

1 they could not eradicate H. pylori in the absence
2 of Ermiprisol.

3 DR. MEGRAUD: It's definitely true, but
4 I think we cannot rely on some -- this kind of
5 studies from so many years ago because that
6 knowledge was not good enough, I think, and those
7 are -- there were very few patients in the
8 studies.

9 I don't think that's true that there was
10 a study with Azithromycin, but Azithromycin turned
11 out to induce resistance in most of the cases.

12 But it was used as the only antibiotic.
13 I think this has to be revisited.

14 DR. JUDSON: Thank you. One final
15 question by Dr. Kirschner.

16 DR. KIRSCHNER: As a non-microbiologist
17 and gastroenterologist, we're talking about the
18 importance of using culture both for identifying
19 resistant organisms and multi-centered trials.

20 And can you tell us something about the
21 relative accuracy and sensitivity of using these
22 different methods like transporting of a frozen

1 sample to a central center. And is that still as
2 sensitive and accurate as if you do it
3 immediately, within 4 hours?

4 DR. MEGRAUD: I think it is. I think it
5 is. And in the last data, I could see concerning
6 multi-centered studies using some type of
7 facilities giving sensitivity of between 80 and 90
8 percent for culture, which is not perfect,
9 definitely not perfect.

10 I speak now at the inclusion, but I
11 think if you have susceptibility data on 80 to 90
12 percent of the patients included, it's really very
13 important to explain at least the failure in some
14 cases.

15 I think it's very important for the
16 understanding of the study.

17 DR. JUDSON: Thank you very much. We'll
18 be breaking for lunch in just a minute, and Ermona
19 McGoodwin has some information on what the
20 possibilities are.

21 MS. MCGOODWIN: Thanks. The hotel has a
22 restaurant just down the hall to the left, and the

1 back part of the dining room has been set aside
2 for the panel members. So there's a buffet. You
3 can --

4 There are also some restaurants in the
5 area, but you may need transportation. Thank you.

6 DR. JUDSON: Thank you. And we will
7 reconvene shortly after noon.

8 (Whereupon, a luncheon recess was
9 taken)

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A F T E R N O O N S E S S I O N

(12:10 p.m.)

DR. FISHER: Dr. Judson and I are going to alternating chairing these sessions so we give each other a little bit of a break. And you get a little bit of a break from each one of us.

What we're going to do now is go on to a second portion of this today's session. And what you will see in front of you in the agenda is also an issue which is being raised, and that some of these talks are going to address and give us some information on.

And then we're going to go at the end and have about a 35 to 40 minute time period for committee discussion and questions and answers.

What I'd like to do, unless somebody has something that's really burning, is have the talks all be done. Have the 6 or 7 -- I guess it's 6 little speeches that we have given first and have people make notes to themselves about it.

And then, we can go ahead after that and ask questions in general, unless there is

1 something really burning. So I'll ask for burning
2 questions after each little talk.

3 Let me read what the issue number one is
4 as it's put here.

5 "Clinical microbiological end points for
6 Helicobacter pylori-associated peptic ulcer
7 disease clinical trials: is there enough clinical
8 benefit derived from eradication of H. pylori to
9 consider eradication alone as a valid end point
10 for the prevention of ulcer recurrence? If not,
11 what other end points should be considered?"

12 Based on that, I'm going to ask Dr.
13 Girardi to go first on eradication and ulcer
14 recurrence.

15 DR. GIRARDI: Good afternoon. It's my
16 pleasure to address everyone.

17 Before I get started, all of you should
18 have a copy of the FDA presentations handout. So
19 if you have trouble looking at the slides, you can
20 follow along on the handout.

21 My talk begins on page 11 of the
22 handout. What I'd like to do is talk briefly

1 about the link between eradication and the
2 prevention of peptic ulcer recurrence. In general
3 in our division of anti-infective drug products,
4 we advocate the use of both clinical as well as
5 microbiologic end points.

6 When looking at new regimens for H.
7 pylori-associated peptic ulcer disease clinical
8 trials, the microbiologic end point ostensibly is
9 eradication or cure of the infection, and this has
10 been generally defined at 4 weeks post-therapy.

11 Clinical end points -- these are
12 examples which I've listed -- include the rate or
13 the speed of ulcer healing, the reduction of ulcer
14 recurrence, which is obviously a very important
15 one. And we've also encountered combination of
16 both microbiologic, as well as clinical end
17 points, in terms of all the overall success.

18 We have seen three definitions of
19 overall success, the first being a combination of
20 the eradication of the microbiologic end point and
21 ulcer healing.

22 The second definition of overall success

1 being a combination of the two clinical end
2 points: healing and no recurrence.

3 And perhaps the most comprehensive
4 definition of overall success has been the
5 combination of all three, the microbiologic end
6 point eradication, as well as the two clinical end
7 points: healing and no recurrence.

8 If we could accept a microbiologic end
9 point as a surrogate, as Dr. Stephen Fredd earlier
10 alluded to, as a surrogate for the clinical end
11 point of prevention of peptic ulcer disease, who
12 might benefit from this?

13 Well, certainly we feel that the public
14 would benefit, because clinical trials could be
15 designed so that newer regimens could be brought
16 to market in a quicker fashion.

17 Certainly, industry would benefit
18 because the cost of doing clinical trials would be
19 reduced, since long-term endoscopic follow-up
20 would not be needed. And we at the FDA would
21 benefit because the amount of data that we would
22 have to review would be reduced.

1 So with this background in mind, my
2 colleagues and I -- Dr. Hopkins, Beth Turney from
3 biometrics -- decided to ask the question, "Does
4 eradication of *Helicobacter pylori* prevent peptic
5 ulcer recurrence?"

6 And we wanted to try to answer this
7 question by looking at the available literature
8 that was out there.

9 The results of this comprehensive
10 literature review in terms of a metanalysis were
11 initially presented internally at the FDA during
12 our scientific round reception in January.

13 We have also had the opportunity to
14 discuss this in Philadelphia at the IVC meeting,
15 present it in abstract form at Edinburgh, and
16 we've also spoken to both the GI as well as the IB
17 Advisory Committees, making them aware of our
18 study.

19 What I thought I'd do now is just go
20 over once again the results of our literature
21 review and tell you exactly what the methods were,
22 in terms of bringing to the foreground our

1 decision to put, into our "points to consider"
2 document, the use of a potential surrogate.

3 Essentially, what we did was use eight
4 overlapping midline searching strategies using 4
5 searching strategies with duodenal ulcer and 4
6 with gastric ulcer in combination with terms
7 pylori, eradication, recurrence, and treatment.
8 And the end here refers to the number of midline
9 titles that were generated.

10 We found a total of 60 papers that had
11 information on both H. pylori eradication as well
12 as recurrence -- prevention of recurrence of
13 peptic ulcer disease, 26 of which were review
14 articles, 34 of which were manuscripts.

15 By reading the references of these
16 papers, we came up with an additional 12 abstracts
17 that were not published in full form yet, giving
18 us a total of 46 studies.

19 I'm must say here that three of these
20 studies included information for both DU --
21 duodenal ulcer -- as well as GU -- gastric ulcer
22 -- so that we could analyze them as separate

1 studies, as well. So really the total number of
2 studies, instead of being 46, were actually 49.

3 We looked at these 49 studies closely
4 and applied requisite inclusion criteria which are
5 listed here.

6 The inclusion criteria that we applied
7 include that the papers had to have defined
8 eradication at least 4 weeks post-therapy, at
9 least two of three endoscopic tests had to have
10 been done, and patients with active ulcer disease
11 had to have been examined.

12 If, for example, patients with other H.
13 pylori-associated conditions such as non-ulcer
14 dyspepsia and the like were included, those papers
15 were excluded from the analysis.

16 Long-term ulcer recurrence greater than
17 or equal to 6 months after the completion of
18 therapy had to have been addressed and
19 importantly, ulcer recurrence had to have been
20 linked to HP status.

21 After applying this inclusion criteria
22 to our 49 studies, 30 studies were eliminated,

1 giving us a total of 19 studies -- 14 studies of
2 which were duodenal ulcer studies, 5 of which were
3 gastric ulcer studies.

4 This particular slide is not in your
5 handout, so please focus your attention up front.

6 In terms of an overall result, what we
7 found was that the recurrence rates among patients
8 who were eradicated of infection for both DU and
9 GU -- as represented in the pink -- were
10 significantly lower from those patients who did
11 not achieve H. pylori eradication.

12 And keep in mind, however, that that
13 analysis did not include any patients who might
14 have dropped out for whatever reason, or patients
15 who did not achieve ulcer healing and who were not
16 assessed for eradication.

17 If we throw those patients back into the
18 analysis -- first, the dropouts -- in a worse case
19 scenario and consider the dropouts as failures,
20 namely that they were eradicated of infection, and
21 that their H. pylori was indeed eradicated, but
22 they did experience peptic ulcer recurrence, we

1 still see a statistically significant difference
2 in the recurrence rates.

3 Similarly, if we took all the unhealed
4 patients who were not assessed for eradication and
5 who were not included in the analyses of
6 recurrence, we find a statistically significant
7 difference in the recurrence rates for the HP
8 negative group as well.

9 And finally, in a even worse-case
10 scenario, by adding both the unhealed patients as
11 well as the dropouts, one still maintains a
12 statistically significant difference, in terms of
13 peptic ulcer recurrence for the HP negative group
14 compared to those patients who were not eradicated
15 of their infection.

16 If you look at all of the 14 duodenal
17 ulcer studies together, one element which is
18 striking is that there was significant variability
19 in terms of ulcer recurrence among those studies
20 for both the non-eradicated population, which is
21 the top figure, as well as for the eradicated
22 population in the bottom figure.

1 So what we decided to do was, by
2 observing this statistically significant
3 variability in recurrence rates among studies, to
4 examine the potential impact of 4 study design
5 variables and whether or not they made a
6 difference in terms of the recurrence rates as
7 seen among the HP negative group.

8 We did not do this for the gastric ulcer
9 studies since there were only 5 and the
10 variability among studies for gastric ulcers were
11 not statistically significant.

12 In the handout, if you jump to page 26,
13 this should correspond to the slide.

14 The first study-designed variable that
15 we examined was the eradication time point. In
16 papers that examined eradication at 4 weeks versus
17 papers that examined eradication at 12 or more
18 weeks, and looking at the HP negative group, there
19 was no difference in recurrence rates among those
20 patients.

21 The second study-designed variable that
22 we examined was the recurrence time point for

1 duodenal ulcer. For papers that looked at
2 recurrence at 6 to nine months or 12 or more
3 months, still there was no statistically
4 significant difference among the recurrence rates
5 for the HP-negative group.

