

1 where the cytochrome P450 enzymes are localized, so
2 toxic injury often takes -- has its greatest effect in
3 the central lobular area, and something that's not
4 apparent normally is that there's a canalicular
5 network through which bile is secreted and flows in
6 the opposite direction to the blood, is exited through
7 the bile ducts. And the bile is an energy -- bile
8 flow is an energy dependent process; so when there's
9 a cholestatic injury, it also shows up first in the
10 area around the central vein by which -- as I've had it
11 explained to me - that's because it has the furthest
12 to go from that area to get out; so that we always pay
13 close attention to the central lobular areas.

14 Now let me show some examples from some
15 diseases that are drug induced. Here's a liver
16 biopsy. This is a little bit lower power. This is
17 portal area here, a central vein here, and another one
18 here, and another one over here some place. And what
19 we have here is severe necrosis of the liver cells,
20 and particularly concentrated in the areas around the
21 central veins; the areas that are most susceptible to
22 these types of injury. That's zonal necrosis, and
23 when we see that, we always suspect a drug. This
24 happens to be a biopsy from a patient who developed
25 injury after Halofane anesthesia.

1 Here's a liver biopsy from a patient who
2 had been taking trimethoprim-sulfamethoxazole. This is a
3 portal area, very high magnification. The rest of the
4 liver tissue is out here, and there was spotty
5 necrosis, hepatitis going on within the parenchyma,
6 and right in the portal area we have a granuloma.
7 These are histiocytes here. Here's a giant cell; and
8 a granuloma has a number of eosinophils.

9 Now when I see this, the first thing I
10 would ask is well then what medication was the
11 patient taking. Granulomatous disease along with the
12 eosinophils strongly suggest a drug.

13 Here's a liver biopsy from a patient who
14 was taking amoxicillin and clavulanic acid. There's
15 a portal area down here, the central vein is up here.
16 This is a cholestatic injury. You can see it looks
17 brown; that's because there's lots of bile in the area
18 in the area around the central vein, but there's also
19 other injury going on as well. There's spotty
20 necrosis of liver cells and inflammatory cells within
21 the parenchyma, and inflammation in the portal area.

22 Now Dr. Cox had asked me if I thought the
23 case that the patient who was taking Telithromycin was
24 reminiscent of what was seen in trovafloxacin. Well,
25 I got this off the Internet. This is the only

1 published picture that I'm aware of trovafloxacin and
2 induced liver injury. There's a central vein here;
3 that's why the quality isn't very good, it looks kind
4 of grainy. But there's a central vein here, and
5 there's an area of necrosis and loss of liver cells
6 surrounding it, and a lot of inflammatory cells, and
7 the arrows are pointing to some of the inflammatory
8 cells. These are almost all eosinophils.

9 This is another -- a biopsy from another
10 patient who was trovafloxacin. This is one from the
11 files AFIP. There's a portal area here, there's a
12 central area here, and another one over here; and both
13 of these central areas have confluent necrosis and
14 collapse, and a lot of inflammatory cells, and I'll
15 show a higher magnification of that one. It's shown
16 here. The central vein is buried in here some place.

17 We have confluent necrosis and a very
18 recent necrosis, and all the liver cells are gone, and
19 there are a lot of inflammatory cells; and at higher
20 magnification they're a mixture of cells, not like the
21 ones that were in the picture that I just showed, but
22 there's some granulomatous inflammation. There are
23 histiocytes here. Here's the giant cell. There are
24 many eosinophils, and there are also a lot of plasma
25 cells.

1 Now this is the first liver biopsy from
2 the patient in Finland who developed the injury after
3 stopping the trovafloxacin -- I mean, I'm sorry; after
4 stopping the Telithromycin, and then had his biopsy at
5 about the time that his eosinophil count was peaking,
6 and there's a central vein underneath all of this, and
7 another one under this. It is reminiscent of the
8 trovafloxacin case though, because there's a lot of
9 confluent necrosis in the central areas. There's also
10 a lot of spotty necrosis all throughout the biopsy.
11 And if we look at this at higher magnification, here's
12 the central vein ~~lower~~, and lots of inflammatory cells;
13 and there are a mixture of cells here. There's
14 histiocytes and almost all of these other cells are
15 eosinophils, which we can see here at high
16 magnification.

17 Now this is very unusual. I'm not aware
18 of any non-drug related naturally occurring liver
19 disease that really looks like this. It doesn't look
20 like autoimmune hepatitis. It doesn't look like viral
21 hepatitis, so with the history that the patient was
22 taking a new drug that hasn't been recognized as the
23 cause of liver injury, and then seeing this soon
24 afterwards, I would say that this is almost certainly
25 drug-induced; despite the fact that he had abnormal

1 liver enzymes before he took the drug.

2 Now, one thing that helps us recognize
3 whether there was an underlying chronic liver disease
4 is to look at a connective tissue stain; and this is
5 the one that was done in Finland. This is a serious
6 red stain. It's used a lot in Europe, but not much in
7 this country; but collagen stains red, and if this
8 patient had underlying chronic liver disease, we would
9 expect to see some significant amount of fibrosis.
10 But here's a low power of his liver biopsy with a
11 serious red stain. There's a little bit of fibrosis
12 around some of the portal areas; and this is the same
13 one at higher magnification, but really not much - so
14 if he did have an underlying chronic liver disease it
15 must have been extremely mild.

16 Now the next slide I'm going to show is
17 going to show this biopsy in the same place, but over
18 here we'll see a connective tissue stain that was done
19 on his second biopsy nine months later. And this is
20 using the Masson Stain which is the one that we use in
21 this country, and they used in this case in Finland.
22 The Masson stains collagen blue, so anything that was
23 red over here would be blue over here nine months
24 later; but in addition, we've got all of this other
25 blue here. That's an awful lot of fibrosis that's

1 occurred in the ninth month interval. It looks like
2 he's got a pretty significant chronic liver disease at
3 this stage; and looking at that at higher
4 magnification, there's a portal area over here which
5 has got some fibrosis around it.

6 This is the central area here, and another
7 one down here, and another one down here. Most of the
8 fibrosis is actually in the central lobular areas,
9 which is the same areas that were injured, that had
10 all the eosinophilic inclusions months earlier. Now that's
11 very unusual.

12 Looking at the history it looks like this
13 ought to have been autoimmune hepatitis. The patient
14 has hypergammaglobulinemia. He has an anti-smooth
15 muscle antibody, and he's got this liver biopsy but
16 it's not quite typical of autoimmune because of the
17 location of the injury.

18 Here are a couple of fields. There's a
19 portal area down here. This area appears central
20 where a lot of the fibrosis is. Same thing over here;
21 this is central here, portal over here. And here's
22 the portal area at high magnification.

23 Now in autoimmune hepatitis the brunt of
24 the injury is usually portal. You have a lot of
25 piecemeal necrosis around it, and a lot of

1 inflammation in the portal areas, but here there's
2 actually more injury going on in the central areas.

3 Well even so, it -- I think if I were to
4 put one diagnosis on it, it looks like it probably
5 should be autoimmune hepatitis, but it is very curious
6 that it followed in the same areas that the patient
7 had the injury nine months earlier. And another
8 feature of autoimmune hepatitis is that typically the
9 major inflammatory cell is a plasma cell, and if we
10 look at these at higher magnification, almost all of
11 these are plasma cells; no eosinophils. So all I can
12 say is this case is really unique in my experience.
13 I'm not aware of any really well documented case of
14 autoimmune hepatitis that have followed a drug-induced
15 injury, but this I suppose could be the first one.

16 I think looking at the overall case, I
17 think the first liver biopsy certainly looks like
18 drug-induced liver disease. The second one, I have to
19 admit, I'm not really sure what exactly is going on
20 there.

21 DR. RELLER: Dr. David Ross will now
22 summarize the FDA presentation before a question and
23 answer period. Dr. Goodman.

24 DR. COX: Thank you, Dr. Goodman. This is
25 Ed Cox. I'll just summarize the hepatic effects, and

1 then Dr. Ross will be up to provide the further
2 summary. So with regards to the hepatic effects, as
3 seen in the pre-clinical studies, we saw
4 hepatotoxicity in dogs, rats, and monkeys. And then
5 in Phase I, the clustering of hepatic adverse events
6 at the 2000 milligram times one dose that I described.
7 There was no clear dose response for hepatic adverse
8 events in Phase I.

9 Then if we move on to the Phase III
10 adverse events, there were similar adverse events
11 rates for Ketek and comparators; no apparent drug-
12 induced hepatic deaths. And then with regards to the
13 hepatic serious adverse events from the Phase III
14 studies, there are two that appear to be plausibly
15 associated with Ketek. One of these events was the
16 case that Dr. Goodman just described the pathologic
17 findings on where a patient had central lobular
18 necrosis and eosinophilic infiltration on pathology,
19 and also was noted to have an elevated ALT and
20 eosinophils on day one.

21 And then we also went through the AST and
22 ALT ladders, which showed elevations in Ketek treated
23 cap patients who were normal at baseline, that were
24 more than what was seen in the comparator treated
25 patients. This was not seen in the studies with

1 patients from studies other than community-acquired
2 pneumonia. And then we also looked at the concomitant
3 combination low level elevations in AST/ALT and T.bili
4 that occurred only in Ketek treated patients.

5 And now I'll turn the podium back over to
6 Dr. Ross.

7 DR. RELLER: Thank you, Dr. Cox.

8 DR. ROSS: I'd like to summarize the -- by
9 giving an overview of risk benefit issues.

10 This is data that Cynthia Whitney and her
11 co-workers published in the New England Journal in
12 December, showing the prevalence of non-susceptible
13 pneumococci for various antimicrobial, so this
14 includes both intermediate susceptibility, pneumococci
15 and fully resistant. And as everyone knows, we're
16 seeing a steady increase over the late 90's for
17 penicillin non-susceptibility, as well as Erythromycin
18 non-susceptibility. And clearly, we're concerned
19 about this. It represents a public health problem.

20 I think it's important though for us to
21 try and define as much as possible what the impact of
22 this phenomena -- phenomenon rather is, because that's
23 really what defines what the benefit is for targeting
24 resistant pathogens, and allows us to weigh that
25 benefit against the risk of new agents. And this --

1 weighing this benefit by determining the impact can be
2 very difficult.

3 In the retrospective studies that were
4 cited in the applicant's presentation, the one by
5 Feikin did not show an increase in mortality
6 associated with penicillin resistance, unless you
7 excluded all patients who died during the first four
8 days.

9 The study -- retrospective study by Turett
10 consisted of retrospective cohort, a retrospective
11 population that was -- had a significant number of HIV
12 positive patients. That's not to say that that --
13 those analyses are not useful, but it does indicate
14 that it can be very difficult to tease out exactly
15 what the impact is of penicillin resistance.

16 As another example of this, let me cite
17 data that Pallares and his collaborators published in
18 '95 from Barcelona. When they looked at patients with
19 pneumococcal pneumonia; either for all cases or cases
20 with concurrent bacteremia, penicillin resistance --
21 and here this meant isolates with an MIC of .12 or
22 greater, so it included isolates that were -- had
23 intermediate susceptibility.

24 Penicillin resistance was not an
25 independent risk factor for mortality in a

1 multivariate regression analysis. Even if you take
2 out conditions that are associated with the infection
3 itself, such as shock or involvement of more than one
4 lobe, penicillin resistance was still not an
5 independent predictor of mortality.

6 Looking at data from the same publication,
7 if you look at fully resistant isolates; and these
8 numbers were small, you do not see a dramatic
9 difference in mortality for patients treated with
10 penicillin or ampicillin, despite the fact that they
11 have infections with resistant isolates, compared to
12 patients treated with other antimicrobial agents.

13 This is not to say that penicillin
14 resistance is not a problem; only that we need to
15 define the impact carefully if we're going to define
16 the benefit, and weigh the risk.

17 In assessing benefits of claims for
18 efficacy against resistant organisms, we need to think
19 about the public health impact. What is the benefit
20 in infections due to resistant pathogens, and if we're
21 talking about out-patient therapy, what is the benefit
22 in out-patients who have mild to moderate disease, who
23 do not require hospitalization. How serious is the
24 infection?

25 If we're talking about community-acquired

1 pneumonia, are we talking about patients who are at
2 higher risk for mortality, such as Fine Category V, or
3 patients who are lower risk for mortality, such as
4 Fine Category I. Are we talking about a condition
5 with lower mortality and morbidity that's associated
6 with it, such as AECIG, or an infection for which the
7 antibiotic treatment effect is less.

8 What is the mechanism of action? Are we
9 talking about out-of-class -- a mechanism that targets
10 out-of-class resistance, where one would not expect
11 biochemical changes that would result in resistance,
12 or are we talking about in-class resistance, where the
13 mechanism of action may be related to the mechanism of
14 resistance. And if we are talking about in-class
15 resistance, what is the potential for concurrent
16 resistance? In the case of Telithromycin, as Dr.
17 Davidson discussed, there's the issue of Erythromycin
18 MICs rising, with Telithromycin MICs appearing to show
19 a shift at the same time. And then finally, what is
20 the evidence for clinical efficacy versus resistant
21 isolates? What is the weight of evidence in general
22 for infections caused by susceptible or resistant
23 isolates? What is the weight of evidence for
24 infections due to resistant isolates? And what is the
25 evidence for efficacy in invasive disease due to

1 resistant isolates, such as patients with pneumococcal
2 pneumonia with concurrent bacteremia? And we say this
3 for two reasons.

4 First, as we all know, these are patients
5 who are at higher risk for a poor outcome. Secondly,
6 as Dr. Davidson pointed out, patients with a positive
7 blood culture are those for whom we have greater
8 certainty as to the identity of the true pathogen,
9 compared to patients where we only have a positive
10 sputum culture.

11 Let me turn to the risk state of the
12 equation. I've shown this data before but this is in
13 a somewhat different format. This shows the change in
14 QTC for Telithromycin when given with ketoconazole,
15 and shows that it's statistically different from
16 placebo. And as Dr. Ruskin pointed out this morning,
17 we need an assessing risk for cardiac repolarization
18 abnormalities to be particularly alert to the
19 possibility of amplifying events that could increase
20 the risk for cardiac repolarization related events.

21 It's also important to recognize that
22 along with metabolic interactions, electrophysiologic
23 interactions could play a role. This is a list of
24 drugs that are associated with the QTC prolongation or
25 Torsades. A few of these have been withdrawn from the

1 market, but the majority are still in wide clinical
2 use.

3 Along with the effects that other drugs
4 may have on Telithromycin, we need to consider the
5 effects that Telithromycin may have on other drugs.
6 In Phase II studies when Telithromycin was co-
7 administered with other agents, the Cmax of
8 simvastatin was increased by 433 percent in the area
9 under the curve by 761 percent.

