occur while you are taking the drug.

With some of the antibiotics, however, and I would include telithromycin, a delay can be seen. That has been classically recognized with Augmentin where it can happen up to 6 or 7 weeks after the drug has been discontinued. It happens with erythromycin, as well.

[Slide.]

So, in conclusion, we have hepatic events that I think are very similar to the comparators in the clinical trials.

The postmarketing acute liver failure cases, if we apply our causality assessment, they are not 12. They are far fewer than that and that has a bearing on reporting incidents and turning that into any kind of other incidents and we have already heard that reporting rates are not an incident, so you have to take that with a grain of salt.

In our analysis, we did not believe that any of the deaths were directly related to acute liver failure, the hepatotoxicity can be delayed

and, overall, the hepatic safety appears quite comparable to other drugs already on the market.

Thank you.

With that, let me introduce Dr. Wanju Dai, who is head of Global Pharmacovigilance and Epidemiology, who is going to now talk about the epidemiology studies.

Epidemiologic Investigations - PHARMetrics

DR. DAI: Thank you, Dr. Lewis.

Now, I am going to, together with Dr. Alex Walker from I3 Drug Safety, to review the results of two epidemiological studies that evaluate the association between telithromycin use and severe liver injury.

To begin with, let me give you a very brief background of why we did these two studies.

[Slide.]

Spontaneous reports are a very good source in detecting severe rare adverse event signals. This is a very good example we just presented this morning about the myasthenia gravis. It is a rare event that you couldn't possibly address this event

from clinical trials.

Therefore, as part of our risk management plan, we have been monitoring the FDA adverse event report database that we obtained via Freedom of Information services.

As detailed in the briefing document, we did two types of analysis using this database. The first one is disproportionality analysis. This one showed us there is a signal of severe liver injury in association with telithromycin use as presented by Dr. Levine earlier today. This similar signal was also observed for Augmentin and some macrolides.

The second type is the reporting rate analysis and it showed telithromycin has a higher reporting rate of liver injury. But, as detailed by Dr. Rullo, there were many biases associated with spontaneous report that may explain the differences.

Therefore, we feel there is a need to do further epidemiological studies based on population-based database to further evaluate this

association.

[Slide.]

There are two studies that were conducted and both were based on the very large database. It's medical claims insurance databases.

The first one is called PHARMetrics Integrated Outcome Database. The study was conducted by Sanofi-Aventis epidemiologists and the results will be presented by me.

The second one is Ingenix Proprietary Research Database. It was independently designed and conducted by I3 Drug Safety and thus will be presented by Dr. Alex Walker from I3 Drug Safety.

We had planned on the study since early this year and final study protocols for both studies were submitted to both FDA and European regulatory agency in August 2006.

Both studies had shown, one, the event of severe liver injury following telithromycin use is very rare; and, two, that risk of severe liver injury following telithromycin use is similar to that experienced by other antibiotics.

Now, let me go on and talk about the first study using PHARMetrics database.

[Slide.]

This database includes data from members of 89 health insurance plans. The database includes data, information on each patient, as well as medical procedure prescription claims that were submitted to insurance companies for reimbursement. It has data from all four regions in the United States and covers data over more than 10 years. During the study period, it has approximately 12 million active enrollees in the database.

[Slide.]

It is a retrospective cohort study and study objective was to evaluate the risk of severe hepatic injury following telithromycin use in comparison with other antibiotics. We included all adult patients, excluded those with cancer.

[Slide.]

The comparison groups included Augmentin, clarithromycin and moxifloxacin. Basically, we tried to choose one antibiotic from each class.

The risk window is 40 days from dispensing of an antibiotic. I will explain in more detail of study outcome.

The study period covered about 1 1/2 years.

[Slide.]

The study outcome of severe hepatic injury is defined by the diagnosis code, ICD-9 code, as well as procedure code, CPT code. It included acute necrosis of liver, as well as liver failure, hepatic coma, unspecified hepatitis, mostly noninfectious, hepatitis and liver transplant.

I want to emphasize here we included only inpatient diagnosis. There are two reasons why we did it this way. One, actually, the event of concern is the severe liver injury and hospitalized cases represented that kind of cases; and two, we know we don't have the right to access medical records using this database, so the cases will be nonvalidated. We know also that hospitalized events will be much more reliable than those detected from outpatient diagnosis.