6 The next two study-designed variables,
7 however, did show a statistically significant
8 difference, the first being the number of
9 diagnostic tests being performed.

10 If papers used two tests compared to --
11 this should read three or more tests, there was a
12 statistically significant difference in the
13 recurrence rates among the HP negative group
14 patients, something on the order of nine versus
15 three percent, statistically significant.

16 And finally, the last study-designed
17 variable that we looked at was the type of
18 publication. Abstracts had a statistically
19 significant difference in recurrence rates among
20 the HP-negative group compared to manuscripts,
21 something on the order of 14 versus 4 percent
22 statistically significant difference possibly

1 suggesting some literature bias.

2 What we concluded was that, based on the
3 studies that we evaluated, based on the literature
4 that we reviewed, we concluded that HP eradication
5 defined at 4 weeks after the completion of therapy
6 should be considered an appropriate surrogate for
7 reduced DU as well as GU recurrence for the
8 purpose of clinical trial design and for patients
9 not taking chronic end stays. And this is what
10 led to that part of the "points to consider"
11 documents which you are familiar with.

12 By accepting a microbiologic end point
13 alone, however, we do recognize that there are
14 certain limitations -- potential limitations --
15 the first being, as I've already stated, the
16 potential for literature biases.

17 The results of our study are based on
18 the published literature.

19 The second potential limitation is the
20 lack of placebo controls. In all the studies that
21 we have analyzed, no study had a placebo control.
22 They all had active therapy.

1 And has been suggested, perhaps
2 investigators in these studies may not be as
3 vigilant in terms of picking up that recurrent
4 ulcer if they knew that everyone got some form of
5 active therapy.

6 Lack of multi-centered trials is always
7 a concern. And as I've already mentioned, in
8 showing one of the graphic slides, only patients
9 who achieved ulcer healing were assessed for
10 eradication.

11 And perhaps this is not -- this is not
12 what we should be doing, and we should be
13 evaluating eradication in all patients, regardless
14 of whether they achieve ulcer healing, because
15 maybe we're not getting a true eradication rate.

16 If we want to assess eradication and
17 healing at the same time, perhaps we should change
18 the definition of healing to 4 weeks post-therapy
19 to coincide with the eradication time point and
20 our analysis could then proceed.

21 And Dr. Hopkins is going to elaborate a
22 lot more in this area during the next talk.

1 Maureen Dillon Parker is kind enough to
2 put up an overhead of a quote which was in the HPC
3 observer last week, which I thought was very
4 interesting and to share with you. And this is
5 from Dr. Elushoff, Capitol Hill.

6 It says that, "Now that we recognize
7 that eradication gets rid of the ulcer, the fall
8 of the acid hypothesis to me is like the fall of
9 Communism. I never thought it would happen in my
10 lifetime."

11 (Laughter)

12 I think this is a great quote. What I
13 think we should do though is call him up and ask
14 him what he really thinks about it.

15 Thanks.

16 DR. FISHER: Thank you, Dr. Girardi.
17 Any burning questions for Dr. Girardi? I have one
18 quick one. I just want to make sure. By "active
19 ulcer disease" --

20 DR. GIRARDI: Yes.

21 DR. FISHER: -- or inclusion in it, in
22 your studies, you meant that the studies said that

1 they had a crater at the time the endoscopy was
2 done and the patient was deemed to be HP-positive
3 at that point?

4 DR. GIRARDI: Yes. That's correct.

5 DR. FISHER: Okay. Thank you. Question
6 at the back mike. Can you identify yourself? Can
7 I just make one statement?

8 DR. FISHER: Can you identify -- oh, I'm
9 sorry. Dr. Hopkins.

10 DR. HOPKINS: Yes, Dr. Hopkins. There
11 were two studies that actually treated and just
12 recently healed the ulcer. But of the 14, there
13 were only two that actually recently healed the
14 ulcer, but they were active within, you know, a
15 week or two onto the study.

16 MR. HANNAKER: Nanath Hannaker from
17 Josman Laboratories.

18 Recent studies have shown that in dental
19 plaque, there is a lot of H. pylori. This has
20 been -- there are at least about half a dozen
21 papers now talking about this now.

22 And looking at the eradication of H.

1 pylori, those treatments that include
2 Metronidazole and clarithromycin, both of which
3 extensively secrete in the saliva, and only when
4 you reach a high eradication rate is there a very
5 low relapse.

6 Does anybody on the panel wants to talk
7 about this -- whether Metronidazole and/or
8 clarithromycin could be doing more in the dental
9 plaque than anything in the stomach, and that
10 could be the reason for the high eradication and
11 no relapse?

12 And when you have resistant organisms
13 for both of these antibiotics, the eradication is
14 low and the relapse rate is high.

15 DR. FISHER: I don't know if anybody
16 wants to take that on the panel.

17 I'd like to keep that short, because I'm
18 not sure that's pertinent to what the presentation
19 is concerned with.

20 DR. MEGRAUD: I just want to comment on
21 the possibilities that dental plaque is a reserve
22 role for H. pylori.

1 I think it's not true. I think that
2 there are a few papers telling that PCR could
3 detect the which may happen to be of H. pylori.

4 But in fact, I don't think this is good
5 data, because they should use at least two kinds
6 of primers to state such thing.

7 There are today only two papers where H.
8 pylori was cultured in dental plaque or in the
9 oral cavity. And I think only two strains. One
10 even was maybe not culture, but just seen in the
11 stain.

12 So I don't think this data are valid.

13 DR. FISHER: Dr. Laine.

14 DR. LAINE: At USC, we've also checked,
15 and we've had difficulty identifying this with PCR
16 and in our saliva samples with our patients.

17 DR. FISHER: Dr. Fredd?

18 DR. FREDD: I just want to sort of tease
19 apart some issues, if I could.

20 One, there are two placebo control
21 trials by Dr. Graham, et al. -- one in active
22 ulcer disease, and the other, after healing in

1 terms of ranitidine placebo versus ranitidine
2 triple therapy.

3 Those papers might not have been
4 included in your metanalysis because they didn't
5 give enough detail on the type of eradication that
6 was done and time for eradication, although they
7 do both specify eradication rates, which are about
8 the same as point estimates, whether you are
9 dealing with active disease or healed disease in
10 those papers.

11 When we are -- when the committee is
12 considering the use of eradication as a surrogate
13 and we consider how to do that rate, whether we
14 are doing it in healed patients or old patients,
15 is that important to the fundamental decision of
16 whether you can use eradication, by any type of
17 mathematical maneuver that correlates with peptic
18 ulcer lack of recurrence?

19 In other words, are there not two
20 questions here? One, can eradication done by some
21 way be useful, and two, what ways should we do it?

22 DR. GIRARDI: Dr. Girardi. Is this on?

1 DR. FISHER: Yes, it's on.

2 DR. GIRARDI: Okay. I'm going to let
3 Dr. Hopkins get into that second point, because
4 his presentation is going to address a lot of
5 those issues.

6 You're right that -- the placebo
7 controls -- what I suggested was that in our
8 analysis, none of the papers that were included in
9 our analysis had a placebo control. So that is
10 why I put that on the slide as a potential
11 limitation to results obtained from our study.

12 DR. FISHER: Dr. Sonnenberg. And then I
13 want to go on.

14 DR. SONNENBERG: I didn't like the last
15 slide that you showed my rates on. It's very
16 funny, but it's not true. That's the problem with
17 this.

18 The moment you stop thinking about it --
19 there are so many holes in this.

20 Acid secretion is still a very important
21 factor in peptic ulcer disease.

22 DR. FISHER: Okay. Dr. Hopkins.

1 DR. HOPKINS: I guess I would respond to
2 Dr. Fredd's comment quickly just to say that Dr.
3 Graham's paper is referenced on page 35 in the
4 non-evaluable studies.

5 I will get into Dr. Sonnenberg's
6 comments as I go along, in terms of discussing the
7 role of eradication in healing. So my talk
8 briefly will be on the association between
9 eradication and the speed of healing or the
10 prevalence of healing post-treatment.

11 One of the problems with analyzing data
12 in terms of determining eradication rates, as Dr.
13 Girardi alluded to, was that you may actually get
14 very different eradication rates depending on what
15 patient population you assess eradication in.

16 And if you assess eradication in just
17 the people who achieve ulcer healing post-therapy,
18 you'll get ten out of ten, which would be a
19 hundred percent, whereas if you assess eradication
20 in patients who only achieve ulcer healing in the
21 regimen B, you may get 70 percent.

22 That's in contrast to the eradication

1 rate that you would see if you assessed
2 eradication in all patients. In regimen A, this
3 would be ten percent or ten over 100, and again,
4 70 percent in regimen B.

5 Admittedly, placebo would probably get
6 better healing rates than we see in this
7 antibiotic, but these are just sort of
8 hypothetical examples to the potential problem
9 with assessing eradication in only patients who
10 have healed.

11 I throw this slide up just to outline
12 what might be a theoretical study design if you
13 were to assess the contribution of eradication to
14 healing. And I called it the pathophysiologic
15 factorial design of ulcer healing.

16 And what you potentially could do was
17 use an anti-secretory agent as Dr. Graham did in
18 his study and then use an eradicating
19 anti-microbial non-bismuth containing regimen.

20 The idea here is that, you know, as
21 Hentshel -- Dr. Hentshel did in his study where
22 you actually get around the idea that, you know,

1 bismuth-containing -- some bismuth preparations
2 may have healing properties. And then you use
3 both the anti-secretory agent alone, plus the
4 anti-microbial eradicating regimen to assess the
5 impact of healing, given different eradicating --
6 eradication rates.

7 And you would assess eradication healing
8 probably at week eight of the study or 4 weeks
9 post-treatment. And then probably, as Dr. Graham'
10 did, even further out.

11 This has not actually been done
12 literally. However, we have come pretty close.
13 This is a paper by Dr. Hotskin where they actually
14 studied classical triple therapy and classical
15 triple therapy plus some Emiprisol.

16 And by the way, if you can't see these
17 slides, they are on page, I think, 45 of your
18 handout.

19 And you see high eradication rates in
20 both regimens, as well as high healing rates.
21 This actually should be 5 weeks post-therapy or 4
22 weeks after microbial therapy, suggesting that

1 classical triple therapy alone may be all that is
2 needed to achieve high healing rates there.

3 Dr. Graham's study in 1991 in the
4 "Annals of Internal Medicine" used what he called
5 placebo or ranitidine versus ranitidine plus
6 classical triple therapy, and again showing vastly
7 different eradication rates regardless of how you
8 assess that either protocol or valuable approach
9 or intent to treat. And that's in contrast to --'

10 And then you see healing rates here,
11 incremental increased healing rates through
12 post-treatment, 68 percent -- 84 percent. And it
13 goes 80 -- I can't read all those slides.