10 With regard to the pharmacokinetics of the
11 major metabolically active metabolite of simvastatin,
12 the beta hydroxy acid, the concentration was increased
13 by -- Cmax was increased by 1400 percent, in the AUC
14 by 1100 percent.

15 For digoxin, a drug with a narrow
16 therapeutic index, the increase in Cmax was 70
17 percent, and AUC 37 percent. For midazolam the
18 increase in Cmax was 162 percent, and the increase in
19 AUC was 511 percent.

20 What is -- what are the clinical
21 implications of drug interactions? It's instructive
22 to look at the example of Mibefradil which was
23 marketed under the trade name of Posicor. This was a
24 calcium channel blocker that was a potent inhibitor,
25 and still is a potent inhibitor of 3A4, and in vitro

1 inhibited the metabolism of various statins to greater
2 or lesser extents.

3 It is important to note in the development
4 program for mibefradil, in patients who received
5 mibefradil concomitantly with a statin, no associated
6 adverse events were seen. Mibefradil was approved in
7 August of '97 for treatment of chronic stable angina,
8 and hypertension. The label given on approval carried
9 warnings regarding a number of drugs that could
10 interact with mibefradil because of the ~~concern~~ over
11 cardiac repolarization.

12 After approval, reports starting coming in
13 of adverse events associated with interacting drugs.
14 Within four months after approval, additional warnings
15 were added to the label regarding use of lovastatin or
16 sinvastatin in particular, as well as use of any
17 statin, and concomitant use of tacrolimus
18 cyclosporin, along with other labeling changes
19 regarding the potential for bradycardia.

20 Finally, less than a year after approval,
21 mibedradil was withdrawn from the market. More than
22 two dozen interacting drugs have been identified.
23 There were continued reports of adverse events from
24 co-prescribed interacting drugs. Because of the
25 number and complexity of these interactions, further

1 labeling changes were felt to be impractical. And
2 despite the nature of the indications, it was not felt
3 that the agent had any special benefits relative to
4 other agents. So with those considerations, let me
5 outline some of the safety concerns with regard to
6 Telithromycin.

7 There is the potential confluence of
8 multiple risk factors. The effect on QTC, the
9 concentration dependence of this QTC effect, and the
10 pharmacokinetic variability that can affect
11 concentration, and therefore affect QTC, arising in
12 part from non-linear pharmacokinetics.

13 There is the potential for hepatotoxicity
14 as outlined by Drs. Cox and Goodman, that could have
15 an effect on hepatic clearance, and also affect
16 concentration. There's the potential for increase in
17 exposure in elderly patients, in those with
18 hepatorenal disease, as well as potential for exposure
19 with concomitant medications. These factors together
20 could potentially lead to clinically significant
21 changes in QT intervals.

22 It's important to note that we have very
23 limited data on at-risk groups. There were few
24 patients in any given risk group, and it's also
25 important to note that there is a limited range of

1 concentration data in the Phase III studies. There
2 were relatively few patients who had a concentration
3 of five or over, despite our concerns over
4 pharmacokinetic variability; so we don't really know
5 what might happen in patients with higher
6 concentrations. I'd also mention again that these
7 concentrations were not necessarily achieved -- did
8 not necessarily represent Cmax.

9 In addition, there's the independent
10 concern over potential hepatotoxicity and uncertainty
11 regarding how the drug should be dosed in patients in
12 special populations, given altered pharmacokinetics in
13 the elderly and other special populations in the non-
14 linearity of the pharmacokinetics.

15 There are the potential affects that
16 Telitromycin could have on concomitant medications,
17 such as the statins. And then finally, there is --
18 even though the -- there were no events associated
19 with QT prolongation, or co-administration of
20 medications in Phase III studies, it's important to
21 remember that absence of evidence in these studies
22 does not equal evidence of absence.

23 As Dr. Soreth pointed at the beginning,
24 these studies are typically not powered to detect weak
25 signals. And given the potentially wide population

1 exposure of drugs for respiratory tract infections,
2 these needs to be kept in mind.

3 This is data that Linda McCaig published
4 a few years ago in JAMA showing prescriptions on an
5 out-patient basis for various upper respiratory tract
6 infections in millions of courses. And as you can
7 see, there were in '92 over 80 million courses of
8 antimicrobials prescribed on an out-patient basis; so
9 this is the sort of exposure that we need to keep in
10 mind.

11 Let me stop here. Thank you for your
12 attention; and my colleagues and I would be happy to
13 answer any questions that the Committee has.

14 DR. RELLER: Dr. Bell.

15 DR. BELL: Thanks. I wanted to pick up on
16 your excellent comments about the need for additional
17 outcome data on resistant infections. The CDC
18 Surveillance Project of pneumococcal infections and
19 resistance has just recently started to routinely
20 collect outcome information, but I wanted to also
21 comment on the two studies that you mentioned, the
22 Feikin and Pallares, which I'm sure you've read more
23 recently than I have. But the Feikin study in which
24 you pointed out that the beneficial impact -- or
25 rather the adverse impact of drug resistance on

1 mortality was seen only after the first few days. I
2 think ~~it~~ -- you know, historically my recollection is
3 that even when penicillin was first introduced, the
4 difference in mortality was only apparent after the
5 first days because the idea being that there's a
6 certain percentage of people who come in with
7 overwhelming infection, or they have some debilitated
8 status, and so I think it would be unfair to suggest
9 that an effect limited to after the first few days is
10 -- you know, is questionable.

11 In the Bellares study -- now my
12 recollection of this also is that his was mainly --
13 you know, the issue here for pneumococcal resistance
14 and pneumonia is that the microbiologic nomenclature
15 of the break points; this is really an issue it's
16 resistant for meningitis, but in these patients who I
17 think were hospitalized and treated with high doses of
18 penicillin, they could easily exceed what was needed
19 for pneumonia. So of course, those patients they
20 wouldn't see any resistant pneumonia difference, but
21 I think what we're talking about here is out-patient
22 treatment orally of mild to moderate pneumonia. And
23 I believe that the Erythromycin or macrolide levels
24 might not be able to exceed so much the concentrate --
25 the MICs, but maybe you could comment on that.

1 I guess I just think that -- you know, I
2 agree with you that we need much better outcome
3 information, but I took away a sense that your -- you
4 know, you may have been questioning that there was
5 adverse outcomes.

6 DR. ROSS: No. Sir, if that was the
7 impression I gave, I apologize. I think -- first off,
8 with regard to the paper by Feikin, I think my point
9 is not to say that that is an ~~infectious~~ study. One of my
10 former attendings is ~~on that~~ paper, so I better not
11 say that.

12 It is simply to say that I think we need
13 to be careful about drawing conclusions. You're
14 absolutely correct that the original studies on
15 mortality in pneumonia showed that the difference
16 really occurs later, rather than earlier. My point is
17 not to say that there's not an effect shown, because
18 there is. I think one thing, for example, from the
19 paper by Turett that appeared in CID, given the number
20 of HIV positive patients in that study -- and I don't
21 remember that study that well, but the -- one thing
22 you might be able to speculate about is, is that a
23 population that's at particular risk for mortality.
24 So the intent is not to say that these studies don't
25 tell us something useful. I think they definitely do.

1 The ques -- the idea is to be just as precise as
2 possible in the conclusions about benefit and impact
3 that we draw.

4 DR. BELL: If I could -- just one follow-
5 up; that I think one piece of information that I find
6 a little troubling is that, as was briefly mentioned
7 I guess by Dr. Seidlin in the company's presentation;
8 it's not only that the Erythromycin resistant rates
9 for pneumococci have been -- well they essentially
10 doubled from '95 to '99, from 10 percent to 20
11 percent, but the median MICs of the most common form
12 here, the M phenotype have increased from four to
13 eight; which means that a large percentage of these
14 isolates are in the range where at least anecdotal
15 treatment failures for pneumonia have been reported
16 with macrolide, so although this is anecdotal, you
17 know, I think it makes us a little nervous.

18 DR. ROSS: Well, I agree with you. I
19 think that, you know, as I said this is multi-drug
20 resistance in streptococcus pneumonia. Streptococcus
21 pneumoniae is a real public health concern. The point
22 as cited in the data from Pallares was not to say well
23 they didn't find anything, we can all go home because
24 that clearly is not the case.

25 I think one of the issues that we would

1 like to say before the Committee is exactly what is
2 the impact of this.

3 DR. RELLER: Dr. Murray.

4 DR. MURRAY: I had a question that maybe
5 our GI Hepatology colleagues can help clarify a little
6 bit.

7 Well, I guess in the case with the
8 hepatitis, I have this concern that with elevated
9 eosinophils, and LFTs or at least one of the
10 parameters that before therapy was given, that I have
11 a little trouble making cause and effect with the
12 drug. But even if we did -- so this is an
13 idiosyncratic sort of reaction that might be seen? I
14 mean, this not a dose related; this is --

15 DR. GOODMAN: That's right.

16 DR. MURRAY: Okay. And do you have any
17 sense of how that would compare with other sorts of
18 rates of idiosyncratic reactions either to liver for
19 drugs that are out there, or for anaphylaxis, or some
20 other sort of idiosyncratic reactions that you can't
21 really predict on a dose related basis? I mean, you
22 gave the figures, or somebody did, for nitrofurantoin,
23 but what about -- are there any data for some other
24 drugs?

25 DR. GOODMAN: That's the only one that I'm

1 aware of that has an estimate. Perhaps Dr. Lee knows
2 of some others.

3 DR. LEE: Yeah. I mean, I think most drug
4 reactions that are idiosyncratic range from anywhere
5 from one in a thousand for isoniazid, to one in ten
6 thousand for other drugs, to one in fifty thousand for
7 terbinafin, so it's in this range. So if you see a
8 signal in whatever it is, 3200 cases, that's
9 remarkable. And by signal, I mean a case as was
10 described that would satisfy Hy's law that there was
11 an increase in bilirubin and transaminase above the
12 limits that they said.

13 DR. MURRAY: Are you concerned with the
14 fact that the LFT, one of the LFTs and the eosinophils
15 were elevated before the patient ever got the drug; if
16 indeed the baseline drug levels were drawn.

17 DR. LEE: I'm not really concerned about
18 that. I mean, it's notable but the numbers were quite
19 small. The eosinophilia was trivial I think, compared
20 to what happened later.

21 What I think is of concern here, perhaps,
22 is that these -- this occurred late in this one case;
23 and yet it doesn't make it unlikely. It still would
24 be in the realm of drug toxicity, and I think the
25 biopsy was very compelling. The question I had was

1. what were the -- how many late ALTs does the company
2. have, or was in that data? I know there was a --
3. there were values on Days 17 to 21 I guess, but I
4. think that's key when we look at all these values is
5. this case unfolded after Day 21.

6. DR. SEIDLIN: There were two levels that
7. were drawn after the first acute episode where the
8. levels had gone back to 53, and they were at 53 twice
9. several months after the first episode. And then
10. there was a period of time where no levels were drawn
11. before the next routine draw when they were elevated.

12. If I may, Dr. Willis Maddrey is here and
13. he's reviewed the case with us; and I'd appreciate it
14. if we could have the opportunity to invite him to the
15. microphone as well, as he's quite experienced in drug-
16. induced liver injury, and I could ask him to comment
17. on that. Would that be acceptable?

18. DR. LEE: Yeah. My question really was in
19. the overall studies, how often did you have late
20. values, how often were you monitoring after 21 days?

21. DR. SEIDLIN: We only did that if there
22. had been an elevation on therapy. We did not
23. routinely monitor them afterwards.

24. DR. LEE: Right.

25. DR. SEIDLIN: Could I invite Dr. Maddrey

1 to the microphone?

2 DR. RELLER: Please.

3 DR. MADDREY: This is a remarkably
4 complicated case. As I read this case, and I've had
5 the opportunity to read it on a number of occasions
6 and see the material, I would agree with the concerns
7 that Dr. Goodman expressed early. However, this
8 patient was on a corticosteroid according to the
9 protocol at the time the study started, which should
10 have kept eosinophil numbers down. And the fact that
11 the eosinophil numbers were up, and the amino
12 transferases were up, make it a complicated case to
13 start with.

14 I would agree that the changes shown on
15 that first box here are surely compatible with a drug-
16 induced liver injury of some type. However, it would
17 be, I think, most unusual for a person to come totally
18 to normal, as this patient apparently did; and then
19 some number of months later show up with another type
20 of liver disease. And Dr. Goodman clearly showed us;
21 I would think this patient does have an autoimmune
22 hepatitis on that second biopsy. The weight of the
23 evidence would suggest that. However, the thing that
24 probably bothers me most is this is the only case like
25 that in this series; and I would be very careful. I

1 realize that that's not -- if this were an absolute
2 straight forward case, as we've seen in a number of
3 other conditions, I would be of more concern than the
4 fact that this is a complicated case for the reasons
5 outlined.

6 Two different types of liver disease,
7 eight months off the drug before the second type
8 appeared; and of course, no one can say that it's not
9 a continuum, because you don't have all the numbers -
10 but I am concerned of defining this drug based on this
11 one case.

12 I would comment even further that we have
13 many drugs on the market that would show percentages
14 of elevated amino transferases in the one to two-fold
15 range that would be similar to what's seen here. I
16 would refer to isoniazid. I would refer to most of
17 the non-steroidal anti-inflammatory drugs.

18 DR. RELLER: Dr. Archer.

19 DR. ARCHER: I'm very confused about the
20 disparate QTC values from the sponsor in the FDA; and
21 I was wondering if I could get some clarification.

22 For instance, the interaction with both
23 cisapride and with ketoconazole, the numbers --
24 prolongation numbers were different in the two. In
25 one case, it actually went down with ketoconazole in

1 the sponsor's numbers, and it was an additive effect
2 in the FDA's analysis.

3 Second, I'd like the FDA to comment on
4 this first, if you don't mind; and then you can get
5 your shot. The second, in their table with subjects
6 with cardiovascular disease, the sponsor's QTC value
7 was 6.5, and then in the table that the FDA had of
8 elderly patients, their value -- this is with 1600
9 milligrams was 12, which is double. And I just don't
10 understand how the same numbers were looked at by two
11 different people, and come up with different values.
12 Could somebody help me out with this?

13 DR. RELLER: Dr. Ross.

14 DR. ROSS: I think part of the reason for
15 the discrepancy is the use of the different correction
16 formulae. The -- because that's in one case -- in
17 other words, the QT interval divided by the square
18 root of the RR interval, and then there's the use by
19 the applicant of the QTn formula, QT divided by -
20 correct me if I'm wrong here, Dr. Benedict, RR to the
21 power of 4.3. Is that -- so I think that --

22 DR. ARCHER: Well the ones that I just
23 quoted though, the elderly patients versus the
24 cardiovascular disease patients were both quoted as
25 QTC.

