

1 So that if something works, even if it's
2 not as good as something else, we're in general
3 supposed to approve it.

4 That rule is not always followed where
5 not doing well is considered bad for the patient.
6 So, in the treatment of gonorrhoea, for example,
7 anti-infectives have set certain expectations and
8 in other settings, other parts of the agency.

9 So part of what goes into that thought,
10 is how bad is it if you don't cure it right away?
11 You can always try something else, so maybe it's
12 not as bad as some other things.

13 DR. JUDSON: Anyway, you're not saying,
14 don't think about any of those things?

15 DR. TEMPLE: No. Right.

16 DR. JUDSON: You're just saying we don't
17 know yet?

18 DR. TEMPLE: They don't come up when you
19 use the real applications and the real data.

20 DR. FISHER: Dr. Laine?

21 DR. LAINE: I think it's fine to wait
22 and use common sense when you see -- I mean I

1 think there is going to have to be some level
2 you're going to have to decide. But I think it's
3 fine to do the analysis you were talking about,
4 Rosemarie.

5 I guess I would say that 90 percent,
6 although theoretically -- I just have somewhat of
7 a problem in the real world.

8 Now in studies, 90 percent would be
9 nice. I just wonder whether in the real world, we
10 can achieve 90 percent.

11 I think even the best regimens probably
12 in the real world may not achieve 90 percent,
13 although that certainly is something to aim for.

14 DR. FISHER: Dr. Sonnenberg?

15 DR. SONNENBERG: No, because I think
16 it's impractical.

17 DR. FISHER: Dr. Smoot?

18 DR. SMOOT: No.

19 DR. FISHER: Dr. Dunn?

20 DR. DUNN: No, but that doesn't mean
21 that the relative risk -- the risk benefit ratio
22 is not important.

1 DR. FISHER: Dr. Parker?

2 DR. PARKER: Yes.

3 DR. FISHER: Dr. Elushoff?

4 DR. ELUSHOFF: It doesn't sound like
5 there's a point in picking a particular number
6 right now, but I just want to comment from a
7 statistical point of view.

8 If such a number is set, you would have
9 to then go on and say, does that mean the observed
10 percentage have to be greater than that.

11 The bottom of the confidence interval
12 has to be greater than that, et cetera, et cetera.

13 DR. FISHER: Thank you. Dr. Comer?

14 DR. COMER: No.

15 DR. FISHER: Mr. Melish?

16 DR. MELISH: Well, I'll say no, but I
17 have not heard a real endorsement for absolute
18 drug comparison with a regimen that we consider to
19 be the best among the best that we can find today
20 with other regimens. That's what I expect to see
21 come along.

22 I also expect to see that over time,

1 probably efficacy will go down as more and more
2 resistance goes around. And then at some time,
3 we'll get something good and efficacy will go up.

4 But I would like to be certain that
5 we're always going to be comparing the regimen --
6 a new regimen with what we consider to be an
7 excellent regimen or what has been established as
8 the best so far.

9 DR. JUDSON: I would hope that would be
10 the approach, but --

11 DR. MELISH: I think we've heard enough
12 today to hear that we don't want to just show
13 something about placebo. We know that we want a
14 drug that will have high levels of eradication of
15 the organism.

16 So someone is going to have to pick what
17 appears to be the best regimen. And I also think
18 we're going to always have to look at what's in
19 trials and not what's in the real world.

20 And I'm also concerned a little bit
21 about when people talk about compliance in a
22 regimen because as I understand it, you're going

1 to have to have a double-blind double-dummy.

2 So if you're talking about taking 17
3 drugs and you're comparing two regimens, you're
4 probably talking about, you know, taking 17 doses
5 a day. You're probably talking about taking twice
6 that.

7 DR. FISHER: Dr. Butt?

8 DR. BUTT: Yes.

9 DR. FISHER: Give us a number?

10 DR. BUTT: I think anything above the
11 present data from H2 blockers which are very
12 benign agents, any number above the present level
13 of prevention and recurrence that we can attain
14 with H2 blockers.

15 DR. FREDD: If we're taking eradication
16 as the end point, then the eradication rate with
17 H2 blockers is zero.

18 Now -- and we're not --

19 DR. BUTT: I'm preventing ulcer, not --

20 DR. FREDD: No. No. I appreciate that.

21 DR. BUTT: -- not treating the organism.

22 DR. FREDD: But the question is

1 basically what eradication rate.

2 DR. BUTT: Right.

3 DR. FISHER: Yes. We're asking for
4 microbiological eradication.

5 DR. BUTT: Yes. I know. I know.

6 DR. FISHER: All right.

7 DR. BUTT: The eradication rates
8 presumably means that there is going to be a very
9 low recurrence of ulcer, less than ten percent.

10 And that's the reason I picked the
11 figure for using the H2 blockers because they're
12 very benign, they're over the counter.

13 And the antibiotics are difficult to
14 take and may have serious nationwide side effects
15 if they're spread throughout the 30 percent of the
16 population with dyspepsia.

17 So I think we need -- we need an
18 adequate efficacy level.

19 I'm worried that we will never see this
20 -- never have this question raised again and
21 that's the reason I want to commit myself now to
22 saying that we need an efficacy level.

1 DR. FISHER: Dr. Azimi?

2 DR. AZIMI: No.

3 DR. FISHER: That was a no? Okay.

4 And then I think we've actually answered
5 part two of issue number two. And we'll go on to
6 the last session of the day. And I'm turning it
7 back to Dr. Judson.

8 DR. JUDSON: Is that all sufficiently
9 clear to the FDA now?

10 Thank you, Dr. Fisher. Our final
11 question of the day is how to implement HP
12 clinical data into the lay plan and clearly
13 related. And Dr. Hopkins is scheduled for another
14 5 minute presentation.

15 DR. HOPKINS: The brief talk I'd like to
16 give now is really not much different than what we
17 were talking about earlier, the idea of how to
18 craft an appropriate label. But I want to --
19 would like to concentrate on exactly is what claim
20 should be used in that label.

21 This is a claim. If you read it, it
22 says, "Bisma-Rex relieves acid stomach in three

1 minutes."

2 And so I just want everyone to
3 understand that it's very important that we craft
4 a label that will actually be helpful to
5 industries that they can create claims and promote
6 those drugs appropriately.

7 This is the indication for current anti-
8 secretory agents, essentially stating simply that
9 they're indicated for short-term treatment of
10 active duodenal ulcer, active benign gastric ulcer
11 and maintenance treatment for duodenal ulcer
12 reduced doses after healing of acute ulcers.

13 The question that comes up -- has come
14 up before is in what population should we be
15 assessing ulcer eradication if we believe that
16 that is the surrogate for reduced ulcer
17 recurrence, and should we be including patients
18 who have a history of ulcers, as well as patients
19 who have acute ulcers in the label as a claim?

20 And in order to do that, we would need
21 data that would suggest that patients who have a
22 history of ulcers have similarly high recurrence

1 risk of ulcers than patients who have acute
2 ulcers.

3 And what complicates the issue is what
4 you do with patients who are on maintenance
5 therapy and what the recurrence risk of ulcer is
6 once you stop that maintenance therapy.

7 And secondarily, if you think not, then
8 should you -- if you want to achieve a claim for
9 patients with a history of ulcers, can you include
10 patients with a history of ulcers as well as
11 patients with acute ulcers in the same clinical
12 trial as has been suggested before?

13 So really the issues -- this issue
14 really has been brought up before, but I didn't
15 know that it would be anticipated and so I state
16 it here again.

17 We have one speaker, Dr. Garry Neil from
18 Astra Merck, to address the natural history of
19 duodenal ulcer.

20 DR. NEIL: Well, thanks once again for
21 the opportunity to speak to you.

22 I think this issue has been touched upon

1 a number of times during the course of the
2 proceedings today where we talked about ulcer
3 healing and acute ulcers and so on and so forth,
4 and who should be included in the trials.