14 But you get an increase in healing rates
15 with time using the anti-microbials plus bismuth.

16 And the caveat here is that -- the
17 question is whether this bismuth subcyclicilate
18 might have contributed more than the
19 anti-microbial agents to the speed of ulcer
20 healing here. And I know there is data on bismuth
21 subcitrate to suggest that that particular
22 preparation will improve healing.

1 And I'm unaware of whether the bismuth
2 subcitrate -- I mean, subsalicylate -- will also
3 do the same thing.

4 And then here is a study by Dr. Rauws in
5 Lancet where he used cholate plus bismuth
6 subcitrate for 4 weeks and then combined that with
7 amoxicillin and Metronidazole showing drastically
8 different eradication rates and slightly improved
9 healing rates of 4 weeks post-therapy.

10 And then finally, Dr. Hentshel, et al.,
11 in the "New England Journal of Medicine," did in
12 1993 a similar study to what Dr. Graham did.
13 However, he used ranitidine alone for 6 to ten
14 weeks, and then ranitidine plus two anti-microbial
15 agents that do not -- and did not include bismuth
16 in his regimen. And he found that -- after 6
17 weeks, he found a statistically significant
18 increase in healing rates and drastically
19 different eradication rates among the two
20 regimens. And I think at ten weeks, this dropped
21 off.

22 And so the point to ponder is, as Dr.

1 Sonnenberg suggested, if eradication does
2 contribute to ulcer disease? Certainly, it does,
3 in terms of reduced ulcer recurrence.

4 Does it contribute to ulcer healing?
5 There is some data that I've shown you that would
6 suggest so. And if so, how do we analyze studies
7 that only evaluate H. pylori eradication in
8 patients that achieve ulcer healing?

9 And should we be assessing eradication ,
10 in patients who achieve ulcer healing as well as
11 patients who do not achieve ulcer healing in order
12 to actually to get a more "true eradication rate"
13 for future clinical trials.

14 We have an exciting lineup of industry
15 presentations starting with Astra Merck, TAP
16 Holdings Pharmaceuticals, Glaxo Wellcome, and
17 Abbott, and they will discuss clinical trial end
18 points for the purpose of Helicobacter pylori
19 study design.

20 This slide is to thank Dr. Barth Reller
21 for coming and participating in our advisory
22 committee meetings past a few years.

1 These are actually -- you can't read
2 this. It says, "Blue Devils," down here. And you
3 thought these were Helicobacters, but actually
4 they're Blue Devils to commemorate Duke
5 University, where Dr. Reller is from.

6 (Laughter)

7 DR. FISHER: Are the size of the Devils
8 related to what their basketball team has done
9 recently?

10 (Laughter)

11 DR. HOPKINS: I think -- I think this
12 one -- I think this represents Dr. Reller after --
13 I don't know how long he has been on the advisory
14 committee meeting -- on the committee, but this
15 represents --

16 But actually, you know, I think what's
17 happening with Dr. Reller is that he is actually
18 infected with Helicobacter pylori and that's the
19 problem.

20 (Laughter)

21 DR. RELLER: I have only one comment for
22 the chair and that is -- I think our worst year is

1 considerably better than Neil's best year.

2 DR. FISHER: I won't refute that, but my
3 adopted school of Michigan is doing a bit better.

4 (Laughter)

5 Dr. Laine.

6 DR. LAINE: Just a comment for Dr.
7 Hopkins, too.

8 The recently presented clarithromycin
9 monotherapy would --

10 DR. FISHER: Loren, can you talk into
11 the mike, please.

12 DR. LAINE: The recently presented stuff
13 on clarithromycin monotherapy -- maybe Abbott will
14 be presenting this -- suggested that not only
15 eradication, but perhaps even suppression of the
16 organism may make a difference in ulcer healing.

17 And that just provides, to me, further
18 evidence that just by hitting the bug itself,
19 you're going to be healing ulcer disease, because
20 clarithromycin had a surprisingly high rate of
21 ulcer healing, just as monotherapy.

22 Yet, obviously, the bacteria was

1 suppressed but not eradicated in as high a
2 percentage of patients as in whom the ulcer was
3 healed.

4 DR. BURKS: That's a point that is well
5 taken.

6 DR. FISHER: Dr. Temple.

7 DR. TEMPLE: I guess I'm slightly
8 confused. The analysis that Dr. Girardi presented
9 and that you all did makes the case that
10 eradication predicts ulcer recurrence.

11 DR. HOPKINS: Reduced ulcer recurrence.

12 DR. TEMPLE: Reduced ulcer recurrence.
13 Right -- predicts reduced ulcer recurrence.

14 One question, then, and obviously a
15 major one for the committee to grapple with: are
16 you then now asking whether one could also say
17 that there is evidence now that treating the bug
18 also contributes to acute healing?

19 DR. HOPKINS: No. I think --

20 DR. TEMPLE: That could be true, but
21 it's a sort of separate question. And you could
22 conclude the former without believing the latter.

1 I mean, you know, you might not be able
2 to add to Emiprisol's healing rates. That's
3 neither here nor there for whether eradication is
4 a good predictor of ultimate recurrence rates.

5 DR. HOPKINS: I'm not suggesting --

6 DR. TEMPLE: Those are separate
7 questions, right?

8 DR. HOPKINS: I'm not suggesting that
9 eradications be a surrogate for ulcer healing.
10 Clearly -- I mean, acid -- there are too many
11 other drugs that are better at healing.

12 However, it is involved and if you --
13 it's a study design issue, really, in terms of
14 when you assess healing.

15 DR. TEMPLE: Right. I guess I'm trying
16 to understand the question you're raising.

17 One question, and I thought the major
18 one, was: should eradication alone be taken as
19 evidence of effectiveness for an antibiotic
20 regimen or an anti-microbial regimen?

21 A perfectly good, very important
22 question. It took a long time to get to that

1 question, many years, but --

2 DR. HOPKINS: And I'm also suggesting
3 that, you know, we did introduce this concept --
4 and it's not new to us -- of overall success.

5 And if you are going to use, for
6 example, a definition of overall success, could we
7 use eradication in ulcer healing, as opposed to
8 using just clinical end points, eradication -- I
9 mean, ulcer healing -- and reduced ulcer
10 recurrence?

11 DR. TEMPLE: As evidence for what --

12 DR. HOPKINS: So you need to find --

13 DR. TEMPLE: -- therapy?

14 DR. HOPKINS: That would be your end
15 point in a clinical trial.

16 DR. FISHER: For ulcer healing?

17 DR. HOPKINS: No. Overall success.

18 DR. FISHER: In terms of overall success
19 for what?

20 DR. HOPKINS: You need to demonstrate --

21 DR. FISHER: For eradication? But
22 you're implying --

1 DR. HOPKINS: It's a new concept.

2 DR. FISHER: I guess that's my problem.
3 It seem to confuse -- it seems to put together two
4 things that are sort of separate.

5 One, if you make the infection go away,
6 does that, in turn, lead to decreased recurrence?
7 One very important and very good question.

8 A second question -- a perfectly good
9 question -- is: can you add to the effects of acid
10 suppression by eliminating the bug and therefore
11 get better acute healing rates?

12 A nice, separate question which you
13 would, of course, do with a factorial study as you
14 just described. But that is a separate question.

15 DR. HOPKINS: Yes.

16 DR. FISHER: I just want to be sure I
17 understood what you were saying.

18 DR. HOPKINS: No. It's a separate
19 question.

20 DR. FISHER: But I guess they intertwine
21 by your saying that. Do you start with a base
22 that's totally healed before you go to create a

1 trial to prove eradication predicts recurrence --

2 DR. HOPKINS: Well --

3 DR. FISHER: -- or can you start with
4 people who are not healed totally and just go for
5 eradication and say you're going to prevent
6 recurrence, when you don't know if you've healed
7 it in the first place?

8 DR. HOPKINS: You can do it a variety of
9 ways.

10 I guess what I'm sort of suggesting is
11 going with patients who have active ulcers and
12 then demonstrating that you both need to heal
13 them, as well as eradicate them.

14 And in so doing, you need to demonstrate
15 that you're going to get an eradication rate in
16 all patients. You're going to get the eradication
17 rate patients who achieve ulcer healing at the end
18 of therapy or 4 weeks, post-therapy. And you're
19 going to get eradication rates of people who have
20 -- who have not achieved ulcer healing.

21 DR. FISHER: Are we muddying the water?
22 If you've got a group with an eradication of 90

1 percent, say, but you've still got 15 percent of
2 those people who are not healed at that point,
3 does that muddy your stream --

4 Can you predict recurrence then if
5 you've never healed them at the end of the time of
6 your trial?

7 DR. HOPKINS: Well, what I'm suggesting
8 is that, in future clinical trials, we should
9 actually assess healing 4 weeks at the end of
10 therapy. And that, in and of itself, might be
11 considered a failure because of your definition of
12 overall success.

13 If you use the definition of "overall
14 success" where you need to achieve ulcer healing
15 as well as reduction of ulcer recurrence -- I
16 mean, as well as eradication -- then you need to
17 do both in order to win.

18 So people who don't heal 4 weeks
19 post-therapy and people who are not -- or someone
20 who is not eradicated but does heal would both be
21 failures in your definition of overall success.

22 DR. FISHER: Okay. But the person who

1 is eradicated and doesn't heal is a failure. But
2 that's a failure of healing and not a failure of
3 eradication as a surrogate marker for recurrence
4 rate?

5 DR. HOPKINS: Right.

6 DR. FISHER: Which are two different
7 things, I think. They're two different areas, to
8 me, at least on GI of investigation.

9 DR. HOPKINS: That's my puzzlement, too.
10 I can imagine a regimen that people thought was
11 very good, but that for, one reason or another --
12 probably because you added it to an ulcer regimen
13 that was too good to improve on in a reasonably
14 sized study -- you would not show any benefit on
15 acute healing.

16 But why should that make any difference?
17 The point here is to eradicate the H. pylori,
18 which is what I think your analysis proved or made
19 a case for and what I thought you believed.

20 So it's not easy for me to understand
21 what the further burden you're suggesting might be
22 needed is for.

1 I'm not trying to settle the answer.
2 I'm just trying to understand the question.

3 DR. FISHER: Dr. Fredd and then Dr.
4 Sonnenberg.

5 DR. FREDD: I think the question is the
6 following -- and I think you have to go back to
7 something that is not before the committee at this
8 point and I should describe -- and that is that
9 the studies are designed, most of them, at the
10 active ulcer stage. And they start both
11 anti-secretory therapy, let's say, and an
12 antibiotic regimen in terms of a couple of
13 cohorts.