1 DR. ROSS: I think the other issue that
2 comes up is whether these numbers looked at -- whether
3 the analyses included all ketek-treated patients, or
4 only those from control trials; because on average,
5 the mean change for patients from uncontrolled trials
6 in our analysis was 0.5. It was a decrease of 0.5
7 milliseconds; see in that -- the difference between
8 that and the ketek-treated patients from the
9 controlled trials was statistically significant - so
10 for that reason we did not combine the two.

11 DR. ARCHER: Okay. Well -- and the other
12 one about the ketoconazole data. I mean, whatever
13 correction factor you used, their's went down, and
14 your's was additive. Their's is on -- let's see, in
15 there analysis I believe, page 57. And it -- they
16 used a different value, but their's went from 10 with
17 ketoconazole, three with Erythromycin alone, and then
18 down to nine, so it was actually lower than
19 ketoconazole. And your data there was a doubling.

20 DR. ROSS: In this instance I would -- the
21 heading for this column is QTn, so I would say it was
22 use of the different formula, because in our analysis
23 we used QTc.

24 DR. ARCHER: Oh, I understand that, but
25 you mean that change in correction actually change the

1 mag -- changed actually the direction?

2 DR., ROSS: Yes. I would --

3 DR. LAZZARA: Could I comment on that?

4 DR. ROSS: Yes, I'd like to --

5 DR. LAZZARA: About the heart rate
6 changes. The QT direction is heart rate dependent.
7 That's very treacherous and one of --

8 DR. SEIDLIN: Could you please speak into
9 the microphone.

10 DR. RELLER: Yes. Dr. Lazzara is
11 commenting, and we'd like to have all of our
12 cardiology consultants weigh in on this very important
13 issue.

14 DR. LAZZARA: My colleagues will have
15 something to say. The -- this -- the bigger
16 perspective from my stand point of having really
17 scrutinized this problem now for over 10 years since
18 we've been trying to extract this very low level
19 signal of a one to three milliseconds up to six
20 milliseconds, from a noise level that's in the order
21 of 20 to 60 milliseconds. The standard deviations are
22 many several times the signal we're extracting so --
23 and it's attributed to the biometricians, which I am
24 not, and the biostatisticians, that we have been able
25 to show significance of these small signals. We do in

1 the terfenadine case for example.

2 But, then when one compares the signals, it
3 becomes even more problematic, a 3.6 versus a 2.5. It
4 becomes virtually meaningless. So the question then
5 becomes heart rate correction among the many factors
6 that cause variability, the heart rate correction is
7 very key; particularly in a drug that changes heart
8 rate. And if a drug amplifies heart rate, it weighs
9 the data against itself in terms of the correction for
10 an amplified heart rate by the QT, by the Bazett as
11 one can see from the graph, will make the change in QT
12 longer. The Delta QT will be greater, so you might
13 end up with a four millisecond, or you'd end up with
14 a one millisecond if the heart rate changed. So my
15 question was going to be, before you brought up this
16 very astute observation, neither group gave us the
17 heart rate changes in any of this data that I could
18 find; so to what magnitude did the heart rates change
19 in the group as a whole, and in elderly versus the --
20 because it's a very key issue.

21 All of these differences could be
22 explained by heart range changes and a different
23 correction factor. That slope which is -- and that's
24 been recognized -- by the way, that did not just
25 appear in the company's data analysis, although their

1 group verifies. That's been recognized for a long
2 time. There's this inverse slope when one uses the
3 Bazett which makes for that false correction.
4 Everybody is recognizing what we -- as Dr. Ruskin
5 pointed out, we continue to use the Bazett by force of
6 habit. So do we have any idea what the heart rate
7 change --

8 DR. ROSS: Well let me separate the answer
9 into two parts. The answer is in terms of what the
10 heart rate change is for the Phase III Studies; no, I
11 think the applicant probably does have that.

12 I think that for that -- that's one reason
13 that we had concentrated so heavily on the Phase I
14 Studies, in which there was -- for example, the
15 crossover studies where there were conditions where
16 you could try to minimize, but certainly not eliminate
17 variability.

18 I don't know. Dr. Throckmorton, would you
19 like to say anything, or not?

20 DR. THROCKMORTON: Well this isn't
21 something that, you know, sort of just appeared with
22 this drug unfortunately, as Dr. Ruskin talked about
23 this morning. I'm Doug Throckmorton. I'm the Deputy
24 Division Director in the Cardiorenal Division, and
25 have the distinct fortune or misfortune as it is to

1 appears sometimes when these issues come up.

2 It is an uncertainty, and in a sense it's
3 -- we're concerned about it because the changes that
4 are reported are relatively small. Just to remind
5 you, we were able to see effects of -- for cisapride
6 versus placebo without correcting for heart rate at
7 all; those sorts of things. So small effects can be
8 detected here.

9 Having said that though, it does seem that
10 the correction factors are critical to some of the at
11 least directionality of the differences that have been
12 reported.

13 I don't think this is the place
14 necessarily to go into that, because the Center has no
15 stated policy. We recognize it as something that
16 needs to be addressed; but also just to remind you
17 that we haven't applied any of these more novel
18 corrections to any of the databases where we know
19 we've had problems before; so it's attractive to
20 believe that if we correct for this inverse slope that
21 you raised, that will make the analysis more
22 sensitive. We don't know that. That's -- we're
23 imposing our own biases on the data to do that.

24 DR. LAZZARA: Well, no; there's a bias
25 imposed both ways. The Bazett formula makes a

1 correction. It changes the value, and the question
2 basically is if a drug does not affect heart rate
3 intrinsically, then it becomes a non-issues.

4 DR. THROCKMORTON: My point is that we've
5 applied Bazetts to detect problems in the past. We
6 haven't applied any other analyses to do that, so a
7 conservative approach is to use the Bazetts,
8 recognizing that that may not be the best approach.
9 Now I'm certainly not going to try to defend it, but
10 Jeremy or Art Moss has done a lot off -- have done a
11 lot of work on that as well. They may want to
12 comment.

13 DR. LAZZARA: But let me contest that
14 though before they -- before I turn it over to them.
15 It's -- it makes for a false change, and a false
16 interpretation if the drug affects heart rate. Now if
17 you apply the Bazett to a drug that doesn't
18 intrinsically affect heart rate, then the changes
19 would not be significant; at least the drug-induced
20 changes. You might have changes that are not correct
21 in terms of random variation in the normal population,
22 but the drug-induced changes would not be significant.
23 But if the drug significantly increases heart rate on
24 a consistent basis, then it would introduce false
25 data, or false changes in the data.

1 DR. RELER: Dr. Lazzara, if I understand
2 correctly, you're saying that one issue in trying to
3 understand this is whether the drug under
4 consideration itself has an affect on heart rate.

5 MR. LAZZARA: On heart rate; yes.

6 DR. RELER: And is there any information
7 that ketolides or macrolides intrinsically affect the
8 heart rate itself?

9 MR. LAZZARA: Well that was my question.
10 They had said earlier that it did, but no values were
11 given; so I guess it's time for the -- someone --

12 DR. ZHENG: I think I have the information
13 about heart rate increase in the baseline study.
14 Actually, for the baseline study, eight baseline study
15 pooled together, and we can come off model how much
16 heart rate would increase with concentration, if we
17 use the Emax model. The maximum increase in terms of
18 heart rate is 14 beat per minute; but if we use the
19 Concentration 2, which is the mean maximum
20 concentration, after single dose, 800 milligram single
21 dose, the increase of heart rate was predicted to be
22 7 beats per minute.

23 DR. LAZZARA: Seven beats per minute, and
24 the Bazett formula would explain away the entire
25 differences, of one versus three milliseconds. She

1 uses the Bazett versus some other formula.

2 DR. RELLER: Dr. Ruskin.

3 DR. ZHENG: I think I have another comment
4 about that QT correction. I understand the QTn is
5 generated by the population data; and if you use that
6 corrected formula to apply each study, and if you look
7 at each study separately, you would say QTn in some of
8 the study is over-estimated. In some of the studies,
9 under-estimated; so if you use the population
10 correction parameter, it may not be appropriate for
11 each study.

12 Actually I did look at the Qtn versus RR
13 interval for each study. Actually, for the study 1045
14 is the ketoconazole study, Qtn is slight under-
15 estimate, QT prolongation. Same thing for the study
16 1040 -- I guess 1041 which is the cisapride study; Qtn
17 also at high heart rate, under-estimated QT interval.
18 I think it's all because the Qtn is generated based on
19 the population data, instead of each study. I mean,
20 placebo data and baseline data for each study, so if
21 you use the population, and then for some of the study
22 is over-estimated, for some of the studies under-
23 estimated. When you pool them together you'll see a
24 flat line.

25 DR. RELLER: Dr. Ruskin.

1 DR. RUSKIN: I guess the -- one has to
2 derive the -- this change for a normal population
3 really off drugs so that you know -- in the population
4 -- at baseline; that's the way that the thing would
5 make sense. And so the larger the population the
6 better you would be, but obviously it would be off --
7 also be better to have a QTn that would apply to the
8 elderly population, to the young population. But if
9 the drug consistently increases heart rate, the Bazett
10 will over-estimate consistently. That's an
11 observation that was made prior to our discussions
12 here, prior to this database; will consistently over-
13 estimate the change, the corrected QT.

14 DR. ZHENG: Yes. I don't think I'm
15 arguing if the Bazett equation is over-estimated when
16 heart rate is increased. I simply just tell the
17 Committee my observation about the QTn.

18 DR. RELLER: Dr. Soreth.

19 DR. SORETH: One point for Dr. Lazzara.
20 You made the comment, does it consistently increase
21 heart rate; and I point you to Study 1049 which was a
22 study of subjects who had underlying cardiovascular
23 disease but had no current infection. They were given
24 various doses of Telithromycin. Those patients did
25 not have an increase in heart rate, so I --

1 DR. SEIDLIN: those patients, if I might
2 interject, were patients with cardiovascular disease,
3 in contrast to the normal volunteer subjects. It was
4 really the normal volunteer subjects who had the
5 biggest increase in heart rate; and that's when Dr.
6 Benedict showed the data, he used the Qtn in that
7 population because they were the ones who had the
8 biggest heart rate change, in contrast to the Phase
9 III Studies where we did not see much of a heart rate
10 change; actually saw a slight decrease, and that's why
11 we chose to present it in that fashion, and that's how
12 the correction factor was used.

13 DR. RELLER: Doctor, when you say, Dr.
14 Seidlín, the normal volunteers, was that a placebo
15 controlled assessment?

16 DR. SEIDLIN: The Phase I Studies were a
17 variety of different studies. Some of them were
18 healthy volunteers. They were healthy young, healthy
19 elderly. There were a variety of others as well.

20 Perhaps I should Dr. Benedict to the
21 microphone so that he can give you the particulars.
22 The correction factor, however, was always developed
23 on the placebo period, so that was before drug
24 exposure; and that's where the correction factor was
25 generated.

1 Dr. Benedict, do you want to comment?

2 DR. BENEDICT: Yes. I think the question
3 from the panel member was outstanding. I think he
4 asked the right question, and I think the response
5 from Dr. Ralph Lazzara is equally important; and I
6 hope Dr. Jeremy Ruskin will make his comment.

7 I think in terms of ~~fair~~ and fair
8 disclosure, I think Dr. Ross ~~did~~ present what they
9 would rather obtain with the QTC value, which is -- I
10 think is perfectly legitimate. I think where we come
11 into conflict is do we consider the fact that
12 Telithromycin had an intrinsic effect on the heart
13 rate?

14 For example, let me give you the heart
15 rate team that Dr. Ralph Ross has about what happens
16 in the ketoconazole study, can have the heart rate
17 response in the ketoconazole study. You will see that
18 -- no, no, that's 1049. We'll come to that in a
19 minute. We'll answer Dr. Soreth's question in a
20 minute. Let me have the ketoconazole data.

21 You will see there when you administer
22 Telithromycin there's a heart rate increase of
23 approximately -- no, you have a curve that shows the
24 heart rate response; if you can pull it up I can give
25 the information to Dr. Ralph Lazzara, there's about an

1 increase in heart rate of what -- yes, please.

2 All right. If you can focus at the bottom
3 here; this is the heart rate response with
4 Telithromycin in this trial, so as Dr. Ralph Lazzara
5 very correctly pointed out, as you administer
6 testimony the heart rate tracks it very nicely,
7 showing that when you start off with low heart rates
8 in the subjects, they started off in about the 60's,
9 they go up to about 70, 72. And here now if you use
10 the QTC as the correction formula, then you are going
11 to sort of show higher and higher QTC changes.

12 To answer Dr. Jenny Zheng's question, we
13 took both approaches. In other words, we did look at
14 the population approach as well as an individual
15 approach. Since we had placebo data, in other words,
16 data from the drug-free period, we used the drug-free
17 period from this population to derive the exponential
18 for this particular population, and then we applied
19 that uniformly to the placebo, as well as to the
20 cisapride, and as well as to the -- sorry, to the
21 Telithromycin period, and as well as to the
22 ketoconazole period. And that's what the data that we
23 shared with you; so clearly as Dr. Throckmorton very
24 clearly pointed out, these are -- we are looking to
25 what is happening. Clearly, we have a drug that has

1 an affect on heart rate, so in terms of looking at
2 relative changes, we wanted to take to the affect of
3 the heart rate out, and that's what we presented to
4 you as a percentage.

5 DR. ARCHER: Can I just --

6 DR. RELLER: Dr. Archer.

7 DR. ARCHER: Well, ~~this~~ is actually a
8 fairly crucial point because the FDA makes the claim
9 or the bringing up the point that there's an
10 interaction between CYP3A4 inhibitors like
11 ketocazole and your product, which increases the QTC
12 in their analysis. In your analysis, there is no
13 interaction that increases the QTC, and it's all based
14 on how you derive the QTC or the QTn. What's right?

15 DR. BENEDICT: Okay. Maybe I can again,
16 if it is okay with you, point to one of the
17 presentation Dr. Ross made towards the end when he
18 summarized the changes.

19 Notice that when we looked at the changes
20 in the QT interval by different cuts, whether it is
21 greater than 60 millisecond or between 30 and 60
22 milliseconds, or 20 millisecond, et cetera; where he
23 commented upon the fact that when you look at the
24 comparators and Telithromycin, those individual who
25 had a change or a prolongation in QT interval between

1 30 and 60, they were comparable to each other. And
2 what he didn't point out is we did not have, or very,
3 very few cases who had a prolongation in QT interval
4 greater than 60 milliseconds.

5 Let me recall to the benefit of the panel the
6 excellent presentation by Dr. Ruskin, as well as the
7 excellent presentation by OPDRA where they said when
8 they looked at ~~the~~ cases of Torsades, on an average
9 there was 1/2 millisecond prolongation in the QT
10 interval. And of course from Dr. Ruskin's percentage
11 and we heard from his own database, you need to have
12 approximately about a 500 millisecond change, or
13 absolute increase in QT before it relates to it.