Therefore, we were focusing only on inpatient diagnosis. We actually included all inpatient diagnosis that were detected from this database. Some of the areas in the briefing document may indicate it only included primary diagnosis. We actually included all diagnosis, all inpatient diagnosis.

[Slide.]

Patient characteristics. There were over 124,000 telithromycin users included in this study, a similar number for Augmentin, moxifloxacin, and there were about double the number of patients in clarithromycin cohort.

Each patient may receive more than one prescription, therefore, there were 137,000 prescriptions for telithromycin and similarly for the other antibiotics.

About two-thirds were female patients, mean age about 45, moxifloxacin patients a little older. About 2 percent of patients had prior history of liver disease. Charlson Index is an index to indicate the severity and frequency of

underlying disease. It ranges from zero to 5, with the zero being the healthiest and 5 being the most sick.

As you can see here, about 80 percent of these 3 cohorts had patients with Charlson Index zero, healthy, and moxifloxacin patients seem to be a little more sicker than the other cohorts.

[Slide.]

There were a total of 64 events with patients that met the prespecified study endpoint criteria. The most common one was non-infectious hepatitis. There was also plenty of liver necrosis, and the distribution was about the same for these various codes across different antibiotic cohort.

[Slide.]

The crude risk. There were 11 cases study endpoints in the telithromycin arm, result in crude risk of 8 per 100,000 prescriptions. Augmentin has about 6 per 100,000. You can see this rate experienced by telithromycin is within the range experienced by other antibiotics.

[Slide.]

Now, I am going to look at crude risk by two covariates. The first covariate is by prior history of liver disorder. This portion only shows those people who did not have prior history of liver disorder. The crude risk was about 6 per 100,000 for telithromycin, again comparable within the range as experienced by other antibiotics.

So patients who had a prior history of liver disorder, the number is small, and the number of prescriptions also small. It appears that the crude risk for every single antibiotic for patients with a prior history of liver disorder was higher than those without liver disorder as expected but, because of small number of cases included in patients with prior history, all the confidence intervals overlap.

[Slide.]

Now, second covariate by Charlson Index. For Charlson Index equals zero, the crude risk for telithromycin 4 per 100,000, again in the range as experienced by other antibiotics, people who are

sicker, you can expect that the risk is higher than those who are healthier, but again notice the somewhat small number of patients and prescriptions, and the risk experienced by telithromycin is still comparable with other antibiotics.

[Slide.]

Since we saw that the risk experienced by Augmentin in this study was the lowest, so we used that as a reference group in this analysis.

[Slide.]

The crude risk ratio for telithromycin versus Augmentin is 1.4. We then adjust this crude risk ratio by these factors in the GEE model result in still about the same risk ratio 1.4 for telithromycin. You can see the risk ratio for other antibiotics. The only one that turned out to be significant, different from one, is moxifloxacin.

[Slide.]

In summary, the epidemiological study using PHARMetrics study database, we found that the

risk of severe liver injury following telithromycin use falls within the range as experienced by other antibiotics.

It should be noted that this kind of risk is used for comparison purposes, it may not reflect the true risk, because we could not access medical records to validate these cases. If these cases were validated, we can expect the number, the risk will be smaller than what I presented here.

However, there is no reason to believe that the rate of validation would be differential amongst different antibiotic groups, therefore, if the rate of validation were non-differential, the ranking of the risk amongst those antibiotics as we just saw is still true.

Regardless, we realize the importance of validating these adverse events, medical events, so we asked I3 Drug Safety, who has the capability to access medical records with their database, to conduct another study.

Now, I am going to ask Dr. Alex Walker to present the study results.

Epidemiological Investigation - Ingenix

Alexander M. Walker, Dr.PH.

DR. WALKER: Thank you, Dr. Dai.

I am going to present results of an analysis that we have done of data available to us of the occurrence of severe hepatic injury in users of Ketek and Biaxin.

[Slide.]

The study was funded in part by a research contract with Sanofi. We had actually gotten started on the planning for this separately from the company. It involves use of PHI and has been passed by the New England Institutional Review Board and the Guidelines for Good Pharmacoepidemiologic Practice.