14 And then they evaluate that either at
15 the -- 4 weeks at the end of therapy for
16 eradication. And then following that, for
17 endoscopy.

18 The question, I guess, before you is --
19 and I think it is somewhat confusing -- how do you
20 determine the eradication rate when you start at
21 the active ulcer stage, 4 weeks after your
22 eradication therapy is over?

1 Do you do it in the total randomized
2 cohort, or do you do it only in those who have
3 healed?

4 And I think that's -- to me, having
5 heard this for some time, I think that is one of
6 the questions. My question is, you know -- well,
7 this may be asking the same question different
8 ways.

9 You saw the numbers up there from Dr.
10 Girardi. But only ten people healed, and all of
11 them, you know, are eradicated, you get 100
12 percent.

13 If, in another scenario, you might get
14 70 percent, but if you accept eradication as a
15 surrogate or as an end point for prevention of
16 recurrence, does it really make a difference of 70
17 to 100 percent for you to conclude that a regimen
18 works?

19 It might make a difference for you to
20 conclude that a regimen is different than another
21 regimen, depending upon the mathematics that were
22 used in order to work it out.

1 So I think there are separate questions
2 being asked here, some of which relates to the way
3 these studies were done, that is, starting at the
4 active ulcer stage.

5 You don't have to start at the active
6 ulcer stage. You could, as Dr. Graham did, start
7 after healing the ulcer to do that.

8 But most of the trials -- and I'm sorry
9 that you don't have NDAs before you at the present
10 time to see what is being talked about related to
11 overall success, active ulcer stage, and numbers
12 related to that -- because I think you have to
13 live with it as Dr. Hopkins, Girardi, Fanning, and
14 myself and my colleagues here have done.

15 DR. FISHER: Dr. Sonnenberg?

16 DR. SONNENBERG: We are developing
17 better and better regimens to eradicate H. pylori.

18 Now, the most recent therapy takes about
19 one week. It is conceptually possible that you
20 have eradicated the bulk of the two weeks after
21 two days, and possibly one week. But it takes the
22 ulcer two weeks or 4 weeks to heal. So you could

1 have a discrepancy between eradication and
2 healing.

3 Secondly, there are two different
4 phenomenon. On the one hand, you have the
5 infection. And on the other hand, you have the
6 ulcer. And in many patients, those go
7 hand-in-hand and are closely related. But this is
8 not necessarily so.

9 We still know that there is a fraction
10 of patients with peptic ulcer disease in whom H.
11 Pylori does not play a role, and this fraction may
12 be anywhere between 5 to 20 percent in stress-
13 induced ulcers, acid-induced ulcers. So those are
14 separate issues.

15 DR. FISHER: Okay. I'm going to want to
16 go on before we get too far behind, if that's
17 okay.

18 Why don't we have Dr. Garry Neil from
19 Astra Merck, who is going to present first.

20 DR. NEIL: Thank you, Dr. Hopkins and
21 Dr. Girardi, for inviting me to speak this
22 afternoon.

1 I'm going to talk first about the
2 surrogate end point. And as we've already heard,
3 I think that there is substantial evidence now in
4 the literature to support the notion that cure of
5 H. pylori infection is, in fact, a surrogate
6 marker for prevention of recurrence of duodenal
7 ulcer disease, emphasizing duodenal ulcer disease.

8 As we've heard several times today, it's
9 now very well established that more than duodenal,
10 ulcers are associated with H. pylori infection.
11 And the NIH consensus statement advocated the
12 treatment of H. pylori infection and cure of H.
13 pylori infection in duodenal ulcer patients
14 whether on first or subsequent presentation.

15 And the question remains, we certainly
16 know this and this has become part of standard
17 clinical practice, and we recognize -- this has
18 already been said, that cure of H. pylori
19 infection certainly reduces the likelihood of
20 duodenal ulcer recurrence.

21 But can this be used as a surrogate
22 marker for prevention of recurrence of duodenal

1 ulcer?

2 And I was very careful to use the term,
3 "cure" for fear of incurring the ire of David
4 Graham. And I notice that he's not here.

5 If you look at the published literature,
6 -- as we've already seen, this is a slightly
7 different cut of it -- but these are 34 study arms
8 from the published literature looking only at
9 randomized and control trials. None of these
10 happen to be double-blinded.

11 But looking at these trials -- 34 study
12 arms -- a variety of different regimens have been
13 used to eradicate H. pylori in these studies.

14 And you have 900 patients who remained
15 H. pylori-positive and another thousand or so who
16 were cured of their infection in these studies.

17 And one can see that there is almost a
18 ten-fold difference in duodenal ulcer recurrence
19 between patients who remain H. pylori-positive and
20 those who are H. pylori-negative are cured of
21 their infection -- 6 versus 58 percent -- with
22 follow-ups which vary from 6 up to 84 months

1 actually in these studies, and the 95 percent
2 confidence intervals are shown there.

3 Now, if you try to be a little bit more
4 rigorous and look at double-blind, randomized
5 control trials from the literature and look at
6 these individually, one tends to see almost
7 exactly the same thing.

8 At the time we did this analysis, there
9 were 4 of these studies available. One we've
10 already heard about, the Hentshel study, but there
11 are two others by Logan and Ulmaran, as well as
12 the study by Bergendorfer.

13 And in all of these studies, one sees a
14 dramatic difference in the eradication rates
15 between negative and positive patients.

16 H. pylori-negative patients in these
17 studies had ulcer recurrence ranging from two to
18 nine percent. So, again, a very dramatic
19 difference even in studies of, shall we say,
20 slightly higher quality.

21 Now, in addition to these published
22 studies, there are some essentially unpublished

1 studies which have been performed by Astra and
2 Astra Merck. These are double-blind controlled
3 trials, and here we're looking at all treatment
4 groups combined, once again, in these studies.

5 And in the case of these studies as in
6 the others, we are looking at patients H. pylori
7 status determined 4 weeks post-treatment. And the
8 patients are followed for 6 months in all these
9 studies.

10 And you can see the ulcer recurrence
11 rates in H. pylori-negative and positive patients.
12 Again, there is a very large discrepancy seen
13 between the positive and negative patients in
14 these studies, confirming what has already been
15 demonstrated in the published literature.

16 And if you do a compilation of these
17 studies, as I have here, one can see that you have
18 a total of 48 percent ulcer recurrence over either
19 6 or 12 months. A couple of these studies are 12
20 month follow-up.

21 In the positive patients, 6 percent, in
22 the H. pylori-negative patients, and this is

1 highly statistically significant in all cases.

2 In fact, I'm really not aware of any
3 studies in the published literature that have been
4 done to date that fail to show this significant
5 difference between the positive and negative
6 patients with respect to ulcer recurrence, so
7 there really is very little controversy in this
8 area as compared to other areas in
9 gastroenterology.

10 So, in conclusion, I think the cure of
11 H. pylori infection or eradication, as is commonly
12 used, in patients with documented duodenal ulcer
13 disease does in fact prevent duodenal ulcer
14 relapse, at least in a large majority of patients,
15 and the cure of H. pylori infection in these
16 patients is an effective surrogate marker for
17 prevention of duodenal ulcer relapse.

18 I'd also like to say something about the
19 timing for measurement of H. pylori eradication.
20 We put in a little bit about that, and the
21 industry standard in the literature is 4 weeks
22 post-treatment, but we have data from other

1 well-controlled trials to support that.

2 Well, we've gone back and analyzed some
3 of the trials that I've already presented to you,
4 which are double-blind randomized controlled
5 trials. There are three of them, and as one can
6 see, this is a two-by-two type analysis of
7 negative and positive patients either at 4 weeks
8 post-treatment or at 6 months post-treatment to
9 see what happens to these patients.

10 And you can see that of those who were
11 negative at 4 weeks, there were 150 of these
12 patients. 141 remained negative at 6 months. And
13 I think that's really the crucial number.

14 And there is similarly good association
15 and agreement. And these are both statistically
16 significant.

17 And I think what's most important is
18 looking at what happens to patients who are
19 negative at one month, seeing what happens to them
20 if they remain negative at 6 months. And this
21 association is very strong with on average of
22 about 94 percent of patients who are negative

1 initially remaining negative at 6 months.

2 I want you to assume that perhaps a few
3 patients could have become reinfected during that
4 time.

5 So, in conclusion, assessment of H.
6 pylori status at 4 weeks post-treatment is also an
7 accurate predictor of H. pylori status at 6
8 months. And therefore, H. pylori status at one
9 month should be used as an end point in assessing
10 H. pylori eradication in clinical trials, using
11 the methodology that Dr. Megraud has already gone
12 over.

13 Thank you very much for your attention.

14 DR. FISHER: Garry, a quick question.
15 In the small number of patients that were negative
16 at one month and turned positive at 6 months --

17 DR. NEIL: Right.

18 DR. FISHER: Which are only nine --

19 DR. NEIL: Nine out of 150.

20 DR. FISHER: Out of 150.

21 DR. NEIL: Right.

22 DR. FISHER: The question is, does it

1 make a different even if they return positive?

2 It has been said that nobody has shown,
3 even if they return positive, that they have -- if
4 they were negative at first and turned positive,
5 that there's an association with the recurrence.

6 With a small number of patients, do you
7 have any data on those nine patients as to whether
8 they recurred or not?

9 DR. NEIL: Off the top of my head, I
10 don't know. Do we -- we don't have that data, do
11 we?

12 No. We don't know. It is a small
13 number, so I'm not sure what it would mean, even
14 if we had it.

15 DR. FISHER: It would only be further
16 supportive of --

17 DR. NEIL: Yes.

18 DR. FISHER: -- the 4 weeks.

19 DR. NEIL: Right.

20 DR. FISHER: 6 months may not make a
21 difference.

22 Any burning questions for Dr. Neil?

1 Dr. Azimi?

2 DR. AZIMI: Do you have any data on
3 long-term observation beyond 6 months? Is there
4 reacquiring of this organism by some of these
5 patients? Is there any information about it?

6 DR. NEIL: Well, we don't have any data
7 in our own trials. The literature includes
8 follow-up for up to 84 months in a small number of
9 patients, looking at continued benefit or reduced
10 incidence of recurrence.

11 But we don't have a long-term follow-up
12 to see how many people get reinfected in these
13 trials.

14 DR. FISHER: Loren?

15 DR. BLAINE: These are a lot of studies,
16 and the biggest difference really is what country
17 you're coming from.

18 If you're in the United States or maybe
19 northern Europe, it will be .3 percent, one
20 percent, maybe two percent.

21 If you're in certain developing
22 countries in Africa or South America, it could be

1 ten, 20, 30 percent a year. So it's -- that's --
2 I think the variability in the U.S. seems to be
3 quite low.