14 Of course, he gave the appropriate caveat
15 about the representativeness, the validity, et cetera,
16 et cetera; but the important thing I would want to
17 share with you is that we are still dealing with a
18 small number, as Dr. Ralph Lazzara mentioned, in a
19 fairly large variability on the population with
20 respect to QT measurement. For example, in one
21 particular individual, within 24 hours a QT can vary
22 by 40, 50 milliseconds.

23 DR. RELLER: Okay. Now a patient Dr.
24 Ruskin now speaks. Dr. Ruskin.

25 DR. RUSKIN: Thanks. I just -- a couple

1 of comments. I just want to offer a correction note
2 to something that Dr. Benedict just said.

3 You implied that there was a change of 500
4 milliseconds required for drug-induced torsades based
5 on the data that I showed; and that's not the case.
6 Those data just suggest that many, and perhaps most
7 cases of drug-induced torsades, when there's a QT or
8 QTc reported, have an absolute QT or corrected QT that
9 is 500 milliseconds or greater. It's not a 500
10 millisecond increase obviously, and I assume that you
11 didn't mean that.

12 With regard to the correction formula, I
13 agree with everything that's been said. The problem -
14 - the key issue I think has been framed by Dr. Archer,
15 and unfortunately I don't think there's an answer to
16 it. The question is which is correct, and I don't
17 think anybody knows.

18 I agree that the Bazett formula when
19 there's an increase in heart rate of 15 or 14 beats a
20 minute, is going to give you an over-correction. You
21 will get falsely prolonged QTc intervals; but the
22 point that Dr. Ross and Dr. Throckmorton made about
23 the fact that all the historical data is based on
24 Bazett is also important, because we have no
25 validation of these other formulae in other databases;

1 so we're to some extent flying blind, and that's part
2 of the conundrum.

3 The other question that I had for the
4 sponsor is that if you have a drug that is increasing
5 heart rate, but having not much affect on QTC, the
6 absolute QT should go down. And I haven't been able
7 to find any data on the raw QT interval; so is it
8 possible for you to show us some of that, that is
9 uncorrected by any formula, just the raw QTs, both
10 mean data, mean max, and outliers, just for QT
11 interval uncorrected.

12 DR. SEIDLIN: Okay. I'm going to ask Dr.
13 Benedict to do that.. There also is data in an
14 exercise induced model where one can compare QT
15 intervals at fixed heart rates, and we'd be happy to
16 show that data as well. Dr. Benedict.

17 DR. BENEDICT: Again, that's a good
18 question. I think we can look at what the straight QT
19 does, and at this point in time I don't know whether
20 we have a slide to show the QT data; if we have, can
21 we pull that up. But while the slide is coming up,
22 what I would like to respond is given the fact that
23 there is a heart rate response that affects the QT
24 interval, there have been different measures to try
25 and get away from the effect of QT interval. Would

1 Dr. Jeremy would like to see the data that we have in
2 this regard while we are trying to get the QT data?

3 DR. RELLER: Why don't you assess the --
4 Dr. Benedict find, if it's available, the uncorrected
5 QT data, and in the interest of time, I'd like to,
6 while that's being done, pursue two other questions
7 for our cardiology consultants to help the panel out.

8 DR. BENEDICT: The slide is up. Can I
9 please that with you now?

10 DR. RELLER: Go ahead.

11 DR. BENEDICT: If you don't mind. Yes,
12 please.

13 Okay. Here is the uncorrected change in
14 the QT interval, and here is the slope for this
15 equation, about one millisecond per microgram per
16 milliliter of the drug from all the eight Phase I
17 studies, ranging from concentration 80 to 3.2 grams.
18 And here is the variability in the data, and here is
19 the -- we have not drawn the line but there is the
20 slope.

21 DR. RUSKIN: Do you have a similar data
22 for heart rate that's graphically the same way?

23 DR. BENEDICT: I think we -- we will look
24 for it. I don't know whether we have one.

25 DR. RUSKIN: So this is independent of

1 heart rate then; right? This is the raw data.

2 DR. BENEDICT: Yes.

3 DR. RUSKIN: Which would suggest unless
4 I'm reading it wrong, that despite the fact that the
5 heart rate goes up, and I don't know if it's a
6 concentration-dependent affect, but if it is, it
7 suggests that the raw QT continues to go up. Does it?

8 DR. RELLER: You will need to get up and
9 use the microphone, please.

10 DR. RUSKIN: Okay. So you're saying that
11 there's a slightly -- the slope slightly lower than
12 one, so it's going down slightly with increase in
13 concentration. Okay. And do you have -- it looks to
14 me like no change basically.

15 DR. SHIN: Can I just clarify --

16 DR. RELLER: Yes, please. Please
17 introduce yourself at the microphone who you are, and
18 so that we have this for the record.

19 DR. SHIN: You know, that's --

20 DR. RELLER: Your name, please.

21 DR. SHIN: My name is Jun Shin. I'm from
22 DMPK Adventis. That slope -- that plot shows the raw
23 QT changes against the concentration. Actually if you
24 model that with the lead-in model, you will see an
25 active slope, but here we show the positive slope is

1 because we take the heart rate as a co-variant.
2 Therefore, the -- because this drug increase the heart
3 rate, and that slope shows the positive or very
4 minimal; just like the QTc, whereas the corrector --
5 heart rate correction, the QTn is about one
6 millisecond per microgram per mil. Here we show same
7 things, these two corresponding each other. Just don't
8 -- it is not -- there is a heart rate effect
9 confounding here, which is not -- cannot be projected
10 on these two dimension plots.

11 DR. RUSKIN: Can I get a clarification of
12 that? I mean what you're saying -- don't go away. I
13 mean, what you're saying is that this model already is
14 corrected for a heart rate because you did a
15 regression in which you included heart rate. Is that
16 what you're saying?

17 DR. SHIN: Yes. That heart rate as a co-
18 variant. Actually we --

19 DR. RUSKIN: So then there is -- it --
20 well there's a correction for heart rate with this
21 model.

22 DR. SHIN: We have our two dependent --
23 I'm sorry, two dependent variables here, heart rate
24 and QT. And we have the concentration of the
25 independent variable. We model this way; therefore we

1 have that slight positive slope.

2 If we model the data QT against
3 concentration strength without heart rate, then I
4 guarantee you there is negative slope.

5 DR. RUSKIN: Can you show us that?

6 DR. RELLER: Dr. Ruskin asked for the
7 uncorrected QT; and it's available we'd like to see
8 it. If it's not available we must move on for the
9 sake of time because what we have is not what was
10 requested.

11 Two questions for our cardiology
12 colleagues. The data, whatever its validity that the
13 FDA showed having to do with QTc intervals, and drug
14 interaction were consistent at least by my
15 understanding with the QTc affects demonstration in
16 vitro in the pre-clinical data. In contrast to
17 whatever the validity, the corrected QTc in this
18 various corrections proffered by Aventis.

19 Based on what we know from the science,
20 should the pre-clinical and in vitro match up with
21 clinical findings, or do we have a mismatch there?
22 How is the Committee to interpret in their
23 considerations the questions soon to be addressed;
24 these differences? That is, what role should the in
25 vitro and pre-clinical, and should it match up with

1 clinical data?

2 DR. THROCKMORTON: It should match up. I
3 think maybe the question you're asking is what should
4 we believe about the human data based on the pre-
5 clinical data and the totality of the human evidence.
6 I think the sponsor and the FDA are in concordance
7 that this product affects cardiac repolarization. If
8 the sponsor wants to disagree with that, but I
9 we've come to that agreement in the past; so based on
10 the pre-clinical evidence and based on the material in
11 the clinical data set, I believe the conclusion that
12 we've agreed to is that in fact it does affect cardiac
13 repolarization.

14 The issue is to what degree, and if you
15 want me to sort of philosophize for just a moment
16 about that. Within the Agency, the observation has
17 been that products that have a large affect on cardiac
18 repolarization; that is that at doses used in the
19 clinic or doses that people achieve regularly, there
20 are big affects on mean QT; 25 milliseconds, 30
21 milliseconds, that sort of thing.

22 Those drugs are also associated with
23 clinical significant arrhythmias that are readily
24 detectible; that is, we see them in sotalol, we see
25 them in a handful of non-cardiac drugs, but if you're

1 up there, you anticipate that you will have those
2 risks. That isn't where we are, at least as best as
3 we can tell. Instead we're in a much more difficult
4 place, the place where you found yourself with
5 moxifloxacin not so long ago; which is, as best as you
6 can tell, it affects cardiac repolarization, but to a
7 much smaller degree. And then the issue is can you
8 detect a measurable increase in risk of cardiac
9 arrhythmias in that -- for a drug in that setting.

10 And what we've been talking about are the
11 ways you try to tease that out. And Dr. Ruskin has
12 spoken eloquently about that this morning, and they're
13 the things that we've talked about. You characterize
14 the dose. You make sure that you understand the
15 potential metabolic interactions, really, really,
16 really well, particularly if you have a compound
17 that's a 3A4 inhibitor, because we know that those are
18 compounds that have gotten us into trouble in this
19 setting in the past. And then you look to the
20 clinical data set, where as is usual, we have not seen
21 any Torsades, but you look at the other things that
22 Dr. Ruskin went over. And then you determine how much
23 uncertainty you have left, and how much you care about
24 uncertainty based on what the other benefits of the
25 compound are, and whether those can be addressed pre-

1 decisional, or whether they need to be addressed, you
2 know, on a post-marketing setting in some fashion. I
3 believe that's where we are.

4 DR. RELLER: Dr. Ruskin earlier pointed
5 out, as others have, that whether or not it's overly
6 sensitive, the QTC by the set formulation is what has
7 been used before. Has that -- and maybe it's a good
8 thing to have an overly sensitive marker to pick up a
9 warning of potential rare events; but has -- have
10 there been drugs that have passed been evaluated with
11 the QTC set correction that have had -- that gave
12 false warnings looking at this from the other side;
13 false warnings that when drugs were put into practice
14 with millions and millions of doses, have never shown
15 a problem?

16 DR. MOSS: We can answer that question,
17 but there are other issues here too. With regard to
18 the question you asked, probably the one drug or group
19 of drugs, or the calcium channel blockers that have in
20 fact -- are associated with QT prolongation, but have
21 not been associated with any arrhythmia problems,
22 induced arrhythmia problems over a huge exposure, but
23 that's a very specific case. We're talking now about
24 diltiazam type of calcium channel blockers, and
25 berapamil, both of which can prolong the QT interval,

1 but are not associated with any arrhythmias.

2 Let me clarify one part of this correction
3 for the heart rate. Up until now, over most of the
4 ~~drugs~~ that have been reviewed where a drug has clearly
5 increased the heart rate, people have accepted the
6 correction of moving from Bazett to Fridericia, and
7 based in essence in the denominator, the RR interval
8 you take it at Bazett as a square root, and the
9 Fridericia is a cube root, so you ~~multiply~~ with a number
10 that is somewhat smaller in ~~time~~ -- when you divide the
11 numerator by the denominator.

12 What has gone on here is they've really
13 taken essentially the fourth route, pretty close to
14 it, so that it makes the data look better. The
15 problem is there's no verification in any other
16 population of using this approach, so that's
17 difficult.

18 The second thing is if the sponsors are
19 going to use this approach, it seems to me they're
20 obligated to provide detailed information on heart
21 rate, and that was not -- it's not been presented; and
22 that's a very important component. We'd like to know
23 what the degree of heart rate change is. If many of
24 the aspects are in terms of two or three beats per
25 minute, it doesn't really make any difference. And so

1 having detailed information in all of the subsets that
2 they've done would be an important way of interpreting
3 this.

4 The other thing that has not been fully
5 addressed is that there is a dose response affect in
6 the prolongation of the QT interval by both Bazett and
7 Fridericia. And I haven't seen any heart rate ~~data~~ to
8 say that the heart rate actually changes ~~with~~ the dose
9 of the medication that's given. ~~Maybe~~ it does, maybe
10 it doesn't; and it was the ~~explanation~~ that the visual
11 difficulty was ~~thought~~ to be maybe due to a vagal
12 effect, which is in fact something that you would
13 expect ~~to~~ slow the heart rate. So I think an
14 essential part of this is to see what the heart rate
15 changes are so that one can make some sense out of
16 this.

17 DR. RELER: Thank you, Dr. Moss. Dr.
18 Chesney.

19 DR. CHESNEY: This is very mundane
20 compared to all the elegant discussion that's just
21 been going on, but the patient or individuals who had
22 a QTC greater than 450 milliseconds were excluded from
23 these studies. If this were to be used in everyday
24 practice, would that mean that every patient had to
25 have an EKG before taking this drug? I guess what I'm

1 saying, we don't know what would happen if you had
2 a QTc greater than 450 milliseconds, and most of us
3 haven't a clue of what our QTc is.

4 DR. BENEDICT: After about two-thirds of
5 the way through the program, approximately about 600
6 or 700 subjects were included after removing that
7 exclusion, so we do have data in particular who have
8 acquired QT prolongation at baseline, and that's one
9 of the sets that I showed you in my main presentation.
10 They have about roughly 180 subjects who had QT
11 prolongation at baseline who were involved with the
12 study, so we do have some data on those subjects. And
13 they're the very subjects who showed about an 18
14 millisecond decrease in the QT interval while they
15 went on Telithromycin. Could be regression to the
16 mean, but nevertheless, they did not show an increase.

17 DR. RELLER: I don't see any other hands
18 raised.

19 DR. WALD: I have a question.

20 DR. RELLER: Dr. Wald.

21 DR. SEIDLIN: Are we going to leave the
22 QTC?

23 DR. RELLER: We are about to leave
24 everything for a break. Any other questions?

25 DR. WALD: I have one question.

1 DR. RELLER: First hear Dr. Wald and then

2 --

3 DR. WALD: I wanted to ask Alma Davidson,
4 when we look at these few bacteremic cases in the
5 pneumonia study, there are 38 bacteremic patients, but
6 we only account for 35 of them. What happened to the
7 other three; did they have resistant organisms, or
8 susceptible organisms?

9 DR. DAVIDSON: They had intermediate.

10 DR. WALKER: And how did they do?

11 DR. DAVIDSON: They were all --

12 DR. WALD: Were they cured?

13 DR. DAVIDSON: They were cured.

14 DR. WALD: Thank you.

15 DR. RELLER: Dr. Davis.

16 DR. DAVIS: I had a similar question.
17 When you look at Dr. Davidson's list 17 that are
18 penicillin resistant, but in the sponsor's book it's
19 16.

20 DR. DAVIDSON: We had a total of 17, and
21 that's with out analysis and the PPb population.
22 That's because one patient was -- we included one
23 patient who had no MIC, which was reported by the
24 central lab. It was not actually reported by the
25 central lab because the culture died, but this patient

1 had resistant organism by occocil and disk
2 methodology, and so we counted them as one.