5 And what I wanted to do is, because we
6 don't have a lot of data, really hard data to
7 address a lot of the questions that have been
8 raised, to see whether there is anything that can
9 be learned from natural history, also from the H2,
10 blockers ulcer maintenance trials and also from
11 some other studies that might be available that
12 can help us to better understand this condition.

13 We now recognize by now, the end of the
14 day, that H. pylori-associated duodenal ulcer
15 really has to be regarded as a chronic infectious
16 disease, although acid and other factors are
17 important. And of course, we have also covered
18 the necessity of doing HP eradication that it's
19 indicated for treatment of these patients. And
20 that in at least patients who have active
21 documented extent ulcer disease that if you give
22 them effective eradication therapy, you reduce

1 their risk of recurrence.

2 All these studies are based on
3 post-healing follow-up or recent healing.

4 But we recognize I think that duodenal
5 ulcer disease is really a chronic, as I said,
6 infectious disease and ulcer diathesis with
7 patients having a crater a part of the time and
8 then having the crater disappear.

9 And what are we going to do for those
10 patients who have a history of documented duodenal
11 ulcer disease, well-documented by endoscopy and
12 who remain H. pylori-infected?

13 Should these patients be treated, even
14 if they are symptom-free on H2 blockers and how
15 should this be put into the label?

16 And, in fact, I'd go a step further and
17 say, is it even possible to distinguish between
18 active and inactive ulcer diseases? Is there
19 really such a condition as inactive ulcer disease?

20 And lastly, I think another issue which
21 will have to be touched upon is what difference is
22 to be expected in the eradication rates for a

1 given regimen if it was to be used in a patient
2 who had an extent crater -- ergo an active ulcer
3 patient -- versus somebody who didn't have that?

4 Now, the concept of ulcer burnout has
5 been raised here a couple of times as we consider
6 this issue of inactive ulcer disease. Dr. Freston
7 mentioned it and also Dr. Sonnenberg just a moment
8 ago.

9 I think that this has been suggested in
10 the literature and we'll look at a little bit of
11 those data from the natural history studies.

12 However, as I'll try to convince you,
13 most of the studies that have been published
14 actually show that there is no moderation in the
15 disease over time; that it remains a chronic
16 disease.

17 And some studies have been published
18 that suggest that the disease may intensify in the
19 first 5 to ten years and then remain constant, and
20 a very few show that there is ulcer activity for
21 at least ten years after diagnosis, followed by
22 moderation.

1 Now this is the famous study by John
2 Frye that you've heard about a couple of times
3 today. John Frye was a general practitioner who
4 practiced in the suburbs of London, and he wrote
5 the Channing Paper in the British Medical Journal
6 in 1964 referring to his professors as deities,
7 which I guess was true back then.

8 But anyway, he had looked back at his
9 practice over the preceding 15 to 20 years because
10 he thought that ulcer disease appeared to be
11 behaving more -- in a more benign fashion than he
12 had seen and during his training in the hospital.

13 And he did this study based on symptoms
14 and he classified patients according to 4 grades
15 of symptoms. And you can see them there, one,
16 two, three and 4, with one being no symptoms. Two
17 being a patient who required some medication.
18 Three being someone who had actually sought his
19 advice in the past year about ulcer symptoms. And
20 4, somebody who had symptoms severe enough to have
21 him sign an absence sheet for them during the past
22 12 months.

1 And you can see that he looked at
2 patients, how they were, what classification they
3 had at onset. Then again, 5 years after the onset
4 of the disease, ten years and then 15 years.

5 Now, these are the medically treated
6 patients. He did admit that about 16 percent of
7 his patients at least had gone on to surgery.

8 But just looking at these medically
9 treated patients, he showed that the majority of
10 patients in the beginning were in a stage two and
11 three and that 5 years more of them were actually
12 at stage three and 4.

13 But, by ten years, most of the patients
14 were either asymptomatic or some medication, and
15 at 15 years, that proportion is even greater.

16 So this study has gotten a lot of press.
17 It has been widely quoted and I think it's a
18 worthwhile study to consider. But there are a lot
19 of limitations here.

20 It's based entirely on symptoms. It's
21 based on a retrospective follow-up from one
22 general practitioner, and it's hard to know

1 exactly how representative that is. And there is
2 certainly a lot more data and I think a lot better
3 data that one can look at.

4 This is a study that was published by
5 Irving Krause who is a Swedish surgeon. This was
6 published in 1963 and this -- this is a group of
7 350 patients that were diagnosed with duodenal
8 ulcer disease.

9 He also included gastric ulcer disease
10 patients in this series, but I'll just focus on
11 the duodenal ulcer disease patients here.

12 And these patients all came from Upsala
13 in Sweden and a very stable population. They all
14 have ulcer disease diagnosed radiographically at
15 the time, between 1920 and 1935. And he followed
16 these patients for more than 25 years and reported
17 on this in 1963.

18 And what he noted -- this is subdivided
19 between males and females that received it. He
20 had many more male than female patients.

21 But he noted that only a small
22 proportion of his patients were completely well or

1 had mild symptoms over time.

2 And what he described as a serious
3 course, patients with multiple recurrences,
4 patients who had been actually recommended to have
5 surgery, but refused, or who had actually had
6 surgery or even died from their ulcer.

7 He called those patients "serious course
8 patients." And the vast majority of them over
9 that course of time would actually develop a
10 serious course.

11 And there is -- there is what happened
12 to them over follow-up with respect to surgery.
13 This is a cumulative number on the Y-axis, and
14 here is follow-up.

15 These are the male patients in red and
16 the female patients in purple who had surgery.
17 And these are the number of deaths.

18 As we've seen, death wasn't actually all
19 that common in his practice over time due to ulcer
20 disease, but there was a continual accumulation of
21 patients who went to surgery.

22 The other interesting thing is that he

1 noted that, as time went by, as patients were
2 followed for a longer and longer period of time, a
3 greater and greater proportion of the patients
4 that he had loved to follow -- admittedly, he had
5 lost some -- fell into his "serious course"
6 category.

7 So if ulcer disease were burning out,
8 one would have expected perhaps to have seen the
9 opposite. But in his case, longer follow-up was
10 actually associated with seemingly a worse course.

11 And this study is not unique. There are
12 other studies from the Scandinavian literature
13 with -- bit studies with reasonably long
14 follow-up, not as long as that.

15 Gustav and Romke, over 80 percent of
16 their patients continued to have symptoms during a
17 6 year observation period.

18 Krarup followed 665 patients between 5
19 and years, and he described 71 percent as having a
20 poor or less favorable result. And then, in this
21 study from Malmros and Hierton, only 13 percent
22 of their patients actually remained symptom free

1 during this follow-up of 7 to nine years.

2 There are other studies like that which
3 tend to argue against Frye.

4 There are a number of other studies
5 which looked at the risk of duodenal ulcer relapse
6 and looking at factors, these are from the H.
7 pylori era. And I might point out that, of
8 course, we don't know the H. pylori status of any
9 of the patients from the Frye study or from the
10 Scandinavian studies even in retrospect.

11 But one can assume, I think, that the
12 large majority would have been H. pylori-positive,
13 given what we know today.

14 But there was a lot of interest on
15 factors that were related to ulcer relapse over
16 the course of the past years, especially when it
17 was discovered that post-H2 blocker therapy, ulcer
18 relapses was a very common phenomenon.

19 Now what you see again and again, as is
20 suggested by this study by Penston, is that one of
21 the factors that seem to predict, albeit weakly,
22 but it seems to predict a higher risk for DU

1 recurrence is the duration of ulcer disease.

2 Now, again, it's circumstantial
3 evidence, but I think that one would have expected
4 that a longer duration of disease would have
5 predicted a lower probably of ulcer recurrence if
6 the disease were following a course towards
7 burnout. And that's not seen in any of the
8 studies.

9 And then some of the earlier studies, I,
10 have shown you longer duration of disease seem to
11 have a worse outcome as well, although the
12 follow-up is not long in these studies.