4 DR. FISHER: But if I'm right, even with
5 that reoccurrence of infection, there doesn't seem
6 -- nobody has shown that there is an increased
7 incidence of recurrence or ulcer disease.

8 Is that correct, Loren?

9 DR. BLAINE: I think that's correct, but
10 there's so few patients. I mean it's an
11 interesting question.

12 Do you have a different -- do you get
13 infected with a different strain and maybe it's
14 not an ulcerogenic strain this time. So that's an
15 interesting possibility.

16 DR. FISHER: Dr. Kirschner?

17 DR. KIRSCHNER: I guess one of the other
18 issues we have to think about -- I think many of
19 the comments probably are relating to adults not
20 getting reinfected.

21 And if we think that possibly there are
22 some physiologic differences why young children

1 may be more predisposed to get this, the recurrent
2 rate in fact may be higher. And in fact, it would
3 be very interesting to look at that as a separate
4 subgroup.

5 DR. FISHER: I might ask just -- we have
6 Dr. -- the committee members had Dr. Petersen and
7 Dr. Waltz's article included in their data to
8 them. Pete Peterson is actually in the audience.

9 Pete, can you add anything to that about
10 the incidence of recurrence with reinfection in
11 your review of the literature?

12 Is there any evidence for it or does it
13 make a difference?

14 Can I ask you to get up to the mike?
15 This is Dr. Walter Petersen from Dallas.

16 DR. PETERSEN: To my knowledge, there is
17 no good data to support it one way or the other.

18 I think that 6 months is probably not
19 enough. I think you need to follow these people
20 for 12 -- 24 months to see if they get a
21 recurrence now that they're reinfected. But the 6
22 month point, I don't think that you can say that

1 reinfection means you either are or are not going
2 to have a recurrence of your ulcer.

3 DR. FISHER: Okay. Great. Thanks very
4 much. Okay, why don't we move on? Thank you, Dr.
5 Neil.

6 Next, we have Dr. James Freston, who is
7 a consultant for TAP Holdings, Inc.

8 DR. FRESTON: Thank you, Dr. Fisher.
9 Good afternoon.

10 One of the disadvantages of being at the
11 end of a panel that is addressing an issue is that
12 all of the arguments, and certainly all of the
13 data, has already been prepared and presented.

14 An advantage is that I can save you a
15 great deal of time by not going over the same data
16 that you have seen.

17 I, in fact, did an analysis of both of
18 the meta analyses that you just heard.

19 DR. FISHER: Is that a meta analysis?

20 DR. FRESTON: It was a smaller meta
21 analysis of two meta analyses.

22 I concluded, to cut to the chase, that

1 both are exemplary studies and certainly represent
2 the state of the art in this field of meta
3 analysis and support the conclusion that -- the
4 data supports the conclusions that this is indeed
5 a valid surrogate for -- eradication is a valid
6 surrogate for prevention of ulcer recurrence.

7 I would like to take just a few moments
8 though to raise an issue that in fact was touched
9 upon in the last discussion. And I think it
10 should be addressed by the panel, and that is the
11 issue of including just patients who have acute
12 ulceration in trials of eradication of HP.

13 Both meta analyses did, in fact, contain
14 patients or studies that would confine two
15 patients who had acute ulcer disease with a couple
16 of exceptions.

17 There were a couple of studies where the
18 ulcers had just healed and then they entered
19 eradication treatment.

20 It's tempting from such an experience to
21 require that trials for agency approval be
22 homogenous to the extent that one include only

1 patients with acute ulcer disease. I think that
2 would be a mistake.

3 The disease of -- peptic ulcer disease,
4 we all know, is a chronic relapsing disorder. And
5 when we see a patient with an ulcer at that
6 moment, we're just seeing a snapshot. That ulcer
7 will in all likelihood be gone in about eight
8 weeks, more or less, and will come back with a
9 frequency of about 70 to 80 percent in the next
10 year.

11 There is no reason to think that
12 patients with an acute ulcer at this time are
13 fundamentally different from the patients who
14 healed their ulcers say 6 months ago.

15 Many years ago, as many of you know, Dr.
16 John Frye, a GP practicing in England, presented
17 some data that suggested that peptic ulcer disease
18 burned out over time.

19 That has never been confirmed in modern
20 trials. In fact, any number of trials in the last
21 15 to 20 years have shown just the opposite, that
22 the disease certainly is chronic, relapsing within

1 a time frame at least of 5 to 7 years.

2 Beyond that, we don't know because the
3 maintenance trials of peptic ulcer disease have,
4 by and large, not extended beyond 7 years.

5 So I would ask you to consider the
6 possibility of including in the trials patients
7 who have acute ulcers and those who have a
8 documented -- well-documented history of duodenal
9 and gastric ulceration within the last year or
10 two.

11 Again, there is no reason for believing
12 that they're fundamentally different from those
13 who have an ulcer at this moment.

14 Moreover, there's no reason to believe
15 that eradication rates will be any different in
16 these two populations.

17 Now, admittedly, that has never been put
18 to the test, but it can be done so in the context
19 of well-designed trials.

20 For example, eradication trials of
21 peptic ulcer patients could include the provision
22 of stratifying for acute ulceration or chronic

1 ulceration. And we could find out if the
2 eradication rates are different in these two
3 populations.

4 This would have two advantages. One is
5 that we would be able to recoup more patients to
6 the trials to serve everyone's purpose better.
7 These patients are getting increasingly hard to
8 find now that everyone is out there eradicating
9 HP. We ought to settle the question while we
10 still can.

11 Secondly, I think those trials would
12 reflect the patients that we deal with in the real
13 world, most of whom have a history of ulceration,
14 rather than an acute ulcer at the moment. And
15 we're being urged to eradicate HP in those
16 patients.

17 The inclusion of the provision I spoke
18 of would allow us to extrapolate the data to that
19 large population.

20 Thank you.

21 DR. FISHER: Thank you, Dr. Freston.

22 Dr. Comer?

1 DR. COMER: I'd like to clarify
2 something from these meta analyses.

3 Did most of them look at eradication
4 only in healed patients? And would you agree with
5 some of the recommendations of the panel that we
6 should really be looking at eradication in all
7 patients, so that we don't have an intent-to-treat
8 bias?

9 DR. FRESTON: I think we should look at,
10 eradication in all patients. But we don't want to
11 get into -- we don't want to get too heterogenous.

12 I believe that most patients who don't
13 have peptic ulcer disease are a fairly homogenous
14 population. So we ought to document that they had
15 ulcer at least -- either have it now or had it
16 within a reasonable recent history, one and two
17 years.

18 DR. ELUSHOFF: What about the
19 patients -- the subgroup that doesn't heal? What
20 do you think about that group, that they don't
21 heal so you can't really say that they -- you
22 can't really comment on whether they've recurred

1 or not?

2 DR. FRESTON: Yes, I think -- quite
3 frankly, I think that's a semantic argument. A
4 very few patients will not heal eventually.

5 There is no precedent for patients,
6 apart from those who continue to take NSAIDs or
7 had Zollinger-Ellison for having continuous ulcer
8 disease.

9 Even under the placebo therapy, as you
10 know, upwards to 40 and even 50 percent in some
11 trials will heal.

12 So that's such a small proportion of the
13 patients. I don't think it's wise to factor that
14 consideration into the trials.

15 DR. FISHER: Dr. Temple?

16 DR. TEMPLE: Can I ask you something
17 even more radical?

18 Why do the people have to have had ulcer
19 disease at all? If you want to know whether this
20 kills the bug, why does it matter?

21 DR. FRESTON: Well --

22 DR. TEMPLE: That's not a position I'm

1 asking --

2 DR. FRESTON: -- question involved. I
3 was asked that, actually, at lunch time.

4 I think again one can argue, as you
5 would, that we should keep these populations as
6 homogenous as possible. It's theoretically
7 possible that some co-therapy -- this is all
8 theory -- some co-therapy for non-ulcer dyspepsia
9 might result in a different eradication rate than
10 one might get in patients with peptic ulcer
11 disease who are on standard anti-secretory
12 regimens.

13 Now, that's a stretch. And I don't want
14 to stretch, but I'd like to see it confined with
15 patients with ulcers first.

16 DR. FISHER: Dr. Fredd?

17 DR. FREDD: Could I just follow-up and
18 ask you whether -- with the same therapy to
19 eradicate HP -- there is any study done looking at
20 that in non-ulcer dyspepsia patients, gastritis
21 patients, or other patients like ulcer patients,
22 to see whether those rates done in the same way

1 are the same or different?

2 DR. FRESTON: Well, since --

3 DR. FISHER: You mean eradication rates?

4 DR. FREDD: Eradication rates --

5 DR. FISHER: Okay. From non-ulcer
6 disease?

7 DR. FREDD: -- from some regimen in
8 various upper GI disease --

9 DR. FISHER: Non-ulcer disease?

10 DR. FREDD: Right. Whether giving that
11 to various conditions results in differences in
12 rates of eradication.

13 DR. FRESTON: It hasn't been put to
14 careful trial. If one looks at the studies,
15 eradication rates in non-ulcer dyspepsia, one
16 finds the same range of eradication rates with the
17 same regimen as in patients with duodenal ulcer.

18 Tomorrow you will be hearing from Dr.
19 van Zamm, and he'll show you some data on that.

20 But the studies were never designed to
21 see if there is a difference in these two
22 populations.

1 DR. FISHER: Okay. Thank you, Dr.
2 Freston. And unfortunately, Dr. Reiller, I think
3 Dr. Freston's women's basketball team would even
4 defeat Yale's basketball team. Go Yukon.

5 (Laughter)

6 Can I have Dr. Ciociola from Glaxo
7 Wellcome, Inc.?

8 DR. CIOCIOLA: I would like to thank you
9 for the opportunity to contribute to this meeting.

10 It's a pleasure to be here to share with
11 you some of our experiences from data that we've
12 generated in the conduct of numerous placebo
13 control, double-blind, multi-centered studies that
14 have involved H. pylori over the past 6 years.

15 Our overall objective for this
16 presentation is to establish the relationship
17 between H. pylori infection and duodenal ulcer
18 disease.

19 In addition, I believe some of the data
20 I'm going to share with you today may address some
21 of the issues that we were just talking about.

22 Now, in my talk today, we will recommend

1 that the eradication of H. pylori infection in
2 healed duodenal ulcer patients can be used to
3 predict a reduction in ulcer recurrence.

4 In addition, we will recommend for
5 future studies of duodenal ulcer disease, it is
6 sufficient to evaluate ulcer healing and
7 eradication of H. pylori infection.

8 Now, to support these recommendations we
9 have considered a series of questions about
10 duodenal ulcer disease and H. pylori infection.
11 And we've developed the answers to these questions
12 during the conduct of our clinical program
13 ranitidine citrate over the past 6 years.