3 DR. RELLER: We will now take a break and
4 convene promptly at 4:00, and we'll launch into the
5 questions for the Committee. Committee vote at 4:00.

6 (Whereupon, the meeting went off the
7 record at 3:44 p.m. and went back on the record at
8 4:01 p.m.)

9 DR. REBER: We must get to the questions.
10 There were ~~two~~ comments at the break not discussed,
11 that I want to have out in the open for everyone.
12 First, Dr. Lee had a question having to do with
13 hepatotoxicity that he wishes to ask. Dr. Lee.

14 DR. LEE: Well, I'm still concerned about
15 the likelihood that there's still a hepatotoxic
16 reaction here that is allergic. And indeed in the one
17 sort of famous now 53 year old man, the disease might
18 not have even been elucidated had he not developed
19 this diarrhea with the rest of his family; because in
20 fact, the significant abnormalities were occurring at
21 something like 17 days after initiation of the drug.
22 So I think it's really of concern; remember that he
23 had fever as well as eosinophilia, and this kind of
24 very late reaction.

25 This drug is going to be used and re-used

1 in these very short bursts, and with a short burst of
2 five days of drug, and then let's say getting toxicity
3 10, or 15, or 20, or 25 days later; this may present
4 a problem in terms of identification of cases. If it
5 is of an allergic nature, a la Halaphane for example,
6 the second exposure or the third exposure may be more
7 severe; and yet you may not know about it because your
8 first exposure has been -- has missed identification.

9 DR. BENTLER: Thank you, Dr. Lee. And Dr.
10 Benedict. From Adventis was going to have one point of
11 clarification; a verbal statement regarding what had
12 corrections applied, what did not. Okay. In the data
13 presented.

14 DR. BENEDICT: Yeah. The brief statement
15 I wanted to share with the Committee is that in the
16 Phase III Program we did not see a significant change
17 in heart rate; in fact a decline in heart rate as the
18 patients improved for about four beats per minutes.
19 So because of that, to place the QT data in
20 perspective, we presented the QTC information, but the
21 other correction formula was also given in your
22 briefing document.

23 In the Phase I data, we had an average of
24 about four to eight beat increase in heart rate
25 depending on the dose that was used, with the higher

1 doses producing the highest heart rates. Because of
2 that defect, we used the QTn formula to correct for
3 the heart rate defect in the study. But I would like
4 to remind the group again that in the Phase III
5 Program, expand the concentration up to 9.9 with an
6 increase of only 8.7 millisecond interval in the QT
7 interval.

8 DR. ~~FRIDERICIA~~: Thank you, Dr. Benedict. And
9 Dr. Ross, ~~DOES~~ like you to verify or confirm that your
10 analyses were done on the -- from data -- from the
11 clinical trials that were control trials only.

12 DR. ROSS: That is correct.

13 DR. RELLER: And Dr. Ruskin, that the --
14 which is the optimal formula to use has not been
15 independently verified or something along those lines;
16 a comment before we go to the questions.

17 DR. RUSKIN: I don't think I can shed much
18 more light on the issue of the formula than the
19 discussion has already done. I would agree that if
20 there is an affect on heart rate, Bazett will over-
21 correct and that clearly one would be better of with
22 Fridericia. It's a little difficult with this mixed
23 database where there are changes in some areas and not
24 in others to know exactly what to do; so just I think
25 in fairness to everybody, I would just like to in a

1 sentence or two give you my take on this because I
2 think we've talked around this issue a great deal, and
3 not perhaps given the Committee a whole lot of useful
4 guidance. And I still may not be able to do that, but
5 my take on this is that even if you take the worst
6 case scenario which is the Bazett, you're looking at
7 changes with the drug in the range of a little less
8 than 10 milliseconds probably, in a worst case
9 scenario, so I believe that the drug has an affect.
10 I believe there's a concentration dependent affect on
11 QTC, but that it is modest, and not terribly
12 dissimilar from what one sees with other drugs used
13 for these indications.

14 I can't distinguish very effectively
15 between this and Clarithromycin, although the data is
16 very limited. But my sense of this is that there's a
17 modest affect. It's real, but that it's not in a
18 range where one would expect to see a high incidence
19 of Torsades. That said, it is in a range where there
20 has to be at least the expectation that there is some
21 risk. I don't think one can put a number on that;
22 just as one couldn't for Erythromycin or
23 Clarithromycin. It isn't zero, and it clearly is not
24 in the range of drugs that we know cause Torsades
25 frequently. And I think I pretty much to leave it at

1 that.

2 I think the decision about what one does
3 is largely based on the potential benefits of the drug
4 in relation to some theoretical risk; and I underscore
5 theoretical.

6 DR. RELJEK: Now while we have a full
7 voting Committee, we must now get to the questions.
8 As the Committee has experienced before, one can
9 disagree, and there's been a lot of discussion. The
10 way they're framed is the way we will take them; so
11 the first question where there are not -- for the
12 record, we had an open public hearing scheduled.
13 There were no scheduled presenters at the open public
14 hearing. Unless we missed someone who should speak up
15 now, the open public hearing is closed.

16 In going to the question, both the FDA and
17 the sponsor Adventis presented data and its generally
18 accepted that this compound, Telithromycin, is
19 effective in the treatment of community-acquired
20 pneumonia, acute exacerbations of chronic bronchitis,
21 and acute sinusitis. So specifically the question
22 before us, and the pharyngitis/tonsillitis has been
23 taken off of the table because of not meeting the
24 efficacy criteria that were addressed earlier.

25 So the question to the Committee, and we

1 want a yes or no, coupled with your name and a vote. And
2 we will start at the right with Dr. Cross. And the
3 issue then is not efficacy, but ~~is~~ this drug safe
4 enough to be approved for use for these indications
5 with the data that we have now.

6 DR. MURPHY: And Barth.

7 DR. RELLER: Yes.

8 DR. MURPHY: When -- again under -- in
9 your discussion, because we would like not only your
10 name and a yes or no, but we also would like attention
11 to the A & B as to whether you have an opinion ~~use~~ to
12 whether they have provided sufficient data ~~for~~ warrant
13 a claim, because we think it affects ~~the~~ claim here.

14 In other words, are -- if you say no, are
15 you saying no because you don't think it should be --
16 that it's proven efficacy for resistant penicillin or
17 Erythromycin too. If you could do that, or do you
18 want to break it out? We thought it was important to
19 roll this whole discussion into one, but it -- again
20 it's up to the Committee if you think it will be
21 easier to break it out.

22 DR. RELLER: Well, we've gotten into
23 difficulty in the past, in you know, doing it a whole,
24 and then breaking it out, and then breaking it out,
25 and getting bogged down and then not being able to

1 come logically back to the whole. And what we were --
2 what I was planning to do was to then go back and
3 address these points, and then we would vote again --

4 DR. MURPHY: Okay.

5 DR. RELNER: -- swiftly around the table.

6 DR. MURPHY: Okay.

7 DR. RELLER: But we could reverse that.

8 Insofar, what would give the clearest message for the
9 FDA. That's what we want to do in our advisory
10 capacity.

11 DR. MURPHY: I think if you could address
12 the resistance issue first; okay? That would be
13 helpful.

14 DR. RELLER: All right.

15 DR. MURPHY: As it applies to these
16 indications.

17 DR. RELLER: Okay. That's what we shall
18 do. So we want -- I will say each person's name and
19 we'll weigh in, so specifically A.

20 DR. BELL: Can I ask a question?

21 DR. RELLER: Yes. Dr. Bell.

22 DR. BELL: This is posed here strictly as
23 an efficacy issue, and I'm just, you know, a guess
24 here; but I wonder is part -- is there some
25 implication in here to what extent is there a public

1 health need for this drug to treat resistant
2 infections that might be weighed against its potential
3 toxicity? Is that something the FDA wants to have
4 discussion on or consider? Because I -- there's some
5 thoughts on that.

6 DR. MURPHY: Yes. Actually, we didn't
7 want to ask you the classic question; is it safe, is
8 it efficacious, is it safe, and have you addressed
9 them as part. We felt that this has to be a balance
10 of what is the potential benefit, particularly is
11 there a place for the use of this product to treat
12 resistant organisms at all, you know. And for poor
13 resistance, and how do we weigh that against the
14 safety issues which are potentials that we need to
15 deal with.

16 DR. RELLER: What I would like to do now
17 is to go and we'll ask A; and if a Committee member
18 votes no, then to say right then and there what
19 additional studies would be necessary from that
20 member's view point. We'll do A, which has to do with
21 penicillin resistance streptococcus pneumonia, and
22 then we'll do B, have to do with Erythromycin
23 resistance. And then we'll come back to question
24 number one, and then deal with C, and number two as --
25 depending on the outcome of the assessments.

1 Now these discussions -- there's been a
2 lot of discussion. What we will have is we will have
3 a vote, what your opinion is in answer to A, and then
4 what additional studies you would recommend if your
5 answer is no. And you can discuss or make -- you can
6 elaborate on your answer as you see fit.

7 What we really want to do is to give the
8 best sense of each Committee Member, and then in the
9 aggregate where the Committee weighs in to the FDA for
10 their consideration, given that the regulatory
11 authority rests appropriately with the FDA, and we
12 give our views for them to take under consideration in
13 their ultimate decision. Dr. Cross.

14 DR. CROSS: Okay. In terms of whether or
15 not there's sufficient data to support the resistance
16 issue, especially in pneumonia, looking at the data on
17 page 30 and 31, there just isn't enough patient
18 information. We have for example, an MM 61. In the
19 case of resistance on MM 60, we're talking about 19
20 patients with penicillin resistance, and only 25 with
21 Erythromycin resistance. I just don't think that's
22 enough data to warrant that indication.

23 DR. RELLER: And what additional studies
24 would you want?

25 DR. CROSS: I think we need more patients.

1 DR. RELLER: Okay. Thank you. Dr. Soper.

2 DR. SOPER: This is to A?

3 DR. RELLER: Yes; A only.

4 DR. SOPER: Yes.

5 DR. CHRISTIE: I'd have to say yes,
6 because in previous times when we have discussed this
7 issue we have taken less numbers for other
8 indications.

9 DR. RELLER: Dr. Wald.

10 DR. WALD: I don't think ~~what~~ we have
11 sufficient data. For the pneumon~~ia~~ patients we're
12 talking about 17 patients ~~who~~ we think had resistant
13 disease, 14 out of 17 cured for sinusitis, 11 out of
14 13. I would not feel good endorsing this drug for
15 resistant organisms on the basis of such scant data.

16 DR. RELLER: Thank you. Dr. Archer.

17 DR. ARCHER: I would also say no. I was
18 interested in the FDA's comment that there was a
19 discordance even though the numbers were the same
20 between Erythromycin resistance, penicillin
21 resistance, which means that some of the patients with
22 penicillin resistance were erm-sensitive, and yet
23 failed therapy with this drug; which to me just means
24 the numbers aren't big enough. I think if there is
25 truly efficacious benefit, or if there is not a

1 benefit, they just ~~would~~ need more subjects.

2 DR. RELLER: Dr. Chesney.

3 DR. CHESNEY: I also would say not enough
4 data, and I'm particularly concerned about the
5 bacteremic pneumonias which is the worst case
6 scenario. And I would also support more studies with
7 clearly resistant organisms. I guess that was all.

8 DR. RELLER: Dr. Murray.

9 DR. MURRAY: I think I ~~would~~ vote yes.
10 There were seven -- 15 penicillin resistant ones in
11 the levo as I recall, with 100 percent cure rate, 17
12 in disk with 82 percent cure rate. They had 38 total
13 bacteremic cases which is a lot with an 89 percent
14 cure rate. I think the failures were the same in the
15 two groups of the two bacteremic groups, and of the
16 two of six failures, one of those was actually a cure
17 of the infection to me, with a re-infection. You
18 know, bacteremia clears and five days after you stop
19 therapy, you have staph aureus in the urine and
20 require other antibiotics, so I think that's in the
21 borderline. And six bacteremic penicillin resistant
22 pneumos is not a lot, but 17 is a fair amount. So
23 it's a -- the vote would be yes; although obviously
24 we'd like to see more data, but it's -- I vote yes.

25 DR. RELLER: I vote no, for two reasons;

1 insufficient numbers of patients, especially those
2 with bacteremia, and also the markedly different in
3 those small number of patients, especially with
4 bacteremic patients, efficacy contrasted with the drug
5 currently approved for resistant pneumococci.

6 DR. EBERT: Steve Ebert.

7 DR. RELLER: Dr. Ebert. Yes.

8 DR. EBERT: I vote no, specifically for
9 the reduced or low numbers I should say of patients in
10 the bacteremic category. And ~~also~~, I would like to
11 see, although I'm not sure that there is an
12 association between the degree of penicillin
13 resistance and macrolide resistance, but further
14 characterization of the upper limits with regards to
15 penicillin resistance.

16 DR. RELLER: Dr. Leggett.

17 DR. LEGGETT: Jim Leggett. I vote no, for
18 all the reasons of the no voters so far. I'd like to
19 reiterate not enough patients, and I also am worried
20 about the fact that penicillin resistant failed even
21 in the absence of Erythromycin resistance, but for yet
22 another reason in addition. If half of the penicillin
23 resistant drugs are going to be Erythromycin resistant
24 drugs, and we do -- the numbers look even less good
25 with Erythromycin, we may see failures because there's

1 also concomitant Erythromycin failure that then leads
2 to failure of the combination drug resistance.

3 DR. RELLER: Dr. Leggett, to even it out
4 we're going to start with you on Question B. Could
5 you go ahead and comment on, is there sufficient
6 evidence in your view that an infection due to
7 Erythromycin resistant streptapneunae has a negative
8 impact on clinical outcome compared with susceptible
9 strains? And if the answer is yes, has the applicant
10 provided sufficient data to warrant a claim for the
11 treatment of community-acquired pneumonia, owing to
12 Erythromycin resistant streptococcus pneumoniae.

13 DR. ARCHER: I don't understand that.

14 DR. LEGGETT: Yeah, I have a question
15 because --

16 DR. ARCHER: That needs to be redefined.
17 That's not a good question.

18 DR. LEGGETT: Gordon said this last
19 meeting too.

20 DR. ARCHER: I mean, what do you mean?

21 DR. MURPHY: I think we actually had this
22 earlier discussion somewhat about do we -- are we --
23 do we clearly understand what the impact of this
24 means, and we know it's not good, but --

25 DR. ARCHER: Do you mean if somebody is

1 infected with a macrolide resistant organism, and gets
2 a macrolide they're not going to do well, and is that
3 important? Is that --

4 DR. MURPHY: Well, I think the -- first of
5 all, they want me to say this would be the first time
6 we're giving this indication; so that's number one.
7 And number two, then do we understand -- do we feel
8 confident in what we think the clinical outcomes of
9 this mean. Having these resistant organisms and the -
10 - not having clearly indicated drugs for them. Do we
11 think that that is an issue.