13 We know as we've heard today studies,
14 especially studies from Ken McCall's lab and
15 others, that H. pylori infection does have an
16 influence on acid secretion. And it seems, too,
17 that at least in patients who develop duodenal
18 ulcers, there is a tendency towards acid
19 hypersecretion in these patients.

20 And of course, it has also been
21 described recently that H. pylori infection over
22 long periods of time can cause gastric atrophy or

1 atrophic gastritis, although this seems to be
2 quite patchy.

3 It would possibly provide a mechanism by
4 which you could say that ulcer disease due to H.
5 pylori might burn out if the stomach was slowly
6 being consumed by the bacteria.

7 What really happens to people over long
8 periods of time? I mean we can assume, I think,
9 that the majority of patients, and we've heard
10 from Dr. Megraud and also from Dr. Sonnenberg,
11 appear to be infected in their early life.

12 And if the disease were -- again
13 assuming that these DU patients are H.
14 pylori-positive, as I expect most of them would
15 have been in this study, we would -- might expect
16 that acid secretion might reduce with age over
17 long periods of time.

18 And the studies that have been done, the
19 study by Carlin which was published last year, and
20 there's a corroborating study in the Italian
21 literature just past published this year, these
22 patients have an elevated output, and it seems to

1 -- it does not significantly decline even when you
2 look at patients who are over the age of 70.

3 And I think this corroborates what many
4 of us, as gastroenterologists, have seen. I
5 personally had a patient who was 100 years old
6 with duodenal ulcer. So obviously you can make
7 enough acid to produce an ulcer.

8 So if you look at all of these data
9 taken together, what we see is that the duration
10 of ulcer disease either slightly increases the
11 risk of ulcer recurrence or it has no effect, not
12 the opposite way.

13 That advancing age -- there are a couple
14 of studies that were done that looked at advancing
15 age, and it does not reduce the risk of ulcer
16 recurrence.

17 In fact, I'm not aware of any studies
18 which really show that.

19 It appears that acid secretion does not
20 decline in older duodenal ulcer patients. Of
21 course, we don't know their H. pylori status. But
22 I think taken together in the natural history

1 studies I've shown you, these findings corroborate
2 the assertion that ulcer disease doesn't appear to
3 burn out.

4 Now what about the -- there are much
5 better studies, of course, from the long-term
6 maintenance trials with H2 blockers, but also goes
7 to this issue.

8 We know, as we've already heard, that
9 chronic acid suppression reduces the frequency of,
10 ulcer relapse. That's certainly true, although I
11 think it's interesting that if one actually looks
12 at some of these studies which were actually
13 commissioned to actually address the hypothesis
14 that said that one of the reasons that H2 blockers
15 might be working to prevent ulcer recurrence is
16 due to an ascertainment bias. They may just be
17 suppressing the symptoms. Patients really have an
18 ulcer but nobody knows because nobody is looking
19 in an asymptomatic patient.

20 And Wormsley, et al., actually did one
21 of these studies where they scoped patients on
22 ranitidine 150 milligrams a day for 6 months,

1 every month, to address this issue. And actually
2 48 percent of the patients on ranitidine developed
3 duodenal ulcer in that study, although most of
4 them were asymptomatic.

5 So I think it does reduce the frequency
6 of ulcer relapse, but it may reduce the frequency
7 of ulcer symptoms more than it does ulcer relapse.

8 We also know though that ulcers very
9 frequently recur after long-term acid suppression,
10 has stopped. That has been very well-documented.

11 But does the risk of ulcer recurrence
12 moderate over time in these studies?

13 If you have patients on long-term H2
14 blocker therapy and then stop it, do they have a
15 lower risk of ulcer recurrence?

16 Well, again, we don't have data to
17 address that question directly, and in many cases,
18 we don't actually know the HP status. But this is
19 a study from Penston where patients who had
20 received ranitidine maintenance for 7 years, and I
21 believe they have longer follow-up now. But when
22 this was published, they had 7 years of follow-up.

1 The patients were then randomized after
2 that to continue ranitidine therapy or to go on
3 placebo for an additional 6 months.

4 And what they saw was that there was
5 about a percent relapse rate in the patients who
6 received placebo, which is a strikingly similar
7 number to the relapse rates that we've seen in the
8 H. pylori eradication trials presented earlier
9 today.

10 If you look at other studies, this is a
11 study by Korman, looking at what happens after
12 cimetidine therapy for one, two or three years
13 together doesn't seem to be any difference,
14 although this is only a short period of follow-up
15 in the rate of ulcer recurrence after either one,
16 two or three years of cimetidine therapy.

17 So I think that those studies again
18 don't seem to corroborate the notion that ulcer
19 disease burns out.

20 The prevalence of duodenal ulcer in
21 asymptomatic H. pylori-infected patients is also,
22 I think, of some interest in deciding what to do

1 with these so-called inactive patients.

2 Now, I'm talking here about patients
3 with a history of duodenal ulcer disease. So we
4 know that these patients have had a duodenal ulcer
5 in the past. They remain H. pylori-infected.

6 And even if they're asymptomatic off of
7 therapy, what is the point prevalence of duodenal
8 ulcer in these patients?

9 Could any of them be walking around with
10 a duodenal ulcer and not know?

11 We actually addressed this in a study
12 where we were looking for inactive patients or
13 looking for patients with a documented history of
14 duodenal ulcer within the last 5 years who were
15 not on therapy, who were H. pylori-positive and
16 who were asymptomatic.

17 And we scoped these individuals. We
18 scoped of them and this is what we found. These
19 are the endoscopic findings from that study. 31
20 percent of them had a duodenal ulcer.

21 .4 percent of them had duodenal
22 erosions, which could be regarded as a form of

1 first ulcer. 4 percent of them had a gastric
2 ulcer. And a couple of them even had adrenal
3 carcinoma of the stomach, which was quite
4 interesting. And only 45.1 of these patients had
5 a totally negative endoscopy.

6 So the point prevalence of lesions in
7 these asymptomatic patients with supposedly
8 inactive ulcer disease is strikingly high.

9 So I would conclude from these data that
10 I've shown you, taken together, that duodenal
11 ulcer does not burn out or become inactive, but at
12 least not within ten years, and probably much
13 longer. And that long duration of disease,
14 duodenal ulcer disease, is if anything, a risk
15 factor for relapse, certainly not the opposite.

16 And I think the concept of inactive
17 ulcer disease is really not supported by the
18 literature. In fact, I'd sum it up the way Regent
19 physician, Dr. Andersen, did in 1947 when he
20 defined peptic ulcer disease, or what we would
21 call peptic ulcer diathesis today, as a chronic
22 gastro duodenitis with or without an ulcer.

1 That was long before Dr. Marshall had
2 discovered H. pylori, but I think it was somewhat
3 pressing.

4 Patients who have a documented history.
5 We're not talking about people with dyspepsia, but
6 patients who have a documented history of duodenal
7 ulcer disease and who remain H. pylori-positive
8 are probably at continued risk for duodenal ulcer
9 recurrence. And most of them are probably at
10 increased risk lifelong.

11 And I think if duodenal ulcer disease
12 hasn't been documented in the past and the patient
13 remains infected, eradication therapy is indicated
14 in those patients.

15 As I've said earlier, I think that we
16 can regard cure of H. pylori infection to be a
17 valid surrogate end point and I know that word was
18 somewhat controversial, but there's a valid end
19 point for studies in patients where we're looking
20 for prevention of duodenal ulcer disease.

21 And I think that we can also -- we can
22 extend that to be -- to having it used as a valid

1 end point for patients irrespective of whether
2 they have an active crater or not at the time of
3 diagnosis or at the time of enrollment into the
4 trial.

5 That would be contingent on
6 demonstrating that the eradication rates were not
7 different between patients who had an active ulcer
8 and patients who did not, because I think that
9 there may be a difference in symptoms which might
10 lead to a difference in compliance, which might
11 lead to a difference in eradication rates for many
12 other reasons.