14 The first question I'd like to address
15 is: what is the target patient population?

16 Specifically, one must study a
17 homogenous patient population to allow treatment
18 results to be reproduced in subsequent clinical
19 studies. We will share with you those patient
20 selection criteria.

21 Second question: what is the prevalence
22 of H. pylori in the target population?

1 It is essential that one accurately
2 assess the true infection rates in the target
3 population using blinded methods. We plan to
4 present studies performed in the United States.

5 The third question we wish to address is
6 the study design to assess the relationship
7 between H. pylori infection and duodenal ulcer
8 disease.

9 Now, there have been several different
10 study designs proposed and even discussed this
11 morning. We will show you the design that we have
12 employed in our critical program.

13 The next question is the appropriate
14 study end points of such a study design.

15 We'll point out how trials have evolved
16 from a clinical focus to more of a microbiological
17 focus. And based on these experiences, we will
18 recommend a clinical study end point that will
19 allow an accurate assessment of the efficacy of
20 the treatment regimen for H. pylori and duodenal
21 ulcer disease.

22 The next question: what is the rate of

1 ulcer recurrence in healed duodenal ulcer patients
2 who are eradicated of H. pylori infection?

3 To answer this question, we will present
4 the relevant results from our worldwide clinical
5 program that consists of eight studies, 6 of which
6 were placebo-controlled.

7 And finally, can the eradication of H.
8 pylori be used to predict a reduction in ulcer
9 recurrence?

10 Now, over the past decade since the
11 recognition of H. pylori by Dr. Marshall, numerous
12 clinical studies have suggested a strong causal
13 relationship between H. pylori infection and
14 duodenal ulcer disease. Therefore, we chose
15 duodenal ulcer patients as the target patients
16 population.

17 However, since our program was worldwide
18 in scope and involved numerous clinical studies,
19 it was critical to accurately define the patients
20 population to facilitate comparability of the
21 study results.

22 The following are the patient selection

1 criteria that we have utilized in our studies: we
2 enrolled only endoscopically diagnosed, active,
3 duodenal ulcer patients into these studies.

4 We defined the ulcer in the break in the
5 mucosa with perceptible depth. The lesion ranged
6 in size from .5 to two centimeters in the longest
7 diameter, and the lesion must have been located in
8 the duodenum, duodenal bowl, or the immediate
9 post-bulbar duodenum.

10 Now, in an effort to ensure a homogenous
11 population, we excluded all patients whose ulcer
12 disease may have been caused by other factors.

13 In addition, as shown on the slide, the
14 use of compounds known to heal ulcers or affect H.
15 pylori status were also limited in the 30 days
16 prior to study enrollment.

17 Now, having defined the target patient
18 population, what is the prevalence of H. pylori
19 infection in this patient population?

20 Now, before I show you the results of
21 our clinical program, I'd first like to define the
22 criteria that we used to diagnose the infection.

1 These criteria were based on the March 1995 draft
2 "points to consider" document prepared by the FDA
3 Division of Anti-Infective Drug Products.

4 The diagnostic tests performed in our
5 studies included CLOtest, culture, and histology.
6 Now, to be considered infected with H. pylori at
7 prestudy, all patients must have had either a
8 positive culture growth, or a positive CLO and
9 histology.

10 Now, as I show you the results -- our
11 prevalence results from our U.S. clinical
12 program -- it is important to note that all
13 studies enrolled all duodenal ulcer patients
14 regardless of H. pylori status.

15 These studies show the prevalence of H.
16 pylori infection in duodenal ulcer patients in the
17 United States. The first line identifies the
18 study number. There were 6 studies numbered 301
19 to 306.

20 The second line identifies the number of
21 qualified duodenal ulcer patients enrolled in each
22 study ranging from 151 to over 1,000 patients.

1 The third line identifies the percent of
2 patients infected with H. pylori. This percent
3 ranged between 71 and 79 percent.

4 Now, we acknowledge that previous
5 studies performed during the past decade have
6 reported between 90 and 100 percent of duodenal
7 ulcer patients are infected with H. pylori.

8 However, these studies evaluated over
9 2500 patients at over 300 centers, which we
10 believe is an accurate representation of the
11 duodenal ulcer patient population.

12 In addition, these studies also employed
13 strict diagnostic criteria with all assessments
14 made by blinded laboratory personnel.

15 As a result, our studies displayed very
16 consistent infection rates across all studies.

17 We conclude the H. pylori infection rate
18 in the U.S. duodenal ulcer patients is
19 approximately 75 percent.

20 Now that we've established the
21 prevalence of H. pylori infection in the patient
22 population, what is a study designed to analyze

1 the relationship between H. pylori infection and
2 duodenal ulcer disease?

3 Glaxo Wellcome initiated its first
4 clinical study of H. pylori disease in 1990. At
5 that time, there were several different studies
6 published, looking at a variety of therapies for
7 the treatment of peptic ulcer.

8 Two of these studies, one published by
9 Dr. Wolland in the New England Journal in 1989 and
10 the second published by Dr. Marshall in Lancet,
11 1988, formed the basis of the Glaxo Wellcome study
12 design.

13 We then consulted with the
14 gastrointestinal drug products division of the FDA
15 and finalized our study protocols.

16 This slide illustrates the study design
17 that we've employed throughout our program.
18 Basically, during the screening phase, patients
19 with a suspected duodenal ulcer were endoscoped to
20 confirm the lesion. Those patients with a
21 confirmed lesion were then assessed for H. pylori
22 infection and then randomized the study treatment

1 for 4 weeks.

2 Patients were endoscoped at the end of
3 treatment to confirm ulcer healing and again
4 assess for H. pylori status.

5 The healed patients were followed for 6
6 months while receiving no further treatment.
7 Endoscopies were performed at one, three, and 6
8 months to, again, assess for ulcer relapse and H.
9 pylori status.

10 Now, please note that the eradication of
11 the infection was defined as having at least two
12 diagnostic tests performed at least one month
13 post-treatment. And all tests must have been
14 negative.

15 Given this study design, what are the
16 appropriate study end points to assess the
17 relationship between H. pylori and duodenal ulcer
18 disease?

19 Now, over the past several years, the
20 focus of duodenal ulcer treatment studies has
21 changed from being primarily based on clinical end
22 points -- that is: did the ulcer heal? Did it

1 recur? -- to more microbiological end points --
2 that is: was the H. pylori infection rate
3 accurately diagnosed, and if the infection was
4 cured, were the appropriate tests performed to
5 confirm eradication of the organism?

6 What we have concluded is that, for this
7 type of study design, a treatment regimen for H.
8 pylori should be evaluated for both end points --
9 that is, we believe a true successful outcome of
10 therapy is for patients who have both a clinical
11 and microbiological cure.

12 We believe that patients must not only
13 be eradicated of the infection, but must also heal
14 and be in ulcer remission.

15 For example, a patient whose ulcer
16 remains unhealed after treatment, but is
17 eradicated over the infection, is not a true
18 successful outcome.

19 Similarly, a patient whose ulcer has
20 healed or who is in remission but not eradicated
21 of the infection is also not a successful outcome.

22 Therefore, when evaluating a treatment

1 regimen using this type of study design, we have
2 employed a study end point that assesses both a
3 clinical and microbiological cure. And we have
4 defined that as ulcer healing and eradication of
5 H. pylori in patients with that previous healing
6 and no recurrence of the ulcer and patients who
7 have healed and who are eradicated of the
8 infection.

9 Now, that we've suggested a study design
10 and an end point, what is the rate of ulcer
11 recurrence in duodenal ulcer patients who are
12 eradicated of the infection?

13 We've evaluated several different
14 eradication regimens with ranitidine bismuth
15 citrate. The range of eradication rates that
16 we've observed and the various treatment arms of
17 our studies are shown on the next slide.

18 As you can see, the eradication rates of
19 ranitidine bismuth citrate -- abbreviated RBC --
20 plus clarithromycin ranged between 82 and 94
21 percent. The eradication rates observed for RBC
22 plus amoxicillin, somewhat lower, and ranged from

1 41 to 68 percent.

2 The comparer arms of these studies show
3 eradication rates between 24 and 36 percent for
4 clarithromycin alone to less than 4 percent for
5 all other treatment arms.

6 Now, having shown you the eradication
7 rates for various therapies that we evaluated in
8 our clinical program, this next set of data
9 represents the correlation of ulcer recurrence
10 with eradication of H. pylori infection
11 irrespective of treatment.

12 Now, these are the results from all
13 studies conducted to date by Glaxo Wellcome that
14 assess H. pylori eradication and also relapse.

15 The first line identifies the number of
16 patients whose active ulcer has healed and who are
17 confirmed infected with H. pylori at prestudy.

18 We then identified patients as either
19 being eradicated or not eradicated of H. pylori
20 following treatment.

21 Second line identifies the percent of
22 patients who were observed to have an ulcer

1 recurrence during the 6 month follow-up period.
2 As you can see, 61 percent of those patients not
3 eradicated of the infection suffered an ulcer
4 recurrence. This is compared to 11 percent of
5 patients who were eradicated of the infection who
6 suffered an ulcer recurrence.

7 Now since these were prospective studies
8 in which the onset of the ulcer elapse is
9 documented, the relative risk was calculated and
10 found to be 5.7.

11 These data suggests that patients not
12 eradicated of the infection have a 5.7 times
13 greater probability of suffering an ulcer
14 recurrence in the 6 month follow-up period as
15 compared to patients who are eradicated of the
16 infection.

17 The 95 percent confidence intervals
18 range between 4 and 8.2.

19 Now, this data strongly support the
20 concept that patients eradicated of H. pylori
21 infection have a significantly lower ulcer
22 recurrence rate than patients not eradicated of

1 the infection.

2 In summary, the data presented today
3 suggests that the H. pylori infection rate in U.S.
4 Duodenal ulcer patients is approximately 75
5 percent. Only 11 percent of patients eradicated
6 of H. pylori infection suffered an ulcer
7 recurrence in the 6 month follow-up period.

8 Patients not eradicated of the infection
9 have a 5.7 times greater probability of suffering,
10 an ulcer recurrence.

11 We conclude, based on the studies that
12 we have conducted today, which assesses H. pylori
13 eradication and ulcer relapse, that the
14 eradication of H. pylori infection in healed
15 duodenal ulcer patients can be used to predict a
16 reduction in ulcer recurrence.

17 In addition, we suggest that for future
18 studies of duodenal ulcer disease, it is
19 sufficient to evaluate ulcer healing and the
20 eradication of H. pylori infection.

21 Thank you for your attention.

22 DR. FISHER: Thank you, Arthur.

1 Questions for Dr. Ciociola? Dr. Laine?

2 DR. LAINE: Actually two questions
3 related to the fact that actually some of the
4 industry-sponsored studies are quantitatively, if
5 not qualitatively, different in terms of results
6 from the published studies.