[Slide.]

The primary objective of this study was to look at acute liver failure within 60 days following use of telithromycin or clarithromycin. We had as a secondary objective to look at other severe hepatic injury classified on clinical criteria.

[Slide.]

The data that we used starts from a very large claims database from an affiliated health insurer where essentially everything that is paid for is recorded in the database. These are adjudicated insurance claims that contain the identification of services and the reasons for services.

The pharmacy claims give, for each dispensing the drug, the amount, the form, fill dates and days of supply.

In the data we worked with, the results of approximately 12 million people in the database as of the beginning of 2005.

[Slide.]

We identified individuals who had received telithromycin and clarithromycin from the latter part of 2004 and through all of December 2005. We were limited to these two products because they were part of a regular drug screening program that we do, called I3 Aperio, so we had a headstart on creating matched cohorts and being able to identify

cases quickly.

Individuals had to have complete demographic and enrollment information, which is essentially the whole database, and at least six months of continuous enrollment in the database prior to the first three-quarter dispensing of telithromycin or clarithromycin.

That baseline period allowed us both to identify relative initiation of these drugs but, more importantly, the whole series of baseline health characteristics that one could infer from health care utilization during that six-month period.

[Slide.]

The clarithromycin patients were matched to the telithromycin patients using a multivariable technique called propensity scores, which allows you to get balance between the cohorts with respect to a large number of predictor variables.

We identified cases initially from the claims data looking for any occurrence of acute or subacute necrosis of the liver or hepatic coma

either inpatient or outpatient record in the claims data.

We then reviewed the insurance claims profiles of these patients to pull out a small number that were obviously missed codes or rule out diagnoses and went to the medical records for adjudication.

[Slide.]

Now, what do we adjudicate? We had several levels of hepatic injury. The primary hypothesis had revolved around acute liver failure and these are essentially cases meeting enzyme criteria of Hy's Law, as it is called. I will show that in the next slide, plus either encephalopathy or coagulopathy.

[Slide.]

The so-called Hy's Law cases were ones that had ALT levels greater than 3 times the upper limit of normal, elevated bilirubin and absence of an alkaline phosphatase elevation.

[Slide.]

We also looked at three lesser levels of

disease, simply an ALT greater than 10 times the upper limit of normal, ALT 4 to 10, and we had a category, because this is still chart review data from abstracted charts and we wanted to allow the reviewer to signal cases that in his opinion were serious but for which the data simply weren't available, such as lab values to place the patient in one of the other categories.

It wasn't part of the case definition that cases should be hospitalized but, in fact, every case that was accepted had been hospitalized.

[Slide.]

Now, from cases identified within these cohorts, we only accepted cases that occurred within 60 days of last use of one of the study drugs. Typically, these were the drugs that we had identified from the cohorts. But we followed the patients through for a year and there was some repeat prescription and some crossover prescription, so patients were eligible to enter to a new period of surveillance for liver disease during those periods.

The exposure assessment--that is, this rule of 60 days--was based on the fill date for each dispensing to which we added the number of days supply to give the potential days of exposure if someone followed the prescription as directed.

[Slide.]

The core analysis was as matched; that is, we had these two cohorts and they were demographically and medically similar to one another. Because of the repeat and crossing over prescriptions, we also did an as-treated analysis--that is, considering each dispensing as a new opportunity for an event.

Because in the as-treated analysis, we came across what seemed to us an unusual number of cases with exposure to both clarithromycin and telithromycin in the 60 preceding days, we did a post-hoc case-controlled analysis to try and understand how frequently that close sequential prescription would occur.

[Slide.]

Overall, we had access to 108,000

initiators of telithromycin and 203,000 initiators of clarithromycin.

We were able to find good clarithromycin matches for 102,000 or about 95 percent of the telithromycin users.

I won't show you all the graphs, I believe you have them in the report, these cohorts were extremely well-balanced with respect to a wide variety of health care utilization characteristics, diagnoses, drugs and procedures from the baseline period.

[Slide.]

The age distribution. These cohorts were basically younger and middle-aged adults, a predominance of women, 60 percent female. The regional distribution of cases reflected the distribution of membership in our sister company.

[Slide.]