13 And I can't show you more of the data on
14 that, but there's no a priori reason to believe
15 that the eradication rates would be different, and
16 there's nothing in the literature which would
17 suggest that the rates are, in fact, different
18 between those two groups of patients.

19 And then since this is a labeling
20 session, what I would say about labeling is that I
21 believe that labeling of HP eradication regimens
22 for duodenal ulcer need not distinguish between

1 active and inactive ulcer disease. I think they
2 should focus on the ulcer disease and not worry as
3 much about the crater.

4 Or as somebody once said, we should stop
5 focusing on the hole in the patient and start
6 focusing on the whole patient.

7 Thanks very much for your attention.
8 Yes?

9 DR. JUDSON: Just to start things off
10 here, what in your mind constitutes adequate
11 documentation of a history of duodenal ulcer?

12 DR. NEIL: I think either endoscopy
13 showing that the patient has duodenal ulcer or a
14 high quality upper GI series demonstrating
15 previous presence of an ulcer. Because although
16 an upper GI series may not show you whether the
17 patients' ulcer crater -- or cannot distinguish
18 between an active ulcer crater and a scar.

19 I think it can fairly reliably tell you
20 that this patient has had an ulcer, at least in
21 the past.

22 DR. JUDSON: So you would not get on to

1 the slippery slope of clinical diagnoses --

2 DR. NEIL: You know --

3 DR. JUDSON: -- heartburn --

4 DR. NEIL: Right.

5 DR. JUDSON: -- point tender?

6 DR. NEIL: Studies that have been done
7 have shown that only about 20 percent of patients
8 who present with these symptoms are actually found
9 to have an ulcer.

10 Now probably a larger proportion may
11 have H. pylori induced gastro duodenitis and
12 actually have an ulcer diathesis. That's more
13 problematic.

14 But I think the majority -- it's
15 probably safe to say that the majority of patients
16 who present with symptoms are not found to have an
17 ulcer. And I think that the ulcer symptoms are
18 very unreliable in the diagnosis of duodenal ulcer
19 disease and are very unreliable predictors of the
20 presence of an ulcer based on some of the data
21 that I've just shown you.

22 DR. JUDSON: So history for you is

1 radiologically or --

2 DR. NEIL: Yes.

3 DR. JUDSON: -- endoscopically
4 documented?

5 DR. NEIL: Yes.

6 DR. JUDSON: Yes, Dr. Burks?

7 DR. BURKS: A fact question for Dr.
8 Neil. I was very struck by the data you showed of
9 the high recurrence rate in patients that had been
10 on maintenance therapy for several years. And
11 we've seen those kinds of data over and over.

12 Are there any data to your knowledge
13 that addressed the issue of what happens if we
14 take people who are diagnosed three years ago,
15 that went through an acute healing phase of
16 therapy and then are on maintenance for two years
17 or three years or 7 years or some number of years,
18 and then they're put on eradication therapy and
19 the maintenance and the secretory therapy is
20 discontinued.

21 Are there any data addressing that
22 point?

1 DR. NEIL: Unfortunately, no. No one
2 has done a study like that. But I'm not really
3 sure it's necessary in light of what we know about
4 the pathophysiology right now because we've got
5 data a reasonably long time out showing that these
6 patients remain at risk, or at least the majority
7 of them do.

8 And you can't really predict who's going
9 to have a recurrence within the time point. And,
10 maybe the recurrence rates that we're getting when
11 we say 50 percent, that's based on symptom
12 recurrence.

13 And looking at some of these other data,
14 I'd venture to say, if we repeated the Ken
15 Wormsley study and did an endoscopy every month,
16 we'd get that number up.

17 DR. BURKS: Thank you.

18 DR. JUDSON: Dr. Reller?

19 DR. RELLER: Dr. Neil, once healed, does
20 one need H2 blocker maintenance therapy if H.
21 pylori is eradicated?

22 DR. NEIL: If -- no. I don't think so.

1 I think the risk of recurrence is sufficiently low
2 that one would not, as a routine, use maintenance
3 therapy in a patient like that.

4 DR. JUDSON: So that's a very
5 interesting point, one therefore from a cost
6 benefit standpoint where you'd want to document
7 eradication of HP and then drop all therapy?

8 DR. NEIL: Right. It doesn't obviate
9 the need for the physician to take a history so
10 that he or she is satisfied that the ulcer disease
11 is not due to something else, like
12 Zollinger-Ellison Syndrome or abuse, but if they
13 believe that this is the association, then they
14 don't need to do the maintenance therapy.

15 DR. FISHER: Would you agree with that
16 even if it was a patient who was elderly, who had
17 coronary disease, who had a major GI bleed on that
18 episode, to feel comfortable just with eradication
19 and not a little longer period of maintenance?

20 DR. NEIL: Well, you have to judge every
21 case individually, as you know. But there are a
22 lot of data out now showing that H. pylori

1 eradication in these patients does reduce the risk
2 of GI bleeding, as well as of the ulcer.

3 DR. FISHER: I have another question, if
4 I could. Before I didn't get time.

5 On the 324 patients that you talked
6 about --

7 DR. NEIL: Yes.

8 DR. FISHER: -- you had that on file,
9 they had been on no therapy for 5 years?

10 DR. NEIL: No. No. They were no
11 therapy at the time that they were scoped and they
12 were asymptomatic.

13 I think they couldn't have been on any
14 therapy within a month or so.

15 DR. FISHER: Okay. I guess what I was
16 looking at, in looking at length of time, because
17 I think sometimes people forget being on NSAIDs or
18 something like that when they had a duodenal
19 ulcer. And if we're take somebody who comes in
20 and says, you know, "4 years ago, I had an ulcer
21 and I've got a little bit of dyspepsia now. I've
22 heard about HP and I want to be tested for it and

1 treated for it.

2 "And I can't remember if, 4 years ago, I
3 was on NSAIDs or not. But I was endoscoped. I
4 had an ulcer, but nobody biopsied it or whatever."

5 So you don't know status then. But you
6 test them and they've got HP now.

7 Do you treat them, one, that's one
8 question, or not? Or what do you think of that
9 sort of scenario? And they've had no symptoms and
10 been on no maintenance therapy from the time of
11 their original diagnosis, say 4 years ago?

12 DR. NEIL: Well, I'm a
13 gastroenterologist and I probably would have
14 tended to rescope that patient anyway.

15 But, I mean, I think if you've got solid
16 documentation that they had a duodenal ulcer and
17 you don't have anything else going on, that's
18 fine.

19 If they tell you that they -- I mean
20 everybody tells me that they had an ulcer. And
21 that is very difficult to be certain that that's
22 what they've had without documentation.

1 But I don't have a problem with wanting
2 to have that documentation available before you go
3 ahead and treat them.

4 DR. FISHER: I guess the other question
5 I had is that even though we've got lots of
6 evidence and that it doesn't burn out -- the
7 incidence of recurrence -- if somebody has a
8 recurrence say within the first 6 months, their
9 chances of incidence of recurrence, again, are
10 higher, the same, or lower of someone who has an
11 ulcer and goes for a year without a recurrence,
12 they're on no therapy.

13 You know, they had an acute 6 weeks of
14 healing, not put on maintenance, and then go out a
15 year with no recurrence, what's their incidence of
16 recurrence -- HP-negative, HP-positive?

17 Do we know that? I guess I'm looking
18 at, should we be saying: it's okay to label acute
19 or non-acute or not including -- you know,
20 including studies, acute and non-acute, if
21 eradication rates are the same.

22 Does there come a point when you say,

1 "Gee, if somebody had an ulcer a year ago, has had
2 no symptoms, has had no obvious recurrence, has
3 been on no maintenance therapy for a year, that it
4 may not be worth treating them for HP if you don't
5 know if they were HP positive a year ago?