7 The first question relates to the 75
8 percent prevalence.

9 I was just wondering: how many of your
10 patients did not happen to have one of the three
11 tests done and were excluded? And did you exclude
12 them and did you put them up into the non-HP
13 category?

14 Was that a large number or a small
15 number?

16 DR. CIOCIOLA: It was a reasonably small
17 number, about 20 percent.

18 Basically, the patients who did not have
19 the appropriate tests performed were considered
20 not evaluable.

21 DR. LAINE: So they weren't in that
22 number?

1 DR. CIOCIOLA: That's correct. They
2 were not in that test.

3 I do have some data to show you. It's
4 approximately what you asked for; that is,
5 patients who had at least one test performed. And
6 I can show you those infection rates if you would
7 like to see those.

8 DR. LAINE: Just could you tell me what
9 the numbers were about?

10 DR. CIOCIOLA: Yes. Basically the
11 numbers increase about 5 to 7 percent. So in
12 other words, the rates were around 83, 84, 85
13 percent. So the number goes up about 5 or so
14 percent.

15 DR. LAINE: And along those same lines,
16 what's striking to me is your study, the Astra
17 Merck studies and the Abbott studies all have a
18 higher recurrence rate in H. pylori-negative
19 patients than do all the studies published.

20 Again, it's still significantly
21 different. The questions that I have are related
22 to that.

1 For you and for the others: do you have
2 H. pylori-infected status at that 6-month or one
3 year follow-up? In other words, how many of them
4 were recrudescant or reinfected?

5 And do you have information on NSAID
6 ingestion?

7 DR. CIOCIOLA: Yes.

8 DR. FISHER: Can I just ask people to be
9 careful? We don't want to get into discussion of,
10 things that might be NDA applications, that might
11 be coming forward as --

12 Can I ask for Dr. Fanning or Dr. Fredd
13 to give us -- are we okay where we are?

14 I don't want to get into things that we
15 shouldn't be discussing because the whole NDA is
16 not being presented here.

17 DR. FREDD: You're okay wherever you
18 want to be, but --

19 DR. FISHER: Thank you, Stephen.

20 DR. FREDD: -- but the point is that if
21 there is data pending and there are reviews in the
22 agency, we would really prefer and would have

1 preferred to have an application reviewed in
2 depth, because many of these questions come out as
3 one is looking at the data and teasing it out.

4 So I'd prefer if we deal with concepts
5 rather than the details of data in these
6 applications which we intend to put before you in
7 detail at some other time.

8 DR. FISHER: Dr. Fanning, comment on --

9 DR. FANNING: I think I would agree with
10 what Dr. Fredd has said, that if we stay with the
11 concepts, I think that will be useful.

12 The presentations were intended to
13 illustrate some of the issues involved.

14 DR. FISHER: So I'm just going to ask
15 the question or it's not to get into a lot of --

16 DR. LAINE: Is it explained by H. pylori
17 reinfection or NSAIDs in general?

18 DR. FISHER: Okay. Conceptually --

19 DR. LAINE: Okay.

20 DR. FISHER: -- is that recurrent or
21 NSAID, in your opinion?

22 DR. CIOCIOLA: Both of those questions.

1 We attempted to rule out all NSAID use prior to
2 study enrollment. And the number of patients that
3 you saw who did relapse, a very small percent
4 admitted to NSAID use.

5 And the same with reinfection, if you
6 will. A very small percent -- less than ten
7 percent -- of those patients were recrudesced or
8 reinfected.

9 Thank you.

10 DR. FISHER: Dr. Bertino? Dr. Judson?

11 DR. JUDSON: This question will reveal
12 some of my ignorance in this field.

13 The studies that were presented earlier
14 I think by FDA, and by, I think, Dr. Hopkins,
15 showed that there was clearly a significant
16 incremental gain by adding usually triple
17 antibiotic therapy to Emiprisol or one of the
18 anti-secretory drugs.

19 Turning the thing around the other way,
20 has -- are there studies that have looked at the
21 cure rates entirely just from triple antibiotic
22 therapy from antibiotics that are believed to be a

1 combination adequate to eradicate or optimal for
2 eradicating H. Pylori?

3 And then to which -- I suppose
4 anti-secretory therapy has been added in the other
5 arm?

6 DR. CIOCIOLA: Actually there have been
7 several studies done just looking at eradication
8 rates of the infection just using antibiotics,
9 using two or three.

10 I can't quote you the numbers off the
11 top of my head, but they are very effective,
12 greater than 80 percent.

13 Perhaps, Dr. Webb, do you --

14 DR. FISHER: Can you identify yourself?

15 DR. WEBB: Yes. Duane Webb, Glaxo
16 Wellcome. A part of the problem may be, when
17 you're considering the compliance of the patient
18 with these complex triple therapy regimens, some
19 of which involve 16 pills a day. And Graham
20 showed that only about 16 percent of his patients
21 could be compliant with that type of regimen.

22 And at that 60 percent level eradication

1 rate was in the 20 percent range compared to what
2 it would be if they were over 60 percent, which
3 was usually in the 70 to 80 percent range.

4 So I think what we're dealing with is a
5 trade-off between compliance and efficacy. The
6 more complex regimens have the highest efficacy,
7 but the compliance isn't what suffers. And so if
8 the patients aren't taking it, it's not going to
9 work.

10 Does that get to what you're asking?

11 DR. JUDSON: Partly. I was just looking
12 at the three studies here. It appeared that the
13 median cure rate for the anti-secretory alone was
14 70 to 80 percent. And that the antibiotics
15 brought that up to 80 to 90 percent or so.

16 DR. FISHER: You're talking about in the
17 acute healing?

18 DR. JUDSON: Right.

19 DR. FISHER: Is what you're talking
20 about?

21 DR. JUDSON: Right.

22 DR. FISHER: So Dr. Fredd or Dr. Temple.

1 may answer.

2 DR. FREDD: I just wanted to answer Dr.
3 Judson's question as best I can.

4 Dr. Graham did a study in which he had
5 ranitidine placebo in one arm, ranitidine triple
6 therapy in the other arm.

7 The different between those were zero
8 eradication for ranitidine, 89 to 90 percent for
9 triple therapy in terms of that randomized
10 comparison.

11 There is a meta analysis which I believe
12 is in your book by Cheba, et al., which deals with
13 single therapy, dual therapy, triple therapy in
14 terms of differences in eradication rates and the
15 paper I gave you by Dixon does something of the
16 same thing, as well as showing you the splay of
17 eradication rates with the same therapy in
18 different hands.

19 DR. JUDSON: Okay. And the cure rate
20 from triple antibiotics therapy alone.

21 DR. FISHER: Healing of the ulcer --

22 DR. JUDSON: Healing of the ulcer.

1 DR. FISHER: -- cannot cure H. pylori.

2 DR. FREDD: In Graham's study, it's --
3 the ranitidine arm was something like 6 or eight
4 weeks, I believe. I'm not quite sure, which it
5 was about 85 percent.

6 There was a significant increment in his
7 study between that and ranitidine plus triple
8 therapy. I don't know whether it was 94 percent
9 healing at that same time point. But it was
10 significantly different in that study.

11 Before holding on to any one study,
12 however, I would say that there may well be
13 studies pending at the agency which we will be
14 able to provide to the committee in depth, where
15 we can go into this question with data that we
16 have been able to review ourselves.

17 DR. JUDSON: The question was about the
18 cure rate for ulcers by treating them strictly as
19 an infection.

20 DR. FISHER: If you look at Hopkins'
21 data on page 45 --

22 DR. LAINE: The problem is that in a lot

1 of those, they have bismuth in them.

2 DR. FISHER: That's right. Okay.

3 DR. LAINE: Like I said, there are some
4 just straight antibiotics.

5 As I said, at the American College of
6 Gastroenterology was that just clarithromycin
7 alone led to healing of ulcers actually more
8 frequently than it led to eradication of the
9 organism, suggesting that suppression and/or
10 eradication was important.

11 There are -- most of the studies,
12 unfortunately, don't look at healing when they --
13 most of the studies have bismuth or anti-secretory
14 drugs. There's very little looking at healing
15 with just antibiotics.

16 But that was very interesting, to me, at
17 least. That was just presented last month.

18 DR. JUDSON: We are viewing bismuth as
19 an antibiotic in this context?

20 DR. FREDD: No. I'm not sure we're
21 doing that.

22 DR. FISHER: Dr. Marshall, a quick

1 point?

2 DR. MARSHALL: There's a Hong Kong study
3 published in the "New England Journal" where they
4 had triple therapy versus triple therapy plus
5 Emiprisol. So this is exactly --

6 DR. LAINE: No. But it has bismuth
7 subcitrate in there.

8 DR. FISHER: It has bismuth in it.

9 DR. LAINE: And bismuth subcitrate alone
10 can heal ulcers. And not that it -- so you don't
11 -- what he's asking is something that doesn't --

12 DR. MARSHALL: But what they did -- what
13 they did -- they only got one week in the triple
14 therapy, and then followed them up with 4 weeks
15 and moved to healing.

16 And the other group had the triple
17 therapy plus the Emiprisol, I think.

18 So it just showed that if you got triple
19 therapy of one and 7 days of antibiotic treatment,
20 the healing rate at 4 weeks was the same as if you
21 gave the antibiotics plus the Emiprisol.

22 DR. LAINE: Bismuth subcitrate, again,

1 may be working only through its effect on H.
2 Pylori.

3 But the question is since people in the
4 past had suggested that it was anti-ulcerogenic,
5 that was the only reason to at least qualify that
6 statement.

7 DR. FISHER: But we also note that there
8 are some instances of water healing duodenal ulcer
9 in a good percent of patients. So I don't, you
10 know, know what that means.

11 DR. FREDD: If bismuth is working
12 through eradication, the rates that were just
13 shown in terms of the eradication rates with
14 bismuth citrate alone were somewhere between zero
15 and 4 percent, suppression may be something that's
16 active, rather than eradication.

17 Bismuth subcitrate has been approved for
18 the treatment of duodenal ulcer in Europe.

19 DR. FISHER: Dr. Comer, a quick
20 question?

21 DR. COMER: I just have a question about
22 the eradication rate in your studies in the

1 overall group, healed and unhealed, and how
2 much -- you know, what's the difference?

3 DR. CIOCIOLA: Basically, the study --
4 the data set that I showed you there that compared
5 eradicated versus non-eradicated was irrespective
6 of treatment.

7 Basically, the previous slide that I
8 showed you was sort of a summary of all the
9 eradication rates with the various treatment arms,
10 and so on and so forth.

