this
13 footprint. They had osteomalacia; they had
14 hypophosphatemia, they had renal wasting of
15 phosphate, and they had impaired production
16 of calcitriol -- 1,25 dihydroxy vitamin D.
17 This is the footprint of fibroblast growth
18 factor 23, the central phosphatonin that's
19 associated with x-linked hypophosphatemia and
20 with oncogenic hypophosphatemia osteomalacia.

21 So to the extent that this was an
22 issue of iron, of high-dose intravenous iron,

1 protracted apparently in that Japanese series
2 of observation, but seen acutely in this
3 situation as an acute reversible event, I
4 think this supports my tentative hypothesis
5 that this is activation of a phosphotonin.

6 DR. HENNESSY: Dr. Brittenham. Then
7 we'll move on to the risk management program and
8 post-marketing pharmacovigilance.

9 DR. BRITTENHAM: I just wanted to ask
10 one further question about the long-term
11 possibility of risk from the product. After the
12 ferric carboxymaltose is given, it's taken up by
13 macrophages. And I'd like to ask about what is
14 known about the fate of that. We know that iron
15 dextrin persists for months or years.

16 Do you have any information on
17 whether this could provide a predisposition
18 to infection or exacerbation of infection of
19 organisms that live within macrophages such
20 as tuberculosis, or in circumstances where
21 there's a immunosuppression, like HIV or
22 other conditions.