The medical record abstraction started with 93 claims-based outcomes that we were considering, 88 of those seemed plausible, at least possible liver failure. We were able to obtain the

medical records for 77 of those, for an 88 percent abstraction rate. Of those 77, 16 were confirmed by chart review.

[Slide.]

Reasons for exclusions or non-confirmation would include little information of LFTs and a whole series of alternate diagnoses that were clearly documented in the record that may not have been apparent in the claims data.

I should say that the charts not obtained were mostly outpatient charts that the hospitalization and treatment rate was very high and subsequent review of those that we couldn't get records for didn't show any case in which it looked like there was some serious illness going on.

[Slide.]

The distribution of cases according to the categorization of hepatic disease in the telithromycin and clarithromycin cohorts, and who had gotten drug most recently, is shown in this figure.

For the primary diagnosis, the acute liver

failure, there were two cases. Both occurred in the clarithromycin initiator cohort, and both occurred while the patient would still have been using clarithromycin according to the dispensing instructions. The other cases were distributed over the two cohorts.

[Slide.]

There was a total of 9 cases in these cohorts. There were 3 cases in which both clarithromycin and telithromycin use was inferred during the 60 days preceding case onset, 2 in clarithromycin initiators and 1 in telithromycin initiators.

[Slide.]

Going to the risk of the outcomes, I have already pointed out the zero and 2 for acute liver failure. Looking at all outcomes together in these cohorts, there were 5 in telithromycin and 4 in clarithromycin, giving rates of about 5 and about 4 per 100,000 in each group.

[Slide.]

We calculated both the relative risks and

risk differences. I will focus on the relative risk on the righthand side of this figure. The relative risk for acute liver failure was, of course, zero since there were zero cases in the telithromycin cohort. Small numbers of cases, so the 95 percent confidence bounds, so the limits of relative risk with which these figures were compatible ranged from zero to a five-fold increase.

The risk difference, not quite as affected by the zero in the telithromycin group--and you see that that was an estimate of 2 per 100,000 better for telithromycin, the 95 percent confidence bounds go from almost 5 better to 1 case per 100,000 worse.

The figures, if we just sum the ones up for all outcomes, we have a relative risk of 1.25 for telithromycin versus clarithromycin with fairly wide confidence bounds, as well.

[Slide.]

An analysis based on dispensings as opposed to individuals and matched into the cohorts

yielded essentially identical results for both the overall rates and then the comparisons of rates.

[Slide.]

I noted those three cases of double exposure. We investigated that by drawing a sample from the cohort of 1,000 persons who were closely matched on propensity score for each one of the cases, so these are people from the cohort who didn't become cases.

We then followed those 1,000 people forward and as of a date which represented the same number of days into follow-up, for each of the controls, assessed whether or not they were within a 60-day window and, if they were, what they were exposed to.

[Slide.]

I will go to the bottom of this figure. As we said, there were three cases that were exposed to both drugs. In the control group, there were 36 out of essentially 6,000 individuals that were exposed both, so that approximately 1/100th as many as the 3/9ths in this group.

If we convert that to a relative risk, you get relative risk estimates of about 110, although, of course, that is simply indicative of a very large relative risk. The lower confidence bound was still high and the upper confidence bound was, of course, enormous.

[Slide.]

Our conclusions. First of all, there were no cases of ALF among telithromycin users and 2 in clarithromycin users.

The as-matched and as-treated analyses both indicated essential equivalence in the occurrence of all events together.

When we did secondary analyses and post-hoc analyses of the treatment patterns, we find pretty much the same results. But we do find this very high increase, essentially 3 observed as opposed to 0.03 expected of cases that had been exposed to both.

The study didn't offer any support in favor of an elevated risk in telithromycin users but, because of the numbers, it certainly doesn't

rule out an elevated risk. But it is information on 100,000 people in each group.

It may be this was an elevated risk of hepatic injury in people with both drugs in close succession. This is an unexpected finding and in our view deserves further confirmation.

Thank you.

The next speaker will be Dr. Judith Jones, who is the President and CEO of the Degge Group.

Expert Review of Epidemiology

Judith Jones, M.D., Ph.D.