11 Basically, we took all those patients
12 and put them into that analysis, a two-by-two
13 analysis and simply look at whether the patient
14 was eradicated or not, irrespective of treatment.
15 And that's the comparison we made to come up with
16 the relative risks.

17 DR. FISHER: Okay. Let's go on. Let me
18 just add that some people may not have noticed
19 around the table, Dr. Art -- thank you -- Art's
20 slides were duplicated and are on this little
21 several sheet for all the members at the table.

22 Dr. Temple?

1 DR. TEMPLE: I'm sorry. I know you want
2 to move on.

3 It seems to me one important question
4 was not addressed which is why you need to
5 evaluate ulcer healing in these trials.

6 To show that ranitidine heals ulcers is
7 not a new finding. You don't really need to do
8 that because you already know it.

9 So why is it so crucial in these trials
10 to even evaluate that?

11 I mean, I put it more strongly: do you
12 actually have to have an endoscopic evidence of an
13 ulcer?

14 But in any event, why is it so crucial
15 to evaluate ulcer healing, when you already know
16 these drugs alleviate ulcers, unless you want to
17 make the claim that the antibiotic regimen
18 contributes to ulcer healing, which is a different
19 question.

20 DR. FISHER: Maybe we can get to that in
21 the committee discussion after we hear from Dr. J.
22 Carl Kraft from Abbott Laboratories.

1 DR. CRAFT: Thank you and thank everyone
2 for presenting before me.

3 From the infectious disease point of
4 view, treating ulcers is easy. They heal and cure
5 the disease.

6 After three years of studying ulcer
7 disease, I can tell you that it's not that easy.
8 The objective of therapy, particularly for the
9 patient, is to cure their ulcer. They only know
10 that you heal their ulcer and you prevent the
11 recurrence.

12 The role of H. pylori is not clear. The
13 patient doesn't know whether he has H. pylori or
14 doesn't have H. pylori.

15 The physician knows the patients have H.
16 pylori but don't have ulcers. They also know that
17 patients have ulcers and don't have H. pylori.

18 Because of this, the NIH consensus says
19 there is no causal relationship between H. pylori
20 and ulcer disease.

21 From our data, we can assure you that
22 there are studies that confirm this data that

1 eradication of H. pylori is not an appropriate
2 surrogate marker for ulcer healing.

3 They are separate and independent
4 events. The ulcer therapy should not be adversely
5 affected by the anti-infective therapy chosen to
6 eradicate H. pylori.

7 On the other hand, eradication of H.
8 pylori may be an appropriate surrogate marker for
9 the prevention of ulcer recurrence, but only if
10 certain stringent conditions for determining the
11 eradication rates are met.

12 What are these conditions? Well, it
13 must be done in well-controlled trials to FDA
14 standards. They must evaluate all randomized
15 patients, including those who didn't heal and
16 those who couldn't tolerate the medication.

17 They must demonstrate reproducibility of
18 the eradication rate in two or more studies. And
19 they must prove that the therapy of bacterial
20 asyllum, not simply suppressing where the organism
21 will regrow at a later time.

22 You can do this by using multiple,

1 accurate diagnostic tests, since no single test is
2 reliable. And by assessing these tests at
3 multiple time points to ensure that you have not
4 missed an eradication.

5 Let's look at this a little bit more
6 closely. In well-controlled trial design, you
7 must assess both the ulcer disease and the H.
8 pylori infection, because they're separate and
9 distinct identities which cannot be tried alone.

10 You must demonstrate reproducibility of
11 your data and you must account for all patients
12 throughout the study.

13 To prove that your therapy is
14 bactericidal, you must assess bactericidal
15 activity at multiple time points after 6 months.

16 You must prove that your organism has
17 been killed -- not simply suppressed -- because we
18 know recrudescence occurs in those with only
19 suppression.

20 It's very easy to make the diagnosis of
21 H. pylori. It's much more difficult to prove the
22 absence of infection.

1 You must combine multiple tests to
2 improve your accuracy and you must use rigorous
3 methods to insure this accuracy.

4 The negative predictive value of
5 eradication preAbbott trials made the predictive
6 value being the likelihood that a negative test is
7 truly negative.

8 Pathohistology is pretty good, but it
9 takes a lot of effort to get this high of a
10 negative predictive value. It requires having a
11 motivated, experienced histopathologist to provide
12 an adequate sample size and using proper stains.

13 If you were to use an experienced
14 histopathologist, you can drop your rates by 20 to
15 30 percent.

16 Culture is necessary because of the
17 antibiotics in this therapy, but it is the least
18 wild one because of the difficulty in dealing with
19 this very sensitive bug.

20 C-13 urea breath test is a quite
21 variable test, mainly because there are no
22 criteria for break points for determining a

1 negative result post-therapy.

2 Because of these problems, no single
3 test can be used to diagnose and confirm
4 eradication rates.

5 By combining diagnostic tests, we can
6 improve the accuracy. Histology is the most
7 sensitive test, but only if you use a motivated
8 and experienced histopathologist.

9 Culture is essential for assessing
10 antibiotic susceptibility, because we must
11 determine the susceptibility before treatment and
12 post-treatment to assess the amount of resistance
13 developing during therapy.

14 The C-13 or C-14 urea breath test⁰ or
15 samples the entire gastric mucosa help in getting
16 away from some of the patchy infection histology
17 or problems that you see in gastric mucosa.

18 Because of the variability in this test,
19 GET alone cannot be used, particularly as a single
20 test.

21 We must guard against factors that
22 inflate eradication rates. These are mainly

1 diagnostic factors such as inadequate number of
2 diagnostic tests, using only a single test,
3 inadequate numbers of biopsies, culture, histology
4 or inappropriate size of the biopsy.

5 Poor handling of the specimens -- most
6 local histologists could not handle this type of
7 assay, and they must be sent to central labs with
8 all of the inherent problems of transporting
9 specimens over long distance.

10 Additional factors that we need to guard
11 against: selective analysis during subset
12 population analysis can elevate your rates and
13 give you unexpected eradication rates when seen in
14 other studies.

15 Static therapies where you only
16 suppress: in the therapy, it may take a long time
17 for these to regrow, and that accounts for the
18 recrudescence that we have seen frequently at 6
19 months to a year.

20 Inappropriate times of your specimens:
21 any single time point may not be appropriate for
22 the assessment of the particular end point.

1 Sufficient evidence of effective therapy
2 can only be obtained by evaluating both ulcer
3 disease and H. pylori infection at multiple time
4 points.

5 What are these time points?
6 Pretreatment, post-treatment, 4 to 6 weeks
7 post-treatment and at 6 months post-treatment.

8 The pretreatment assessment is essential
9 since if you don't know whether you have an ulcer
10 and you don't know whether it's associated with H.
11 pylori, you can't study the disease.

12 Post-treatment assessment is the best
13 time for establishing your ulcer healing rate. It
14 is inappropriate to assess H. pylori infection,
15 because organisms will only be suppressed at this
16 point and not eradicated.

17 4 to 6 weeks is a good time to look at
18 your ulcer disease one more time, but this is the
19 best time for establishing a base line eradication
20 rate for H. pylori.

21 6 months post-treatment: this is the
22 ideal time to assess ulcer recurrence, because, by

1 6 months, the majority of your ulcer recurrence
2 will have occurred both for those that are H.
3 pylori-negative and those that are H.
4 pylori-recurrent.

5 If you have shown that you have no H.
6 pylori ulcer recurrence, then, for those patients
7 who are believed to be eradicated, you will prove
8 that you have bactericidal therapy.

9 Once you prove the bactericidal therapy,
10 your 4 to 6 weeks post-treatment evaluation or
11 eradication rate for that bactericidal therapy can
12 be linked to your ulcer recurrence.

13 Once you've linked the ulcer recurrence
14 with the 4 to 6 weeks, the 4 to 6 week post-
15 treatment evaluation of H. pylori-associated
16 ulcers becomes a surrogate marker for those
17 patients in the future.

18 So, in conclusion, eradication is not an
19 appropriate surrogate marker for ulcer healing,
20 but your anti-infective therapy should not
21 adversely affect the healing rate of your ulcer
22 therapy.

1 Eradication may be an appropriate
2 surrogate marker for the prevention of ulcer
3 recurrence, but only if the following conditions
4 are met: it's done in well-controlled FDA standard
5 trials, all randomized patients are evaluated,
6 eradication rates are reproducible in two or more
7 studies, and therapy is proven bactericidal in
8 multiple diagnostic tests which are accurate and
9 are assessed at multiple time points.

10 Thank you.

11 DR. FISHER: Thank you, Dr. Kraft.

12 Questions for Dr. Kraft before I throw
13 it open for some general discussion?

14 Dr. Megraud?

15 DR. MEGRAUD: I just want to say that I
16 agree with most of the things you said, except
17 that I differ with urea breath test.

18 I talked this morning about the urea
19 breath test, but there is now a European protocol
20 to perform this test, and this was the protocol
21 which was used in the study. So I am not aware of
22 the program with the U.S. breath test, but I can

1 tell you that in Europe, it works.

2 DR. FISHER: Okay.

3 DR. CRAFT: We would agree that the
4 European break points are better defined, but I
5 still think there are problems with either the
6 break points or other inherent problems with
7 getting the breath test into the tube with a good
8 stopper, or getting it into a container that
9 doesn't have vacuum.

10 So none of these tests is 100 percent
11 reliable in anyone's hands.

12 DR. FISHER: Okay. Dr. Laine.

13 DR. LAINE: I know that you've qualified
14 at the end, but it would seem to me that if
15 everybody agrees that HP is a surrogate marker for
16 eradication -- and that others have shown that 4
17 to 6 weeks is the same as 6 months in terms of
18 eradication -- that is, a lot of people don't --
19 aren't shown to actually be positive.

20 Assuming all your -- you know, obviously
21 you do good diagnostic tests. I know you did --
22 it would seem to me that 6 months really isn't

1 necessary.

2 DR. CRAFT: I think it is the first time
3 you do a particular therapy because I don't think
4 that the therapy and the literature would hold up
5 to this scrutiny, particularly for recrudescences.

6 And there are many articles such as
7 those where he shows recrudescences anywhere from
8 zero to 50 percent in what we would consider good
9 therapies with high eradication rates.

10 So I think until you've done that and
11 proven that the particular therapy you're using is
12 reliable, it's hard to confirm that you really can
13 make a surrogate marker for everything.

14 DR. LAINE: I mean, obviously every
15 study is a clear exception, but most of the
16 studies presented here and the industry studies
17 seem to have not shown that.

18 So you did not find in your studies a
19 difference between 4 and 6 weeks and 6 months, did
20 you?

21 Did you find a significant change?

22 DR. CRAFT: In --