12 DR. RELLER: Actually, maybe I think
13 differently, but it's -- one could change the wording
14 around a little bit. But to me, this question is
15 simply the following; should the drug if it were
16 approved, have a specific indication for the treatment
17 of Erythromycin resistant streptococcus pneumoniae.
18 And then I think we should have a comment from each
19 Committee Member that's yes or no; then a comment that
20 we feel that there are data to suggest that if one has
21 Erythromycin resistance among *S. pneumoniae* that that
22 makes a difference clinically owing to the limitations,
23 or owing to anything; limitations of dosing, because
24 there's been discussion earlier that up to a certain
25 limit of penicillin resistance, beta lactams can be

1 used and are efficacious.

2 Are we dealing with the same thing, that
3 if you just give enough of the macrolide, or are we
4 saying that if you have one that by NCCLS criteria is
5 resistant, we would expect a lower success rate. And
6 then a corollary of that is, clearly there are
7 differences in this compound from Erythromycin itself,
8 but there has been a lot of discussion having to do
9 with the kicking in of the different mechanisms of
10 resistance to Erythromycin, and an assessment from the
11 Committee Members as to whether those trends or changes
12 in your view would affect the assessment or the
13 activity of Telithromycin.

14 We've heard data from the sponsor that it
15 doesn't, and we've seen MICs that suggest that maybe
16 it's a warning that -- so -- but that's not -- it's
17 not for me to say until it's my vote. It's for you to
18 comment on those two issues; both of which are
19 specifically delineated, comment on the potential for
20 its comment on, and also comment on do you think that
21 Erythromycin resistant organisms do less well with
22 Erythromycin than do susceptible organisms in patients
23 with community-acquired pneumonia.

24 I think those things are embedded in the
25 concept of whether you think the data is sufficient to

1 get a specific indication with this compound, which is
2 the specific question delineated in B.

3 DR. MURPHY: Thank you, Barth. You can
4 see why -- we re-wrote this question numerous times
5 and it just got longer.

6 DR. RELLER: So should it be approved for
7 Erythromycin resistant strains; yes or no? And then
8 comment on the implications of Erythromycin resistance
9 in community-acquired pneumonia, and cross-resistance
10 with the ketolide. Jim.

11 DR. LEGGETT: Jim Leggett. Several
12 comments; first, I do not think it should receive a
13 specific indication for Erythromycin pneumococcus, but
14 I do think we could -- I would favor wording it
15 somewhat like we did with the amoxicillin in sort of
16 high risk patients, or if it comes across not to worry
17 about it. And for the -- my reasons are this.

18 We have data on otitis media that
19 Erythromycin resistant pneumococci can do harm. I
20 don't know that we have data about pneumonia per se.
21 Given the fact with otitis media, and the fact that if
22 you don't treat the pneumococcus, 90 percent of the
23 time it's not going to go away. I would by
24 extrapolation, in the absence of data, say the same
25 thing for the lung. That's why I think that the drug

1 will probably be useful; that's on the one side.

2 On the other side there's no -- not enough
3 numbers. We only got five out of nine responses in --
4 where we had bacteriologic for blood from ERSP and
5 DRSP together. Data from acute sinusitis for me is
6 much more suspect, because of the 30 to 40, depending
7 on your study, percent better viruses. And I don't
8 know if in the sinusitis cases, that I believe those
9 numbers, even though they're 18 of 21, and 9 of 11. I
10 don't know that we can extrapolate from more serious
11 pneumonias to an acute sinusitis situation; so I put
12 less faith in that acute sinusitis data than I do the
13 pneumonia data.

14 And then finally, to not get long-winded;
15 I don't think we can increase the macrolides for
16 telithro like we've been able to increase amoxicillin.
17 So whereas, I think of MIC creep for the penicillins
18 and better -- me believing that they're better than
19 the cephalosporins in that regard. We can't push our
20 macrolides. We're at the top; sort of like we are
21 with the quinolones, or at least for the most part.

22 I don't know about increasing
23 Telithromycin MICs going along with the Erythromycin,
24 and in the absence of data, I'd hate to box you in by
25 giving an indication that you didn't have to back away

1 from, given the pressure to bring drugs to the market,
2 and then the turn around, and then limit and take them
3 off the market. I think you can do that one too many
4 times in the new administration era; so long-winded
5 answer. I'll leave it at that.

6 DR. RELLER: Dr. Eberle. Dr. Leggett,
7 thank you for your comments on the differences between
8 sinusitis and pneumonia. This question we're
9 specifically voting around the table about the
10 indication for community-acquired pneumonia.

11 DR. LEGGETT: The first part, B didn't say
12 that. So then I'll just reiterate, I think that we
13 should -- you could phrase it in the high risk groups,
14 but I would not give a specific indication for
15 Erythromycin resistant pneumococcus for community-
16 acquired pneumonia. And in terms of fixing the
17 situation, might consider using a group of patients
18 who would be much more likely to have that, however
19 you find that population; whether it's oral treatment
20 of people who are hospitalized or some such thing to
21 get -- bring up the numbers of pneumococcus and
22 Erythromycin.

23 DR. RELLER: Thanks, Jim. Dr. Ebert.

24 DR. EBERT: I'm going to vote yes, but
25 it's going to be a tentative yes. I thank you for

1 your clarification, Dr. Reller, that this is
2 specifically dealing with pneumococcal pneumonia. As
3 was mentioned earlier today, I think there are now an
4 increasing number of case reports of failures for
5 pneumococcal pneumonias with macrolides. Certainly
6 there has not been a controlled clinical study that
7 has looked at this, but I do feel it's an increasing
8 problem.

9 With regards to the cross-resistance
10 between ketolides and macrolides with pneumococci,
11 again my impression is that's primarily mediating
12 through the *erm* B mechanism, at least at this time,
13 which seems to be a relatively uncommon mechanism of
14 resistance. However, I am concerned that in the
15 future that may become a problem.

16 DR. RELLER: I just want to make sure we
17 have this straight. Dr. Ebert, you would recommend
18 that this compound get a specific indication for
19 Erythromycin resistant strains and streptococcus
20 pneumoniae.

21 DR. EBERT: Well again, I think the
22 caveat, much like with penicillin resistant
23 pneumococci would be again in the bacteremic
24 population. I feel more strongly with the non-
25 bacteremic population than I would with the bacteremic

1 pneumonia.

2 DR. RELLER: I vote no for specific
3 indication for Erythromycin resistant strains and
4 community-acquired pneumonia because the numbers are
5 small. The success rate in that very small number of
6 patients with bacteremic pneumococcal pneumonia was
7 marginal. The effectiveness, and I think the data --
8 it may work, but the data are simply not sufficient
9 now to warrant that indication.

10 I agree that resistant strains, if they
11 are truly the pathogens, are unlikely to respond. And
12 although impressive data were presented about the
13 differences between Telithromycin and Erythromycin
14 itself, for those strains possessing one or more
15 mechanisms of resistance to Erythromycin, I'm
16 concerned about the creep. And I'd like to see far
17 more data in cross resistance and follow-up before
18 being comfortable with any specific indication for the
19 treatment of Erythromycin resistant strains;
20 especially given most therapy in this arena is
21 empirical. Dr. Murray.

22 DR. MURRAY: I think to be consistent I'll
23 vote a weak yes. I think it should be restricted to
24 mild to moderate disease for community-acquired
25 pneumonia. I think caution should be taken, whatever

1 that means, because I'm not completely comfortable
2 with Erythromycin mechanisms not having an effect.
3 There is an increase in MICs with the *mef*. It's
4 clear, and I think there is the potential for
5 emergence of resistance with the *erm*. But the same is
6 -- has been true for other drugs in other classes, for
7 other indications. I think it's almost certainly
8 should be better than clari for Erythromycin resistant
9 organisms, but probably is not as good as moxifloxacin
10 or a drug that -- or levofloxacin, I'm sorry, that had
11 a 100 percent cure rate with its 15 penicillin
12 resistant pneumococci. So I think it's probably
13 better than what else may be out there, but not as --
14 better than some things, but not as good as all.

15 DR. RELLER: Dr. Chesney.

16 DR. CHESNEY: I -- excuse me. I also vote
17 no, partially to be consistent; but many penicillin
18 resistant strains are going to be Erythromycin
19 resistant. And since I voted no for that, but I'm
20 also very concerned that this is going to be empiric
21 therapy. And I'm just not won over by the numbers of
22 bacteremic cases that are reported, and they're not
23 the 100 percent response that we did see with
24 Levoquine. And I'm also very concerned about the
25 emergence of resistance on therapy with -- because of

1 the creep which is very impressive. And I would agree
2 that we need more data on cross-resistance, and we
3 just need more numbers.

4 DR. ARCHER: I also vote no with a heavy
5 heart. Looking at the MICs of this drug, I would --
6 I'd hoped the clinical data would be better, because
7 I really think we need another alternative to the
8 quinolones, to prevent quinolone resistance emerging.
9 I think we need this drug; but I think we need more
10 data. The data are just not good enough clinically.

11 I'd also like to say, to weigh in a little
12 bit on the Erythromycin as an indication; the
13 macrolides are one of the mainstays of therapy of
14 community-acquired pneumonia, so therefore it seems to
15 me reasonable that you should consider the major
16 resistance class to those antibiotics. In fact, I
17 think macrolide resistance is more important in many
18 ways than penicillin resistance, because I think the
19 data shows in failures on macrolide therapy that the
20 MICs to macrolides correlate better with treatment
21 failures than do penicillin susceptibility data. And
22 so I think it's really important to have an indication
23 for macrolide resistance.

24 At our hospital, 50 percent of our -- all
25 of our pneumococci are macrolide resistant. And it's

1 been a huge issue in devising treatment protocols for
2 community-acquired pneumonia about what to use; and we
3 have eliminated the macrolides as a class because of
4 that, rightly or wrongly. And so I think we need more
5 options. I'm just disappointed that this -- the
6 clinical data aren't there yet for this drug.

7 DR. RELLER: Dr. Wald.

8 DR. WALD: I would also vote no for the
9 reasons that were stated; that is that there's simply
10 insufficient data. I would say that as an empiric
11 drug for community-acquired pneumonia, I will
12 ultimately vote yes, but we're asking the specific
13 question for either penicillin resistance or
14 Erythromycin resistance. And if we knew those to be
15 the case, or if the patient was particularly high
16 risk, I wouldn't endorse this on the basis of these
17 data.

18 I must say it troubles me less that the
19 bacteremics break through, because if you suspect a
20 patient has bacteremia you hospitalize them; so this
21 is not for the patient that we look at and think is
22 terribly ill. This is for the patient who has mild to
23 moderate disease.

24 DR. RELLER: Dr. Christie.

25 DR. CHRISTIE: Thanks. I'd have to say --

1 I'd have to cross the bar and say no. I don't think
2 we have enough information here, and I believe we
3 should gather more data.

4 DR. RELLER: Dr. Soper.

5 DR. SOPER: To remain consistent, I'll say
6 yes. And I agree that we need more information, but
7 looking at the MICs I'm reassured. I think that there
8 is concern about potential cross-resistance because of
9 the mechanisms involved. I doubt it will be 100
10 percent penetrable, and I think there is a need.

11 DR. RELLER: Dr. Cross.

12 DR. CROSS: Yes. Again, I think that
13 while the data on the pneumonia in the absence of the
14 bacteremia is encouraging, I think that again we still
15 need more data; especially in view of the small
16 numbers with the pneumococcal bacteremia. Although I
17 do agree with Dr. Wald that if a patient were truly
18 toxic from the pneumonia, and we suspect that they had
19 bacteremia, we would hospitalize them and wouldn't use
20 this drug.

21 In terms of the issue of creep, I would
22 feel -- I don't recall hearing what the maximum serum
23 level of the drug was. In the presentation, it
24 appears that the level of the antibiotic was obtained
25 to correlate with the EKG level, and I'd like to have

1 a better sense of what the maximum achievable
2 concentration in the blood is, in order to interpret
3 the clinical pharmacology with the in vitro
4 microbiology.

5 DR. RELLER: Dr. Cross. Did I understand
6 your vote ~~made~~

7 DR. CROSS: No. Exactly.

8 DR. RELLER: So although not unanimous,
9 the Committee weighed in seven to three, ~~not~~
10 necessarily the same seven each time, ~~against~~ a
11 specific indication for either resistant -- penicillin
12 resistant or Erythromycin resistant pneumococci as a
13 specific indication were this drug to be approved.

14 So now we'll come back, Dr. Murphy, to
15 question one. And then we'll segway to C, and number
16 two. So today, with the data available and the
17 controversy surrounding electrophysiology and hepatic
18 function, given the risks as best as we can understand
19 them as of the moment; does the efficacy of
20 Telithromycin in respiratory infection support its use
21 all things considered, taking into consideration
22 comments made in the public health interest, et
23 cetera, support its use for community-acquired
24 pneumonia, acute exacerbations of chronic bronchitis,
25 and acute sinusitis. And the reason we're bundling

1 these is that the issue here is not efficacy, but
2 rather does the safety profile the number of patients
3 potentially treated empirically, drug interactions,
4 age spectrum, etcetera. On balance, public health,
5 needs for therapy given that there would not; if the
6 Committee's advice were followed, specific indications
7 for resistant organisms.

8 On balance, did the merits for efficacy
9 outweigh the potential risk for toxicity? Is that a
10 fair assessment, Dr. Murphy?

11 DR. MURPHY: Correct. Is the benefit of
12 having this product for these therapies, because we're
13 not arguing -- we're mostly in agreement with the
14 efficacy statements made by the sponsor, are the
15 benefits -- do they outweigh the risks as we know them
16 at this point; again knowing we can't as clearly
17 defined have a precise assessment. We do know certain
18 things, and we know certain things about history; so
19 we're asking you your level of certitude of the
20 benefit versus the level -- which we're fairly certain
21 that it has efficacy. Does it outweigh the risks as
22 defined at this point?

23 DR. RELLER: Dr. Wald has a comment.

24 DR. WALD: I just wonder if we do a
25 disservice to bundle them, because the -- I would see

1 the question -- I would see the answer as being
2 different for different of these indications, because
3 if --

4 DR. MURPHY: Yes, I meant for different
5 indications. Do them -- do each indication
6 separately.

7 DR. RELLER: Okay. Fine.

8 DR. WALD: I'm sorry. I thought you meant
9 --

10 DR. MURPHY: We weren't going to ask the
11 efficacy and safety separately. We're --

12 DR. RELLER: Right. Right.

13 DR. MURPHY: Okay.

14 DR. RELLER: Okay. Well we can do them --
15 I mean, whatever is going to give the cleanest,
16 clearest message to the FDA.

17 DR. MURPHY: We do indication by
18 indication.

19 DR. RELLER: Indication by indication.
20 Now one of the -- Dr. Soreth I believe succinctly put
21 this as approve with further safety studies up front,
22 and with further post marketing surveillance for
23 adverse reactions afterwards.