DR. JONES: Thank you very much. Dr. Edwards, members of the Committee, I have a mercifully short talk but I have been asked by the sponsor to provide some remarks to allow us to step back a few feet to look at the tremendous amount of data that you have been exposed to today and actually will hear some more this afternoon after the break and provide some perspectives on this.

In part, I think I was asked because, like Jim, I have been involved in drug safety for about 28 years when I had a job very similar to Dr. Dal

Pan at FDA, and have subsequently just devoted my life to drug safety and also as a student of Hy's. I will allude to one study I did as a result of that.

[Slide.]

I think we have heard very clearly in many presentations that there is no question that there is some rare risk of hepatic events that is analogous to other antibiotics.

In fact, if you look at the record from Dr. Rullo's presentation and many other presentations today, this has been known since prior to approval and has been confirmed, and it has been an existing signal.

What we need to focus on is what the current questions are. Dr. Soreth really reminded us of that earlier today, and that is, in comparison to what. Is a hepatic risk really different with respect to comparison to other antibiotics on the market?

The second question is, is this acceptable given Ketek's particular benefit and risk And that

is critical and that relates to both the presentations this morning and also those that you will be hearing tomorrow.

[Slide.]

With respect to the significantly different from comparators, the basis for answering the question is, one, the signal has been known for some time and, obviously, it has been strengthened in a variety of ways, through the reporting rate analysis and the data mining disproportionality analysis. Even though those are non-quantitative, they do support and verify the signal.

[Slide.]

But as also explained by different presenters, the signal analysis of spontaneous reports are of limited value with respect to answering the quantitative risk question.

Spontaneous reports should not be quantified. There are many reasons for this but perhaps the most graphic representation was Dr. Rullo's time series of reports. Depending on when you measure the reporting rate, you are going to

get different reporting rates as she demonstrated.

There are many reporting biases. Remember, to have a report, an event has to be detected, attributed to a particular drug and, of course, there are many drugs that cause hepatic problems. But if it is attributed at that point to one of several, it might be attributed or not at all and then it has to be reported. We all know that only a tiny percentage of many events are reported although hepatic failure and serious reports are reported more frequently.

There are marked secular trends as mentioned earlier. The reporting rate has increased tremendously over the last 20 years and the reporting rate for hepatic events has doubled just in the past 5 to 10 years, essentially, reporting rates are just not a reliable estimate of incidence.

Now, actually, we have looked at this and published a paper in 1997 in Archives, actually looking at three types of spontaneous reports, hepatic, skin and GI, and, actually compared the

reporting rates to an epidemiologic database, in fact, the one that Dr. Walker has talked about, where, in fact, there is verification.

There was no correspondence between the reporting rate of those events and the actual validated events in that database and that illustrated it.

Actually, in 1983, at the request of Dr. Zimmerman, I analyzed all of the hepatic reports in the AERS database at the time, and the paper, which was published in 1983 in Seminars in Liver Disease, illustrate in many different ways various types of biases that are inherent in the database.

Finally, we recently have seen a New England Journal commentary published in the New England Journal, that relate to the Ketek hepatic events. It is important to realize for the reasons I have just mentioned that, in fact, this is a misleading commentary.

It is also misleading because it uses an estimate of denominator that is person-time. Now, with respect to short-term use drugs, you should

not use person-time, you should actually use individual exposures as an estimate of your denominator.

Person-time is very useful in epidemiology for chronic exposure but not for this type of exposure. So this is a crude estimate and probably does not reflect any estimate of risk, also because the spontaneous reports are not quantitative.

[Slide.]

Therefore, the only possible basis for really answering the question are through formal epidemiologic studies that have a defined denominator of exposure where you literally can identify every person by their demographics as to who is exposed and a detectable outcome or numerator. We will come back to that.

Now, Dr. Bradley mentioned that in the best of hospital worlds, you would really like to have a large randomized trial to look at these events, I mean that would be the most satisfactory evidence.

However, to do that for the rare events we

are talking about, we would have to have something larger than a Women's Health Initiative. We all know that took a number of years and was very complex. So we really have to come back to doing epidemiology studies to do this.

But they have a lot of advantages in the sense that you have a defined population, a short-term event and a sufficient large population.

[Slide.]

Now, there are a few features of these databases that I wanted to just point out.

The cases of severe liver injury are temporally associated with antibiotics that we heard but they are not necessarily causally related. It is very important to point that out.