6 DR. NEIL: It's hard to get data out of
7 any of the studies to tell you what to do with an
8 individuals patient.

9 It worries me when I look at these
10 endoscopic findings though in asymptomatic
11 patients, and we had a couple of cancers in there.
12 And I think -- this is my own personal bias, but I
13 think if they had a documented ulcer, it's hard to
14 know that the risk of recurrence is going to be
15 zero and that next recurrence is not going to be
16 associated with a GI bleed or perforation.

17 And I also don't think that that H.
18 pylori infection could be doing them any good. So
19 my personal preference would lean towards treating
20 that patient anyway.

21 DR. FISHER: I guess I'm just looking
22 again though for incidence of recurrence.

1 If you don't -- if you go for a year
2 without a recurrence on no therapy, are your
3 chances of having the recurrence less than if you
4 had a recurrence within 6 months? Or if you had
5 two recurrences within that first year, are you
6 more likely to have a recurrence again?

7 DR. FREDD: Rosemarie, could I ask you,
8 do you mean an endoscopic recurrence or
9 symptomatic recurrence?

10 DR. FISHER: Either which way.

11 DR. FREDD: But I mean, if you haven't
12 been seen, how do you know what's going on in
13 the --

14 DR. FISHER: Right. But you don't --

15 DR. FREDD: -- duodenal belt at the
16 time?

17 DR. FISHER: No. You're absolutely
18 right. When you get into --

19 DR. FREDD: The point is, you know, if
20 there -- if over the course of time, people with
21 ulcer diathesis because of balances between
22 aggressive and defensive factors, are ulcerating

1 and healing, ulcerating and healing, and symptoms
2 are not a guide to that recurring.

3 DR. FISHER: Agreed.

4 DR. FREDD: And that ulcer leads to
5 perforation, bleeding, death potentially in some
6 small proportion of those, how can one say that
7 such a person did not have continued ulcer
8 disease?

9 DR. NEIL: That's well-said and that's ,
10 my point, too. You can't really know, but I think
11 it's --

12 DR. FISHER: But there is data out there
13 somewhere -- I'm asking is there data out there
14 somewhere, looking at endoscopic recurrence or --

15 DR. FREDD: To answer specifically that
16 question, no.

17 DR. FISHER: Okay. Thank you.

18 DR. JUDSON: Dr. Butt, did you still
19 have a question?

20 DR. BUTT: Yes. Since a great number of
21 these patients will have reflux symptoms in
22 addition to their ulcer problems, treatment of H.

1 pylori is not going to affect those symptoms?

2 DR. NEIL: No.

3 DR. BUTT: And those patients are going
4 to have to continue on some kind of -- some kind
5 of suppressive therapy.

6 How do you -- since this is a labeling
7 section, how will you -- how would you suggest we
8 handle that particular problem?

9 DR. NEIL: Well, I think you don't have,
10 to use maintenance therapy as a routine, but I
11 think, you know, you're well-advised to continue
12 to follow the patient because, of course, it may
13 unmask symptoms that may have been covered up.

14 But, you know --

15 DR. BUTT: Continue treatment?

16 DR. NEIL: Those patients require
17 treatment for esophagotosis. But you know, the
18 incidence of esophagotosis increases with age
19 anyway after the age of 40. And so some of those
20 patients may -- induce them to do that anyway.

21 DR. BUTT: Yes. The expectation, of
22 course, the patient who's being treated is that

1 the symptoms are going to clear. So some way, it
2 has to be conveyed to them that not all their
3 symptoms may clear.

4 DR. NEIL: Right. It's not -- it may
5 cure short stature coronary artery disease and
6 cancer, but I don't know about heart murmur.

7 DR. JUDSON: Okay. To try to finish up
8 at 5, if we can, which is within reach, we'll go
9 on to the third issue and the initial phrasing is,
10 how should clinical trial data be implemented into
11 labeling?

12 That's obviously a very broad question.
13 I'd like to go on simply to the next part, which
14 is listed as A on the slides and nothing on the
15 agenda.

16 And the question there is, if -- and I
17 think I understand this question -- if clinical
18 studies only include patients with active duodenal
19 ulcer disease, should claims be made regarding
20 patients with a history of duodenal ulcer disease?

21 And why don't I -- we'll have the chairs
22 hold up until last, I guess, and head off to the

1 right.

2 Is there any further clarification
3 there? I'm assuming as I asked the question
4 before that there is documentation of that history
5 of ulcer disease, when we asked that question.

6 So can they pull into the label history,
7 along with active?

8 Dr. Reller?

9 DR. RELLER: And it assumes they have HP
10 at that time.

11 DR. FISHER: HP at the time of
12 presentation, I think is what you're saying.

13 DR. JUDSON: Right. Right. That's how
14 I'm interpreting that.

15 DR. FISHER: Patient who comes has
16 dyspepsia, has a history of an ulcer a year and a
17 half ago or something. And you test them for HP.
18 They have HP. Should they be included in that?
19 Should they be allowed to take it, based on the
20 claim?

21 Is that correct, Dr. Hopkins, Dr.
22 Girardi?

1 DR. HOPKINS: Yes, that's correct.

2 DR. RELLER: I do not believe that a
3 label should extend beyond the database. I like
4 the criteria for objective documentation of
5 history that was given. It seems pretty
6 reasonable to me.

7 And there are sufficient numbers of
8 patients in whom H. pylori presence could be, I
9 think, documented and they could be followed.

10 But if one wanted to extend this
11 treatment to H. pylori-positive patients with a
12 documented history of duodenal ulcer disease, one
13 could do that if you provide the data for same.

14 So specifically, no. I don't think one
15 should extrapolate from clinical trials results
16 based on a group of patients, 200, 300, whatever
17 the number is, with active duodenal disease, with
18 the discussions we have had before, and then just
19 blanket extend that to -- this is also true for
20 patients with a history.

21 I don't think it's necessary and I think
22 it's ill advised.

1 DR. FISHER: Can I add a second part to
2 that question which may save some time in going
3 around because Dr. Neil raised it.

4 Is that if eradication rates could show
5 -- could be shown to be the same in patients with
6 an active ulcer versus those who would have a
7 documented duodenal ulcer in several trials, would
8 you then agree that the claim could be -- that
9 that could be included in the label, if that were,
10 proven to you?

11 DR. RELLER: Again, I think it would be
12 wise to be very precise. I mean, if one takes
13 patients who have a history and those who have
14 active -- and have H. pylori and you show that you
15 eradicated H. pylori. And if you should claim for
16 whatever you're giving them that's associated with
17 that eradication that it eradicates H. pylori.

18 DR. JUDSON: Okay.

19 DR. RELLER: Which is a good thing in
20 these patients.

21 DR. JUDSON: Dr. Henry.

22 DR. HENRY: Well, I would echo Barth's

1 sentiments.

2 I think that they have to be able to
3 substantiate what's put on the label, and you
4 can't be making it a bit more diffuse by including
5 people.

6 I think if they were to do a study and
7 stratify those patients and find that there's no
8 difference, and so as far as the second part, you
9 know, if you say, no, then what should you do?

10 I think that if they're going to include
11 them, they need to have them included in studies
12 in a stratified fashion to make certain that
13 there's no difference between the two groups.

14 DR. JUDSON: Dr. Kirschner?

15 DR. FISHER: Dr. Temple, could you --

16 DR. TEMPLE: Could you also address what
17 you mean by "active"? Active could mean the whole
18 study started with people with a duodenal ulcer or
19 it could mean something more like the studies that
20 have been done where someone was observed by the
21 same investigator to have an ulcer. It got healed
22 and then they randomized.

1 I mean, is that active enough for you to
2 know they didn't start out the trial with an
3 active ulcer or how much of a distinction is being
4 made here?

5 DR. JUDSON: Well, that would be enough
6 for me for a study. But we're talking about
7 labeling, aren't we?

8 DR. TEMPLE: I guess I'm asking whether
9 there's a distinction between those two kinds of
10 activity.

11 I understand the difference between
12 someone who had an ulcer ten years ago and who may
13 or may not be active now.