24 Ultimately, in Question C and Two, we're
25 going to get to these issues. Would it be an

1 efficient way to categorize these right up front?

2 DR. MURPHY: Yes.

3 DR. RELLER: With those options.

4 DR. MURPHY: Yes.

5 DR. RELLER: And then the nature of -- I
6 mean if there were restrictions on the front end, rear
7 end, the nature of those could be discussed. ~~Not~~
8 would that be an effective way to deal with this?

9 DR. MURPHY: Please.

10 DR. RELLER: Okay. So let's take them one
11 by one. Community-acquired pneumonia, approval,
12 approval with -- or non-approval with some requirement
13 beforehand, or approval with some requirement after
14 approval in terms of post marketing surveillance. So
15 actually it gives the options of saying exactly what
16 you would do if you were in the FDA's position. Alan.

17 DR. CROSS: Okay.

18 DR. RELLER: For first -- we'll go around
19 the table with community-acquired pneumonia, and then
20 we'll go left to right for acute exacerbations of
21 chronic bronchitis, and then back to you for the final
22 round for acute sinusitis.

23 DR. CROSS: Well, I think this is a very
24 useful drug, especially considering the use of the
25 quinolones and the problems associated there. I think

1 the efficacy data presented is convincing, and I think
2 the perspective that Dr. Ruskin added at the end about
3 the meaning of the change in the QT was helpful.

4 I was also interested in Dr. Soreth's
5 quotation from Dr. Temple saying we really for safety
6 need to see lots and lots of data; and we're in a
7 Catch-22. We won't see that data unless there's ~~some~~
8 widespread use; and so the best of all possible worlds
9 I would say yes, I would approve ~~this~~, but I would
10 like to see at least a period ~~in~~ which we have a go at
11 the larger safety data with wider use, so it would be
12 a yes.

13 DR. RELLER: Thank you. Dr. Soper.

14 DR. SOPER: Yes, with post marketed --
15 marketing surveillance for both cardiovascular adverse
16 effects, and hepatotoxicity.

17 DR. CHRISTIE: I guess I have to say no.
18 I'm concerned about the adverse effects as were
19 outlined today, and especially the cardiac problems.
20 I'm not sure that I have sorted it out in my mind that
21 this drug would be safe.

22 The other issue too is that if it's given
23 for one, it might be given for all. And I'm also
24 concerned about its use in children, children less
25 than 12 years of age; so as we work through these

1 issues I'd like to see some data presented in the
2 future on children.

3 DR. RELLER: Dr. Wald.

4 DR. WALD: I would say yes, with post
5 marketing surveillance. I think that the -- this
6 class of drugs looks like it's very attractive for
7 lower respiratory tract disease. I think that is its
8 niche. I'm hopeful that will show that it is
9 effective against resistant pneumococci and that we'll
10 have increase in usage, but I think as an empiric
11 selection it looks quite good.

12 DR. RELLER: Dr. Archer.

13 DR. ARCHER: Yes, we post marketing
14 toxicity surveillance for all the issues raised.

15 DR. RELLER: Dr. Chesney.

16 DR. CHESNEY: I would say no, I'm fine
17 with the efficacy, but I'm very concerned particularly
18 about the liver disease. I'm not as concerned now
19 about the QTc issue, but I would favor looking at an
20 additional several thousand patients specifically
21 focusing on liver function tests before, during,
22 after, whatever else it takes to clarify the liver
23 issue.

24 DR. RELLER: Dr. Murray.

25 DR. MURRAY: I would vote yes, and I guess

1 I'm willing to accept the toxicity because I think it
2 offers a benefit for some of the resistant organisms.

3 I am concerned probably more about the
4 potential liver than the cardiac. And also, the
5 comments made about the repeat dosage I think is a
6 good one, that I think people are likely to receive
7 repeated courses, and there are no data on that. And
8 I believe in some of the other toxicity that people
9 that had gotten multiple fluoroquinolones or priatrova
10 as I recall had some -- they were the ones that may
11 have been brought out later on by liver toxicity.

12 DR. RELLER: I would vote no without
13 substantial pre -- I mean I don't know the mechanics
14 of how this is done, but of the three options Dr.
15 Soreth outlined, I'd like to see more patients
16 enrolled in streamlined clinical enrollments to get
17 the greater experience with this drug, going to the
18 safety issues. Especially because most therapy is
19 given empirically, and although the comments have been
20 clearly heard about the less severe patients who may
21 not have bacteremia at the time the patients
22 presented; we don't know, but those are the ones that
23 I look to because those are the ones I'm certain had
24 pneumococcal pneumonia. The others, there are always
25 questions about them; not questions because of the way

1 the sponsor did the studies, but just questions
2 because of the clinical reality. The ones with
3 positive blood cultures we know had pneumococci, and
4 we've got the organism and know exactly how
5 susceptible or resistant it was.

6 You know, I see such broad use for these
7 indications, and the potential for cross-reactions in
8 an older population, including older women that I am
9 uncomfortable with the numbers that we have, with the
10 potential warning signals that are there; to give
11 unfettered approval at this time, especially when one
12 takes resistant organisms off the table, which
13 eliminates at this point, the argument about not
14 having other drugs. Dr. Ebert.

15 DR. EBERT: A question first; should we
16 direct our comments as far as severity of disease at
17 this time, or are we going to defer those with regards
18 to indication?

19 DR. RELLER: I think we can slice it too
20 much. I mean the indication is community-acquired
21 pneumonia.

22 DR. EBERT: Okay. I would vote yes, with
23 continued post marketing surveillance for adverse
24 effects, and for hepatotoxicity.

25 DR. RELLER: Dr. Leggett.

1 DR. LEGGETT: I'll try not to belabor it.
2 I'm glad I'm not part of the FDA and have to make this
3 decision. I would vote a fettered yes, on whether
4 that's studies before it comes out or studies
5 afterwards; I think that those should be mandated.

6 I would -- the reason I would vote yes, is
7 I think that the drug does offer some benefit, and
8 it's exactly those patients who are beta lactim and
9 floraquinolone, etc cetera, et cetera who might have
10 problems; so I think they do add something, but I am
11 most worried about the 3A4 interactions, and the
12 possible hepatotoxicity. But I think that I view this
13 as much a class action, as a specific drug action in a
14 lot of things.

15 It to me appears that the possible cardiac
16 toxicity is in the ball park with Clarithromycin and
17 Erythromycin. It also looks to me that the
18 hepatotoxicity, except in terms of the LFTs is in that
19 same ball park. I don't know what to make about the
20 idiosyncratic reaction, and the repeated drug uses,
21 but I -- there's also the abacavir story, and repeated
22 use that makes me a little bit worried.

23 I am particularly worried about not
24 forgetting to do some additional studies that I think
25 need to be done, and that is to clearly -- to better

1 define just exactly what happens to Cmax and AUC in
2 the elderly. Those over 65 are going to have most of
3 the time decreased hepatic and renal function. We can
4 see that with drugs that aren't -- don't even go
5 through CYP such as ceftriaxone, where people over the
6 age of 65 have their drug levels go up several-fold.
7 So I think that we need to ~~catch~~ catch up on those, and I
8 think we need to make ~~some~~ sort of statement about
9 limiting the 3A4 ~~substrate~~-inhibitors in a box.

10 What I would do for the term the possible
11 ~~Toradol~~ de Pointes is sort of do something as with
12 Clarithromycin as in the warning, whatever it's
13 called, that this may happen. But I'm worried without
14 more data with the 3A4 drugs and the higher levels,
15 just exactly we don't know what's going on.

16 DR. RELLER: Thank you, Dr. Leggett.
17 Could you then start the round for acute exacerbation
18 of chronic bronchitis.

19 DR. LEGGETT: No. The drug is not needed.
20 The pneumococcus is not a big problem. Tincture of
21 thyme, some steroids and inhalers are the therapy for
22 chronic bronchitis exacerbations. I don't think we
23 need this drug for chronic bronchitis exacerbations.

24 DR. RELLER: Dr. Ebert.

25 DR. EBERT: Also no, I agree there are

1 plenty of other options for treatment.

2 DR. RELLER: I vote no, including the role
3 of the Big Three and Haemophilus being right at the
4 brink in terms of achievable concentrations with the
5 MICs. No.

6 DR. MURRAY: No.

7 DR. CHESNEY: No.

8 DR. ARCHER: No.

9 DR. WALD: No.

10 DR. CHRISTIE: No.

11 DR. SOPER: No.

12 DR. CROSS: I vote no, and also with
13 regard to this type of infection, we just need more
14 data on what is the effect of repetitive dosing on
15 these votes. I'm sorry; repetitive episodes. I vote
16 no.

17 DR. RELLER: Thank you. Now Alan, could
18 you start round three for sinusitis, acute sinusitis.

19 DR. CROSS: Well, I think the data
20 presented in general looks good for -- but I just
21 don't think we have enough data in terms of the
22 Erythromycin and penicillin resistance. It's very
23 hard to get bacteriologic data on this, but what we
24 have overall in terms of the non-resistant isolates,
25 I think it shows efficacy. And again, the only caveat

1 I would have is in terms of repetitive treatment of
2 this episode, and there is the same toxicity issue
3 that we had on the bronchitis, so I would vote a --
4 what was said, a fettered yes, but I leave it at that.

5 DR. RELLER: Dr. Soper.

6 DR. SOPER: Yes.

7 DR. RELLER: Christie.

8 DR. CHRISTIE: No, I don't think so. No.

9 DR. RELLER: Wald.

10 DR. WALD: I would say no, because I think
11 there are so many other choices for drugs. And while
12 I have to say I'm not really worried, especially about
13 the toxicity of this drug, either cardiac or
14 hepatotoxicity; while we're using it for pneumonia, we
15 can learn a lot more about toxicity and then say it's
16 okay for sinusitis. So until we know that, I'll hold.

17 DR. RELLER: Dr. Archer.

18 DR. ARCHER: I agree with Dr. Wald. I'm
19 kind of on the fence, but I think that questions of
20 toxicity in this case don't warrant its use for a
21 relatively trivial infection like sinusitis, so I
22 guess I would say no.

23 DR. CHESNEY: No.

24 DR. RELLER: Chesney is a no. Dr. Murray.

25 DR. MURRAY: I think I would vote no. I

1 think it probably works for the resistant organisms,
2 but I'm not sure the toxicity issues are strong enough
3 to -- or outweighed enough by the need.

4 DR. RELLER: No.

5 DR. EBERT: Dr. Ebert. I also vote no for
6 all the reasons listed so far. In addition, the fact
7 that this drug shows some activity against anaerobes
8 concerns me that by approving this for acute
9 sinusitis, we may be opening a Pandora's Box and be
10 using it for chronic sinusitis as well.

11 DR. LEGGETT: Leggett. I concur with most
12 of what's been said before, and vote no; because I
13 think the risk benefit analysis is -- weighs more
14 towards the potential risk in acute sinusitis.

15 DR. RELLER: Okay. Tom Perez has the
16 tallies here, so for the question number one, we have
17 seven to three yes for community-acquired pneumonia,
18 a unanimous no for acute exacerbations of chronic
19 bronchitis, and eight to two no for acute sinusitis.

20 So let's move now to Question C; that then
21 would logically be what kinds of restrictions in
22 labeling or populations, or specific things to be
23 looked at in additional studies or surveillance,
24 limitations in access or distribution, how would you
25 control these things, Dr. Cross, for community-

1 acquired pneumonia?

2 DR. CROSS: Well as mentioned, I think
3 that we need to have a study with large amounts of
4 patients, a so-called simple study in which we
5 enumerate the -- a much larger population the risk and
6 side effects. But also on top of that, I think that
7 what has been mentioned is even though it hasn't been
8 discussed here, it ought not be used in a population
9 of children. And even though we have some data on 13
10 to 18 year olds, I think we really have to note that
11 there really isn't sufficient data in this population
12 to warrant its use.

13 DR. RELLER: Dr. Soper.

14 DR. SOPER: I think the provider needs to
15 be warned about this 450 drugs, and I -- whatever we
16 did for amoxi, amoxicilin with the QT, whatever ended
17 up being the final thing there, probably should relate
18 to this one too.

19 DR. CHRISTIE: We should come to know the
20 potential drug interactions as listed before. We
21 should not use the drug in children, people with
22 previous liver disease, underlying cardiac disease as
23 mentioned before, and we should get larger numbers.
24 And again, I'd like to see data in children.

25 DR. RELLER: Dr. Soreth.

1 DR. SORETH: Just a note for Dr. Soper
2 with regard to what we did with moxifloxacin, it's not
3 metabolized through the P54 system, so that's not an
4 issue in terms of concomitant drug use.

5 DR. SORETH: QTc also. The box, the QTc
6 box.

7 DR. SORETH: Thank you.

8 DR. RELER: Dr. Wald, how would you frame
9 the --

10 DR. WALD: Restrictions.

11 DR. RELER: Yes.

12 DR. WALD: I mean, I think I would agree
13 with what's been said. Certainly, we're not talking
14 about children today at all, as I understand it; and
15 I would agree that any concurrent use of those drugs
16 that prolong QT should be prohibited, so I think in
17 taking care especially of geriatric or complicated
18 cases, this really means some counseling for the
19 patient to go over an extensive list of other drugs
20 that they might be on.

21 DR. MURPHY: Could I ask a question about
22 that? Since our experience is that even when we list
23 these contraindications of concurrent drugs, or at
24 least drugs that we want you to ask about; that one of
25 the reasons we, as Dr. Soreth said, have problems is

1 that apparently that is not always paid attention to
2 at the level we would like it to be. So there -- I
3 guess one of the question we have is when you say post
4 marketing surveillance, that's one thing; are you now
5 also suggesting that there are some other models of
6 restricted distribution or use where one has a
7 physician's register with the pharmacist or
8 registries? Is that what -- are you -- so that they
9 would basically have attested that they understand the
10 use of these products, or you're not saying that. I'm
11 just trying to understand if that's what you're
12 getting at or not.

13 DR. WALD: What other drug do we that for
14 besides Accutane? Is there any other drug?

15 DR. MURPHY: Accutane was one. Yeah.

16 DR. WALD: And no other drug?

17 DR. MURPHY: I mean there's others,
18 Thalidomide of course, but I mean there are some
19 others that are under discussion for doing that. And
20 of course, there are other approaches where, you know,
21 patients have to have tests before they get the drug.
22 That's another approach, but I just -- when you said
23 make sure they reviewed the concurrent drugs, that
24 made me wonder if that's what you were trying to get
25 at; because we do have those systems in place for

1 other things.

2 DR. WALD: I guess I hadn't thought of
3 something so formal as that, but that might be a very
4 effective strategy. Either that or at the pharmacy, I
5 guess that would be the other alternative. I don't
6 know which is a more fail-safe method. Certainly if
7 people have to be licensed to dispense the drug, then
8 I think that would be a very effective way to make
9 sure they reviewed all the potential
10 contraindications.