You cannot study even if you had a much larger database acute liver failure, because, in fact, there is not an ICD diagnosis code for that. It would be very difficult. Again, you would have to have a huge database to have 1 per million.

The other issue has to do with the fact that even though you have a heterogeneous group of

diagnoses, hospitalization in these administrative systems serves as a fairly unambiguous marker of severity. There just isn't much fraud in the whole area of coding for hospitalization. Maybe codes vary but hospitalization is unambiguous.

Both studies that were presented just a few minutes ago were powered to rule out the very high risk estimate that we have seen expressed in the briefing book and in the New England Journal. The PHARMetric study was specifically powered to allow 4 times greater risk of severe liver injury.

[Slide.]

Another thing that you heard just a few minutes ago, but I want to point out, is that we have two separate populations of 12 million people, which is almost 10 percent of the U.S. population and they are separate. They are separate populations.

[Slide.]

The actual sample population represents about 5 percent of those who took telithromycin.

The other thing I want to point out is

that these are very, very large studies. In fact, I think they are the largest epidemiology studies of antibiotics and effects that have been done. The one in the PHARMetrics data had 124,000 people. That is very large.

As Dr. Dai presented, there was comparability between the antibiotics except for moxifloxacin and actually it was higher.

[Slide.]

The second database again looked at 102,000 people, which is important and, as Dr. Walker presented, there were a very small number of cases in the database.

I wanted to point out a couple of things. One is that there were a small number of cases that actually have severe liver disease but also the primary purpose of the analysis was to look at severe liver injury.

Now, when you have such marvelous database as that, and the ability to actually look at records, you do have the ability to look at other and broader types of liver disease, and, in fact,

this is what he did, but the primary outcomes were severe liver injury and the actual numbers of cases are very small.

It is important to point out that enzymatic elevations are not necessarily equivalent to severe liver injury. They may be, but they aren't necessarily.

[Slide.]

Further, again, the ability to look at multiple exposures is a very interesting finding. But it was not the purpose of the study and obviously serves as a signal and needs further exploration as Dr. Walker said. But it is not, in itself, a finding and it is only based on 3 cases.

[Slide.]

So, in summary, we had a signal in clinical development and spontaneous reports, and the data from these two retrospective cohort studies in PHARMetrics and Ingenix, which are the two largest health insurance databases available in the United States. You have data on over 200,000 people exposed to telithromycin in two independent

studies, which were actually done with a different methodology but came up with fairly similar findings.

It is clear that acute liver injury is a very rare event among these users and it appears that the risk does not differ from those for other oral antibiotics on the market.

[Slide.]

Just to summarize, I would just like to remind us to look at the data both with respect to the data you heard today and also what you are going to hear this afternoon.

[Slide.]

Essentially, the whole process of postmarketing safety is really based on case reports and other information about signals, that give you those signals, and a lot of the work, it really involves verifying and characterizing those signals, getting reporting rates, disproportionality analyses.

As you heard from Dr. Lewis and also you will hear this afternoon from Dr. Lee and Dr.

Brinker, you need to analyze those cases from a pathophysiologic standpoint, in fact, independent of the quantification, we need to find out what the pathophysiology and cause of these liver injuries are or we will never get anywhere in terms of preventing them and identifying them earlier.

The important thing to emphasize, however, is that these are non-quantitative. We will hear a lot of expressions of 1 in, whatever, 1 in 1 million, 10 in 10 million but, in fact, every time you make that estimate, you will probably get a different estimate because of secular trends in reporting, different definitions of what you are talking about, depending on how you are defining it, and it just should not be quantified.

[Slide.]

So you really need to go, if you can go to clinical trials, it is great. But many times in rare events you cannot because you need to quantify the risk, you need to compare the risks, and you really need to identify the risk factors.

This is what has been done here and I

think we have a situation where we have an assessed and quantified risk.

[Slide.]

So, going back to the question: does the data support that Ketek is significantly different from comparators? I don't think so. Two separate epidemiologic studies suggest that that is not the case.