14 But does activity mean the study was
15 done in people who started out with a whole --

16 DR. JUDSON: Yes.

17 DR. TEMPLE: -- or does it mean that
18 they definitely, unequivocally had an
19 endoscopically diagnosed ulcer very recently?

20 Because you could imagine those
21 different settings.

22 DR. JUDSON: That's why I asked I think

1 you or the companies need very clear definitions
2 of what a history of duodenal ulcer would be. And
3 that would probably have to include time frame, as
4 well as diagnosis procedure.

5 We settled diagnosis procedure, but we
6 didn't say whether it was within one, two, three
7 years or two months.

8 We cut you off, Dr. Kirschner. Did you
9 want to --

10 DR. KIRSCHNER: No. I guess I could --
11 you know, I'm assuming that the history is
12 excluded in the other cause for ulcer in these
13 patients. I mean, that they weren't on aspirin
14 and they weren't on NSAIDs.

15 And I guess that's what bothers me. An
16 history of an ulcer all by itself.

17 DR. JUDSON: Except they do have HP now.

18 DR. KIRSCHNER: I realize that. And
19 we're not endoscoping them at all to find out
20 whether they, in fact, have any active disease?

21 DR. JUDSON: We're accepting a
22 history --

1 DR. KIRSCHNER: Breath test.

2 DR. JUDSON: -- that they were
3 endoscoped 6 months ago, 12 months ago. Didn't
4 determine that.

5 DR. KIRSCHNER: They were scoped at some
6 point?

7 DR. JUDSON: Well, yes. We're going to
8 say that that constitutes a history. There has to
9 have been --

10 DR. KIRSCHNER: And the physician --

11 DR. JUDSON: -- documentation by
12 endoscopy and/or --

13 DR. KIRSCHNER: And the physician felt
14 that HP --

15 DR. JUDSON: -- rates.

16 DR. KIRSCHNER: -- that HP was the cause
17 of the ulcer at that time?

18 DR. JUDSON: HP is present -- well, they
19 may not have done that. But now they come to you
20 with a history, documented those ways, and the HP
21 test is positive. I guess --

22 DR. KIRSCHNER: By what mechanism?

1 DR. JUDSON: Some way.

2 DR. KIRSCHNER: The acceptable standard
3 at the time the patient is coming to see you,
4 whatever that mechanism may be.

5 DR. JUDSON: They have documented ulcer
6 in the past. They have documented HP now. I
7 don't know how they documented it.

8 DR. KIRSCHNER: I think I'll pass on
9 that.

10 DR. FISHER: Dr. Fredd?

11 DR. FREDD: Can I try to clarify some
12 aspects behind this question that I don't
13 understand the way you're responding?

14 The sample of patients -- do you -- you
15 know, one of the points in my head is do you
16 believe that ulcer disease is a chronic relapsing
17 condition?

18 If one believes that, then the sample of
19 patients taken with that underlying chronic
20 relapsing condition, in order to identify the new
21 clinical studies has been active ulcer crater
22 noted on endoscopy.

1 So that's the way the clinical trial was
2 done and they found an acceptable eradication rate
3 which you may be able to correlate with reducing
4 the risks.

5 So you got that information. Now the
6 question is, having sampled that particular
7 portion of the population with chronic relapsing
8 disease, will you recommend that the indication
9 only be for the population you sampled or for the
10 underlying disease which waxes and wanes?

11 That's what I'm trying to understand
12 from this, and I hear the answer is stick to
13 exactly the population that you sampled.

14 DR. JUDSON: I think what --

15 DR. COMER: I think we need to stick to
16 this -- to what we've -- what they've studied.
17 And I think that somebody -- if one of the
18 sponsors demonstrates unequivocally that these
19 people with a history act in no way different from
20 the people with active ulcer disease and they show
21 that, then maybe in future studies we could make
22 that extrapolation.

1 But I think that somebody has to show it
2 once.

3 DR. FREDD: Act in no way different. Do
4 you mean in terms of the eradication rates --

5 DR. FISHER: Eradication rates.

6 DR. COMER: The eradication rate and --

7 DR. FREDD: -- or in terms of the
8 history of disease?

9 DR. COMER: The eradication and
10 recurrence and everything else has to be
11 demonstrated in a scientific way that they are the
12 same.

13 Once a sponsor has demonstrated that
14 these patients are no different than the other
15 patients, then I think we would be prepared to
16 extrapolate to other studies.

17 DR. FREDD: Again I'm sorry to push. I
18 just want to know what you mean by "no different."
19 No different --

20 DR. COMER: That there is the --

21 DR. FREDD: -- from eradication?

22 DR. COMER: -- same eradication rates

1 and the same lack of recurrence.

2 These people have not been studied at
3 all.

4 DR. FREDD: Well, they have been in the
5 David Graham study. But we can get to that.

6 DR. JUDSON: Well, I think you've
7 clarified that. And the first three of our panel
8 members to comment are still expressing that
9 they're not willing to assume that these are
10 identical populations.

11 Yes?

12 DR. COMER: Yes. And I also say no with
13 the same qualifications.

14 DR. JUDSON: Okay. Did we get to you
15 Skip, Dr. Francis?

16 DR. FRANCIS: I think I have to define
17 what I see is active duodenal disease because it
18 seems to be quite a spectrum of what it is
19 supposed to be.

20 I don't know if the time limit is the
21 situation or rather the person has some definitive
22 proof of an active inflammatory duodenal process

1 that we presume to be associated with the
2 Helicobacter.

3 If that's the case, then I think the
4 claim that can be made is for persons who have
5 documented proof, either by a history or
6 acceptable by the gastroenterologist, or some
7 previous documentation through endoscopy or biopsy
8 in the past of inflammation caused by
9 Helicobacter. That claim can be made in those
10 situations. You can do it.

11 What I'm concerned about is that in
12 defining a population, I'm having trouble
13 sometimes seeing how you're going to differentiate
14 from just over the counter.

15 Because a lot of people who come in and
16 make similar claims that are very strong without
17 the proof that I think a lot of us want, and why
18 not just put everything in Pepto-Bismol and give
19 it to everyone?

20 I can see that possibility, depending on
21 how you want to interpret that claim.

22 I think we're trying to mirror that a

1 little bit. For me, I think that physical proof
2 is very important. And I guess there are a lot of
3 ways to do that.

4 I don't think the time is quite as
5 important because as you pointed out the
6 situation, the chronicity of the disease is very
7 important.

8 DR. JUDSON: Dr. Bertino? Was that a
9 yes?

10 DR. FRANCIS: That was a yes.

11 DR. BERTINO: No.

12 DR. OWYANG: No. I share Gail's
13 comments. I think there's some portions that at
14 least there should be some studies showing that
15 unequivocally that these group of patients do
16 follow the same course in terms of response rate
17 eradication as well as healing as to active ulcer.

18 DR. JUDSON: Sir, I'm sorry. You're
19 saying?

20 DR. OWYANG: No. It's no.

21 DR. JUDSON: Dr. Banks?

22 DR. BANKS-BRIGHT: I'm voting no also.

1 I entirely agree with Dr. Comer. I don't know
2 that we can extrapolate.

3 DR. BANKS: No for the same reasons.

4 DR. THORPE: No or the same reasons.

5 DR. CRAIG: I'll say no, but --

6 DR. JUDSON: Dr. Craig?

7 DR. CRAIG: -- I agree that the
8 populations may be the same. But I also have some
9 suspicions that there might be some difference in
10 efficacy.

11 If the local pharmacology of the
12 antibiotic is important in the efficacy, I could
13 clearly see where the local pharmacology would be
14 different in somebody with an active ulcer as
15 compared to somebody with a healed ulcer.