11 DR. RELLER: Dr. Archer, how would you go
12 about it?

13 DR. ARCHER: I agree. I think that all
14 the risk groups, including the risk of Torsades in
15 women as opposed -- higher incidents, and the problems
16 in elderly and all of those things need to be noted,
17 and the same kinds of things that we've done in the
18 past.

19 I think that -- I don't really think there
20 should be restrictions. I think we need the drug to
21 be used in as many groups as possible so that we can
22 assess the toxicity, and find out if these issues are
23 real. I'm not totally compelled by all the toxicity
24 data. I think it's very -- it was very confusing to
25 me. I think it raised a lot of red flags, but I think

1 this is something that needs to be looked at when the
2 drug is used widely.

3 DR. CHESNEY: I would I guess have big
4 boxes about drug interactions, and another box about
5 QTc. And my two questions or issues in addition to
6 what's already been said, recognizing that I said no;
7 I don't know if -- how strong a recommendation you can
8 make about getting liver enzymes at the onset of
9 therapy, or making a very complete of pre-existing
10 liver disease before the drug is started, with some
11 very strong wording that the risks are unknown at this
12 point in time.

13 I also wondered, having heard on Monday or
14 Tuesday about a patient insert in a box. I wonder if
15 that would be a possibility; that every patient who
16 takes this drug is given something that also outlines
17 these things, in case the physician forgets to clarify
18 that.

19 DR. MURPHY: Well at the end of our labels
20 we have the patient information, so Dr. Chesney, are
21 you talking about the -- what we call the med guide
22 where every -- the med guide, there's a mandate that
23 every patient receive this piece of paper versus the
24 insert which can be part of the label which they may
25 or may not get. So I guess what I just want to ask

1 you is are you -- is that what you're talking about;
2 is a med guide where it's mandated that each patient
3 get it?

4 DR. CHESNEY: That's -- I would think
5 about a med guide.

6 DR. MURRAY: Well, I certainly would
7 encourage studying the drug in kids. I think that's
8 where more resistant organisms are, so that's where
9 you really need it.

10 I'm trying to remember if LFT elevations
11 were excluded before -- it was an exclusion in the
12 clinical trials. I mean, I'm not sure they're in --
13 I mean, yeah I'm concerned about the possible liver
14 toxicity, but there were no data really to suggest
15 that if we knew they had an elevated LFT, that they
16 were any worse; so I really couldn't see checking LFTs
17 on people before they took the drug. But I do think
18 that some statement about potential prolongation of --
19 or the prolongation potentially of QTc needs to be --
20 a statement needs to be made, and perhaps a wording
21 for potential for liver as well.

22 DR. SORETH: So would that imply, Dr.
23 Murray, that everyone would need a baseline EKG for
24 you to determine --

25 DR. MURRAY: No. I'm just worrying that it

1 is -- that some prolongation has been noted, but no,
2 I did not mean a baseline EKG.

3 DR. RELLER: I would -- having voted as I
4 did, I would take a somewhat different approach from
5 my colleagues. And I don't know what -- I don't know
6 enough to know what restrictions with confidence I
7 could place on a label. I'm -- there are -- for
8 applying this drug widely, with the potential for
9 many, many drug interactions, the age issues, the
10 question of older women, the empirical therapy; I
11 favor finding out more about the drug up front, to
12 possibly minimize all of the boxes and warnings after
13 the fact. Because after the fact, or even with the
14 warnings in the boxes, I don't know the data of how
15 closely they're followed, whether they're followed,
16 and what effect they have.

17 Has anyone ever done a controlled trial of
18 having a box or not having a box, a warning or not a
19 warning, if it affects practice one iota? So
20 consequently, what I would prefer to do is see what
21 would be basically unfettered use of the drug in terms
22 of enrolling patients, but close monitoring or
23 gathering data on those patients to see whether there
24 really is a risk.

25 Now I realize that if it's an event that's

1 one in a million, it's impractical. But once widely
2 available, I mean the potential market is in the
3 millions; so as a consequence, I'd like to see a lot
4 more than 1,500-2,000 patients. And it's not an issue
5 of demonstrating efficacy any more; it's an issue of
6 focusing on those things that might give a good
7 indication of toxicity when applied more widely for
8 the indication of community-acquired pneumonia. And
9 there are a lot of people out there who are getting
10 treatment. I think we need to observe them in a
11 monitored way prospectively before the drug is
12 released generally, if that's possible to do somehow.

13 DR. MURPHY: So if I could paraphrase; I
14 think what I heard you say, Dr. Reller, is that it's
15 a large not so simple trial where use is unfettered,
16 as you said; but we have some parameters of monitoring
17 that we would collect before approval, to look at some
18 of these issues.

19 DR. RELER: Right. Specifically, for
20 example, you know, let's treat older women with
21 pneumonia and document what drugs they're getting
22 concurrently, and see what happens in those patients.

23 DR. MURPHY: Just as a -- we have never
24 marketed a product with one -- with a certain label
25 versus having it marketed in a different area with a

1 different label and studied that, so there is no
2 controlled study on that. We do have unfortunately
3 experience on the point that Jan was making; if we
4 don't get it right the first time, we have experiences
5 where we said -- we put in black boxes. We've sent
6 out numerous "Dear Doctor" letters, public health
7 advisories, and behavior does not change once a
8 practice pattern has set with the original approval;
9 not significantly enough in a number of cases, let's
10 put it that way.

11 DR. REUTLER: Exactly. And you know, the
12 sponsor appropriately and you know, in the context of
13 the controlled trials that were done, had all of these
14 restrictions on who could enter the trial. I'd rather
15 lift the restrictions and enroll thousands to
16 preserve, if I were king, the market for millions.
17 Dr. Ebert.

18 DR. EBERT: I agree. It should also not
19 be used in young children, but that it does merit
20 study. I would favor, at least initially, placing a
21 warning in the package insert similar to what one
22 might see with Clarithromycin. If the drug
23 interaction data and adverse data were to be borne out
24 as being minimal, that could be petitioned to be
25 removed at a later time.

1 I feel that it should be promoted only for
2 use in patients who do not warrant hospitalization, so
3 for patients who would be treated on an out-patient
4 basis. And perhaps maybe something a little bit
5 different, but in -- if there are some concerns about
6 this drug being used inappropriately, or in patients
7 who are at high risk, or patients who are receiving
8 multiple other medications, perhaps the policy of how
9 the drug is sampled should be considered, and whether
10 -- certainly there is going to be less recordkeeping,
11 more of a potential for harm if the drug is sampled
12 liberally rather than if it were only available by
13 prescription.

14 DR. RELLER: Dr. Leggett.

15 DR. LEGGETT: I sort of won't say what I
16 just said a few minutes ago when I addressed the issue
17 in the other question. But I think we do need
18 primarily to address the toxicity issue, and to sort
19 of concur with Dr. Murphy; I agree that it's better to
20 get it right the first time, so whether that means
21 putting up a road block before allowing its use, or
22 coming up with some new strategy to better look at the
23 way things have been done in Phase IV than has been
24 done in the past for many drugs. I don't know the
25 answer to that.

1 DR. RELLER: Dr. Leggett, to finish the
2 afternoon session with the last question, if the
3 Committee has not recommended approval, please provide
4 recommendations for additional studies. The only two
5 indications that got a majority of no votes were acute
6 exacerbations of chronic bronchitis and acute
7 sinusitis.

8 What would you require to consider again
9 those indications? Or one option would say get it
10 worked out for acute pneumonia -- I mean, excuse me --
11 community-acquired pneumonia. In other words, that's
12 -- those are a couple of the options. What would you
13 do about the two that got a no on balance?

14 DR. LEGGETT: I would address the toxicity
15 issue. I don't think I had a problem with the
16 efficacy, despite the fact that those are notoriously
17 hard things to know for sure, about efficacy. I think
18 five days will probably work for anything, but that's
19 just what I think; so I -- if it's easier to address
20 the toxicity by looking at community-acquired
21 pneumonia folks, I don't think we would necessarily
22 have to go back and re-do toxicity with AECB and acute
23 sinusitis.

24 DR. RELLER: Dr. Ebert.

25 DR. EBERT: My only suggestion would be if

1 those two indications were to be pursued, to
2 aggressively target patients who were infected with
3 penicillin resistant or macrolide resistant strains to
4 really build up the numbers as much as possible there,
5 with the hopes of -- and especially with Haemophilus
6 influenza as well, to try to specifically target those
7 pathogens.

8 DR. RELLER: I would put the emphasis on
9 getting the safety data before approval with
10 community-acquired pneumonia with a larger number of
11 patients as mentioned; and then that having been
12 settled, one could come back and reconsider expanding
13 the indications. The controlled trials are there for
14 efficacy. I think the place to find the safety
15 information is with community-acquired pneumonia.

16 DR. MURRAY: If you -- if the toxicity
17 issues are allayed by extensive use in other patients,
18 then the concerns about using it in a relatively minor
19 disease like acute sinusitis are lessened. Similarly,
20 if the increase -- if there's an increase in resistant
21 organisms so that the benefit is great, and the
22 efficacy data is continued, then again our concerns --
23 my concerns would be allayed. So it's one or the
24 other, either get -- allay my concerns about toxicity,
25 or make the resistance in sinusitis more common and of

1 a bigger issue.

2 DR. CHESNEY: I agree with everything
3 that's been said. I think -- but I think I would do
4 them both. I would look very closely at toxicity
5 issues that would make us all less anxious; and if it
6 could also be shown that you had ~~way~~ more resistant -
7 - pneumococcal resistant isolates, both Erythromycin
8 and penicillin and that it was very effective, then I
9 think none of us -- I wouldn't have any problem with
10 it.

11 DR. ARCHER: I agree with those sinusitis
12 statements. I don't think we need any antibiotics for
13 chronic bronchitis period, so I don't think that's
14 anything that I would think they could do anything
15 about. But I think sinusitis, the issues of
16 resistance and toxicity, once they're solved, I think
17 that would be a nice indication.

18 DR. WALD: I agree that -- again I think
19 the special niche for this drug and for the macrolides
20 is lower respiratory tract disease. If you want to
21 sell it for upper respiratory tract disease, I think
22 you need to show that it's going to be effective for
23 resistant organisms. That will make it special and
24 make it recommendable. And then just as was said, as
25 we establish safety with community-acquired pneumonia,

1 then I think we can use it.

2 DR. CHRISTIE: I agree with everything
3 that has been said. Specifically, I'd increase the
4 numbers, and make sure that the toxicity is improved,
5 and get enough numbers to look at the resistance data
6 in a better way. Looking at things like drug
7 interactions, ECGs ~~for~~ longer time, LFTs throughout,
8 and of course, a plug for children; because I still
9 see that once you approve a drug, even though it's not
10 approved for children, it may be prescribed for them,
11 so we really need to pay attention to that population.

12 DR. RELLER: Thank you. Dr. Cross.

13 DR. CROSS: Okay. I also agree with doing
14 a lot about toxicity from the pneumonia studies. I
15 agree. I don't see any use for this in exacerbation
16 of bronchitis, and I'd like to see more numbers with
17 the Erythromycin. But I would like to return to the
18 last question, which is in effect related to this, and
19 I don't know whether it's putting too fine a point on
20 it; that in terms of what to put in in a box, that
21 there is a known -- if there's a patient known to have
22 a QTc of greater than 450, that was an exclusion
23 criteria. And you know, it appears to me we don't
24 have enough data on that group, such that I wonder
25 whether or not that also ought to be specified in the

1 labeling which we have on that last question.

2 DR. RELER: Thank you. Dr. Soreth and
3 Dr. Murphy, anything else you wish of the Committee;
4 to say to them, or ask of them?

5 DR. SORETH: Maybe I could just summarize
6 the last few minutes of discussion to make sure I
7 understand it correctly.

8 I think it a fair statement that as the
9 Committee looked at the indications of community-
10 acquired pneumonia, acute exacerbation of chronic
11 bronchitis, and acute sinusitis; there was for the
12 latter two sinusitis and bronchitis, a consensus, if
13 not unanimity, a consensus that at this point the drug
14 should not be marketed for those indications. This is
15 resistance off the table for the moment, because we
16 already summarized that. And so, to that end for
17 things to go forward, and in order to understand the
18 risk management perhaps more clearly than we do at
19 this point, how the drug would be utilized in a
20 patient population at large, now talking about
21 community-acquired pneumonia.

22 There were comments made across the table
23 for investigation, not so much in the realm of
24 efficacy, for we feel we understand that in cap for
25 susceptible organisms, but rather further

1 investigation to help clarify and either validate our
2 concerns with regard to QT prolongation and potential
3 liver toxicity, or allay fear that in broad use it
4 could be used wisely, prudently, effectively, and
5 safely. And that to that end, there -- we have
6 mechanisms, obviously, to either investigate that
7 prospectively, in something like a large simple safety
8 trial, which I will grant you; I think we do not have
9 a large experience with doing that. More often what
10 we have is marketing a drug and looking post marketing
11 in some way, either through passive surveillance which
12 sometimes makes it difficult to figure out precisely
13 what's going on, or taking a step back and looking at
14 the paradigm and considering an approach that is
15 prospective.

16 Again, not to delineate anything with
17 efficacy with susceptible organisms for we understand
18 that, or think that we do; but rather to delineate
19 certain safety issues; concomitant drug use, drug
20 interactions, et cetera. And that we will take all of
21 that under advisement and proceed at this point in
22 working with the company to see then which of the
23 various, you know, ways of gathering more safety
24 information is at this point prudent, and in the best
25 interest of the public health.

1 DR. RELER: And at the same time in so
2 doing, would accumulate larger numbers of organisms if
3 resistance continues to increase or maintain, that
4 would give the numbers that might enable an accurate
5 assessment on efficacy ~~using~~ resistant organisms.

6 I want to thank all the presenters for
7 their efforts. I think we have a vigorous discussion
8 on ~~issues~~ that don't have simple answers, if an answer
9 at all as of now, and to the Committee Members for
10 faithfully staying to the end.

11 Tomorrow's meeting for the Committee
12 Members, a closed meeting begins at 9:30 in the
13 morning in this room.

14 DR. SORETH: That's a good question. Is
15 it in this room? It is.

16 DR. RELER: In this room.

17 DR. SORETH: And it's informal dress-down
18 Friday, so I hope you packed your jeans, because
19 that's what we'll be wearing.

20 DR. RELER: And thank you again. The
21 meeting is adjourned.

22 (Whereupon, the above-entitled matter
23 concluded at 5:19 p.m.)
24
25

C E R T I F I C A T E

309

This is to certify that the foregoing transcript
in the matter of: COMMITTEE MEETING

Before: FDA / CDER

Date: APRIL 26, 2001

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
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Rebecca Davis

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