16 So I think we do need to have those
17 studies to demonstrate that the eradication rates
18 are the same.

19 DR. JUDSON: Yes. Dr. Megraud.

20 DR. MEGRAUD: I would say yes. I think
21 the patients are the same. Ask the question many
22 times and the pharmacology is not a good reason

1 because any way you treat the gastritis, H. pylori
2 gastritis with antibiotics, you don't treat the
3 ulcer per se, the crater per se. So I think it's
4 --

5 DR. JUDSON: I think that's a wonderful
6 tradition. Sorry.

7 DR. MEGRAUD: I say yes.

8 DR. JUDSON: Okay. Thank you. I think
9 one of the problems we're going to have as we look
10 on down the line and as therapy of ulcers become
11 more and more established is that increasingly
12 people will have been treated previously with one
13 regimen or another. And the failure to one thing
14 or another is going to be a larger consideration,
15 especially microbial resistance from some of the
16 data that you presented.

17 So that going into it and setting it
18 right now in a fairly virgin population is going
19 to be different than it may be 5 years from now.

20 DR. LAINE: I think that H. pylori is
21 clearly -- H. pylori eradication clearly
22 dramatically decreases ulcer recurrence. And to

1 me that's very, very clear, far more than I think
2 this panel has been willing to accept, and far
3 more dramatically than the association that was
4 discussed between blood pressure and strokes, for
5 instance.

6 I think it's quite clear that ulcer
7 disease not related to NSAIDs or ZE is a chronic
8 disease that virtually always recurs or in the
9 vast majority of patients recurs.

10 We don't have any evidence that there is
11 going to be a difference in terms of H. pylori,
12 major difference of H. pylori eradication. And if
13 it's 5 or ten percent, it's not going to matter.

14 So to me, it seems quite clear that -- I
15 would say yes.

16 DR. FISHER: But would you like to see
17 one or two -- one even or two -- I mean we've got
18 David Graham. Would you like to see one other
19 study to say that eradication rate is no different
20 to reassure yourself?

21 DR. LAINE: I actually don't think I
22 need it clinically to reassure myself.

1 I think it would be interesting. It's
2 always fun, so to speak, to gather data and I
3 think it would be interesting.

4 But I really do believe that there is
5 such a dramatic decrease in ulcer recurrence, and
6 we can quibble about whether it cuts down to two
7 percent or 5 percent or 15 percent. And we know
8 that the large majority of patients who have
9 ulcers are going to have recurrence ulcers if they
10 don't have -- if they have H. pylori and no other
11 obvious causes; that it just -- the decrease will
12 still be quite marked.

13 And again we may quibble about the
14 relative decrease in ulcer recurrence, but it's
15 still going to be quite marked in those groups,
16 and therefore I would be willing and clinically, I
17 would definitely treat those patients in the same
18 way.

19 DR. FREDD: And the committee has
20 already said that you're not setting a minimum
21 level for efficacy of an eradication. So if you
22 get an eradication rate in what you call acute

1 ulcers or active ulcers of 80 percent and you get
2 75 percent, you know, in the healed population,
3 both, I take it, you would consider effective?

4 DR. JUDSON: Right. But the committee
5 members I think are -- again it gets down to the
6 question of which should be approved for labeling
7 versus what can be assumed.

8 Yes?

9 DR. TEMPLE: I guess we understand by
10 this that the argument that ulcer -- duodenal
11 ulcer disease in the absence of an NSAID, the
12 argument that that is a chronic disease and that
13 whether you happen to notice an ulcer at any given
14 moment is sort of an accident of whether you put
15 your endoscope in there, doesn't persuade the
16 committee.

17 I would be interested in why not because
18 it sounds pretty persuasive and has obviously
19 persuaded some of the consultants to the
20 committee.

21 And then the second part of that
22 question is, is there the thought that if you can

1 eradicate H. pylori in the presence of an active
2 ulcer, you would not be able to eradicate it if
3 the ulcer weren't there?

4 Is that a worry? One of those two
5 things I suggested must be the reason for this.

6 DR. JUDSON: Well, I think Dr. Craig
7 phrased one theoretical concern is that -- that is
8 that the local milieu in which the antimicrobial
9 agents are working may be different in the absence
10 of inflammation or a hole.

11 DR. LAINE: Inflammation is still there,
12 no matter what. It's just a localized hole, which
13 is about a, you know --

14 DR. JUDSON: Yes. But it's probably
15 going to vary over time.

16 DR. LAINE: Well, the inflammation stays
17 pretty constant if the H. pylori has been treated.
18 I mean and I'm not sure that anybody has shown
19 that inflammatory so infiltrates.

20 DR. FREDD: Where is the H. pylori
21 living? Only in the hole or throughout the
22 stomach?

1 DR. LAINE: The H. pylori is obviously
2 living on the surface. It's not living in the
3 gastric mucosa.

4 DR. JUDSON: I don't know, but I --

5 DR. FISHER: Could we finish going
6 around?

7 DR. JUDSON: Yes. Let's go ahead and
8 finish up.

9 DR. SONNENBERG: I don't know.

10 DR. JUDSON: Okay. Pass. Abstain.

11 DR. SMOOT: I would also have to say
12 yes. I think that the populations are similar
13 enough that there wouldn't be any difference.

14 I understand those who would like to see
15 well-controlled studies. I would just ask that
16 there would be well-controlled studies showing
17 this; that it would not be a burden that this
18 needs to be shown with every regimen that is later
19 being brought forth. And that once it's shown
20 once, then everyone could use that data.

21 DR. JUDSON: Dr. Dunn?

22 DR. DUNN: I would say no. I think the

1 risk ratios don't have to be the same.

2 If you have a patient who has no
3 symptoms, then you start to treat them. They may
4 then have symptoms they didn't have before. And
5 to them, it may make a big difference.

6 DR. JUDSON: Dr. Parker?

7 DR. PARKER: I want to see at least one
8 study showing that the recurrence rate is reduced
9 by eradicating the organism in this historic
10 population.

11 After I see that, I'll change my vote.
12 But right now, I'm going to say no.

13 DR. JUDSON: Okay. Dr. Elushoff?

14 DR. ELUSHOFF: I would say no. I think
15 the longer it has been since there were active
16 symptoms or active documentation, the lower the
17 risk of occurrence in the next 6 months. And
18 therefore I think at some point along the line,
19 you're going to get to where the benefit shown by
20 eradication gets to be very small and not
21 important.

22 DR. JUDSON: Dr. Comer has voted clearly

1 previously.

2 Dr. Melish?

3 DR. MELISH: My vote is also no but I
4 wouldn't require that every regimen be tested in
5 the currently inactive patients; just that we show
6 that there are a similar population.

7 I think that can be separated in
8 labeling.

9 DR. JUDSON: Dr. Butt?

10 DR. BUTT: No.

11 DR. AZIMI: A point of clarification.
12 These are asymptomatic patients right now --

13 DR. JUDSON: Yes.

14 DR. AZIMI: Who had a history of
15 duodenal ulcer and we know that they are positive
16 for H. pylori now?

17 DR. JUDSON: Correct.

18 DR. AZIMI: And the claim is that if
19 they use the medication, that the H. pylori would
20 be eradicated?

21 DR. JUDSON: Correct.

22 DR. FISHER: You would have less

1 recurrence.

2 DR. AZIMI: My vote is yes. I feel
3 comfortable with that.

4 DR. FISHER: I'm actually going to say
5 yes. I agree with Loren and Duane.

6 But I would just like to urge the
7 companies that have some stratification within
8 that because I would like to see the numbers or
9 the similarity of eradication on the patients who
10 have a healed DU and those who have a history of a
11 healed DU and who have an active DU.

12 Since I said yes, the question was also
13 since the last -- should there be a time
14 restriction on it?

15 I'd like to say that I think the
16 positive should make sure that the patient did not
17 have just an NSAID-associated ulcer some time ago
18 and just be HP positive now, and that it really is
19 with the physician to tell what's going on.

20 DR. LAINE: It is reasonable to choose
21 some time period as your next question and ask,
22 perhaps -- I mean if it was 20 years ago, I don't

1 think anybody would --

2 DR. FISHER: Yes. I think it should
3 have been --

4 DR. LAINE: -- suggest we --

5 DR. FISHER: -- probably within the
6 past, no longer than two years ago.

7 DR. FREDD: If the patient is on
8 maintenance H2's and is HP positive and has been
9 on maintenance H2's for 5 years and says, "I don't
10 want to keep on this. This is costing me a lot of
11 money every month. You can eradicate my HP and I
12 will not have ulcers anymore," what do you do?

13 DR. JUDSON: Okay. Let's finish up the
14 voting. I haven't voted yet.

15 Were there any others who were missed?
16 I -- assuming that the natural history data that
17 we have is, in fact, accurate and will continue to
18 be our view of things for some time to come. So
19 based on that, I'm voting yes.

20 DR. FISHER: Do you want to put a claim
21 -- length of time on it, if --

22 DR. JUDSON: And this is for labeling.

1 I think for studies, we want to continue to
2 stratify and -- Yes?

3 DR. THORPE: For purposes of studies,
4 why focus on the patients who have active craters?

5 And that's not been made clear to me.
6 If we're talking about a continuous chronic
7 recurrent disease, then it seems to me not
8 necessary to enroll only those patients who have
9 active craters.

10 And so I'm not sure why we're focused on
11 this point. I think that maybe if the question
12 had been turned around that the same people that
13 voted no might well have voted yes.

14 That is, is it necessary to have an
15 active crater for the treatment, the eradication
16 treatment to be useful?

17 And I think most of us --

18 DR. FISHER: Would say no.

19 DR. THORPE: -- you don't have to have
20 an active crater.

21 DR. JUDSON: Dr. Reller?

22 DR. RELLER: Dr. Comer put this so

1 clearly. I mean, it doesn't make any difference.
2 I mean, you studied people with an active history
3 of duodenal ulcer disease or those with an active
4 crater, however you want to define it in time
5 frame.

6 I think those of us who voted no is
7 saying, "You can do either one or you can do both.
8 Just tell us what you did so that we know what you
9 did."

10 I think it's really a slippery slope if
11 you start putting extrapolations in that are not
12 based on a database that is clear.

13 I mean once an ulcer, always at risk for
14 an ulcer until H. pylori is eradicated, then it
15 shouldn't be a big deal to be able to show that
16 there is not a substantive difference in terms of
17 response to therapy for H. pylori in these
18 patients with this diathesis.

19 And to stick to the database and the
20 label might be a good precedent for what may come
21 up in the future.

22 DR. JUDSON: Dr. Francis.

1 DR. FRANCIS: The question I guess I
2 wanted to ask is perhaps along the same line. But
3 is it -- Dr. Laine could help me or someone --
4 every person -- individual who has the
5 Helicobacter will have some demonstrable and test
6 for inflammation of a chronic manner?

7 Is that right?

8 DR. LAINE: They'll virtually all have
9 histologic gastritis, inflammatory cell --

10 DR. FRANCIS: Okay.

11 DR. LAINE: -- infiltrate in the mucosa.

12 DR. FRANCIS: Everyone that has the
13 infection?

14 DR. LAINE: Yes.

15 DR. FRANCIS: So strict attention that
16 really the ulcers are almost irrelevant in that
17 respect. Is that correct?

18 DR. LAINE: No. Well, I mean some would
19 say that. I think what we're saying is only let's
20 say 15 percent of people who have H. pylori and H.
21 pylori-associated gastritis will have an ulcer.
22 And those are the ones who have a potential for

1 getting problems.

2 Those who have gastritis at the present
3 time alone, it's just a histologic -- of
4 histologic interest, but not something that should
5 be treated.

6 Now some would say everybody with H.
7 pylori should be treated, but --

8 DR. FRANCIS: But then the natural
9 history of the people who did not have ulcers is
10 not clearly known then. Is that correct?

11 DR. LAINE: Well, I mean that assumption
12 is -- it appears that most -- there are a couple
13 of studies that look at 10 to 15 years and show
14 that perhaps 10 to 15 percent of people who have
15 H. pylori will develop ulcers.

16 The assumption is that the other 85
17 percent, at least over that time period, it's
18 extrapolated for life. But those others won't
19 because they either have different H. pylori
20 strains or there are different host factors.

21 There's something about them that
22 prevent them from, you know, cause them not to get

1 an ulcer. Or, you know, they smoke, other things
2 could be going on.

3 DR. FISHER: Which is why we are looking
4 at documented history, you know, of ulcer.

5 DR. LAINE: But there is no evidence of
6 histologic gastritis causes symptoms or is a risk
7 for development of bleeding, let's say.

8 It may be a risk for cancer and
9 lymphoma, certainly. But we're not talking about,
10 that now anyway, so --

11 DR. FRANCIS: Because based on your
12 answer then I would have to change -- I'd be more
13 inclined to change the yes to no because I was
14 under the understanding that that group that
15 doesn't have an ulcer but has a disease has a
16 demonstrable disease that needs intervention also.
17 But that's correct? You don't -- no one really
18 knows. Is that right?

19 DR. LAINE: And most people would say
20 those other 85 percent or whatever the number is
21 --

22 DR. FRANCIS: Those would be the people

1 who come up and say, "I have an ulcer." And you
2 would say, "Well, maybe you don't." And if that's
3 the case, then that definition would have to be
4 very narrow with some kind of documentation.

5 DR. LAINE: Well, that's what we're
6 saying.

7 DR. FISHER: That's what we said.

8 DR. LAINE: Only with endoscopic of --

9 DR. FISHER: We said documented by
10 endoscopy and test.

11 DR. JUDSON: Yes. They must have had
12 endoscopic and/or radiographic documentation.

13 DR. FISHER: Not somebody, you know,
14 told me, years ago, "I had an ulcer and I took
15 some antacids and I got better, and that was it."

16 DR. JUDSON: Yes.

17 DR. KIRSCHNER: I could be really wrong
18 about this, but I thought the NIH consensus said
19 that they were not addressing the issue of
20 gastritis at all? I mean I can tell you --

21 DR. LAINE: They specifically said no
22 reason for routine detection or treatment of those

1 in the absence of ulcers.

2 DR. KIRSCHNER: But I think they said
3 they didn't address the issue of gastritis. They
4 didn't make any recommendations for treating
5 anybody else. But they didn't address the issue
6 of gastritis.

7 Because I can tell you, in pediatrics,
8 70 percent of the kids that have H. pylori have
9 nodular gastritis. They're very symptomatic.
10 They're extremely symptomatic, and they don't have
11 ulcers.

12 And I think as we educate people about
13 what H. pylori disease is and whether they should
14 be treated asymptomatic or not, it's absolutely
15 undecided in my mind.

16 And I think most pediatric
17 gastroenterologists would say that H. pylori
18 disease is probably very symptomatic. We need to
19 study it. And you don't think we could make any
20 statements at all that it doesn't need to be
21 treated.

22 DR. JUDSON: Okay. Well, thank you.

1 The score was 12 no to 4 yes. And so that allows
2 us to go on, the way I'm interpreting this, to the
3 second or last part of the question which is, if
4 no, should patients with a history of duodenal
5 ulcer disease be included with active ulcer
6 patients in order to make the claim that --

7 DR. FISHER: I think --

8 DR. JUDSON: Yes, I think we've --

9 DR. FISHER: Yes. I think you're
10 hearing that the people are saying to include
11 that, you should include the patients --

12 DR. JUDSON: Okay.

13 DR. FISHER: -- with an active disease
14 in the future, stratify them and get some answers
15 and show that they act the same.

16 In a way, it's almost the same as some
17 of the people who were saying yes and said, "I'd
18 like to see you study this." You know, "I'd like
19 to see data that the eradication rates are no
20 different."

21 DR. JUDSON: Okay. Well, it's two
22 minutes after 5:00 p.m. If there are any other

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questions, we'll handle them individually and
we'll be adjourned until tomorrow morning.

Thank you.

(Whereupon, at 5:02 p.m., the
hearing was adjourned.)

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