Is it acceptable given Ketek's benefit-risk? Given the effectiveness data, and that has not all been presented. So that remains for tomorrow in part. But the issue of the profile of resistance in susceptible patients suggests that it should be looked at carefully. But, with respect to liver, the relative safety and rareness of events suggests that certainly the risk issue I think has been addressed and we will hear about the rest tomorrow.

Thank you.

DR. EDWARDS: Thank you. We are going to take a 15-minute break now and I would like to resume at 3:45.

[Break.]

DR. EDWARDS: We are going to move back to the FDA. We will begin with Dr. Allen Brinker, Epidemiology Team Leader, from the Office of Surveillance and Epidemiology, who will present their analysis of the hepatic adverse events.

Dr. Brinker.

FDA Presentation

OSE Analyses of Hepatic Adverse Events

Allen Brinker, M.D., M.D.

DR. BRINKER: Thank you very much.

I would like to point out, that was a great introduction, too, because you made a specific point to note that I was going to be describing our analysis, this FDA, in fact, this DDRE-specific analysis.

You have heard already one analysis presented by the sponsor of this case series, and we did another analysis this past winter, which I am going to describe. Then this past autumn, I have been engaged with two colleagues, special consultants from the outside, to realize a third

case series.

My job today is to walk you through the case material as adjudicated by DDRE and our remedy or recommendations, at least, to address this safety signal.

I am going to be followed in turn by Dr. Leonard Seeff, acting as an expert consultant to FDA, who is going to outline some principles of ALF causality assessment, ALF being acute liver failure. Then Dr. William Lee, also acting as an expert consultant to FDA, who is going to outline the telithromycin ALF causality assessment, as realized by this adjudication team.

[Slide.]

As an overview of my presentation today, I am going to summarize the DDRE review, specifically, the recommendations from that review, the conclusions and recommendations.

Second of all, I am going to breeze through the Methods Section because earlier speakers have already touched upon many of the caveats of spontaneous adverse event reporting.

Then, I am going to describe again rather quickly given the hour an analysis of the cases as adjudicated by FDA, and then in order to put these cases, this telithromycin and associated ALF into context, describe the concept of reporting rates as it falls within pharmacoepidemiology.

To do that, I am going to highlight two previous supporting ALF reporting rate analyses, which offer relevance and precedent to telithromycin reporting rate analysis that will follow and, finally, conclusions and status as of September.

[Slide.]

I would like to begin the DDRE review of telithromycin-associated ALF realized a broad spectrum of drug-associated injuries and, per our review, these 12 cases of telithromycin and associated acute liver failure were clinically remarkable with specific interest in their short time to onset of 4 days for the cases adjudicated by FDA, the level of profound hepatic injury including 4 deaths and 1 transplant and the fact

that many of these patients appeared relatively healthy and had few confounding factors.

[Slide.]

That being said, a reporting rate for telithromycin-associated ALF, as calculated by DDRE, was found to be similar to ALF reporting rates for selected comparators, specifically, moxifloxacin and gatifloxacin, given variation inherent in spontaneous adverse event reporting. Let me repeat that again.

Given inherent variation in spontaneous adverse event reporting, a reporting rate calculated for telithromycin-associated ALF was found to be similar to an ALF reporting rate for the chosen comparators, specifically, moxifloxacin and gatifloxacin.

[Slide.]

So we deemed, given that these reporting rates were similar, we recommended regulatory actions which were consistent with actions advanced previously for the newer fluoroquinolones.

In fact, these DDRE recommendations for a

warning for ALF within the telithromycin labeling were realized in June of this past year, one month following completion of the DDRE review.

[Slide.]

So, in addition, the DDRE review set a reporting rate level or bar, perhaps an arbitrary bar, for further regulatory action for telithromycin based on our experience with trovafloxacin-associated ALF. I will touch upon that during my presentation.

[Slide.]

Earlier today, you have already heard a lot about spontaneous adverse event reports. These are also known as MedWatch reports, because of the program that facilitates recovery of these reports from the general population.

In my opinion, they are designed to detect rare, serious and unexpected adverse events in association with drugs, and they are subject to substantial variation in information quality report to report.

[Slide.]

The fraction of incident adverse events attributable to a selected drug and reported through MedWatch or through the manufacturer is unknown. Estimates of 1 percent to 10 percent are commonly cited. In my opinion, these are likely to be overestimates and we know that there is variation between products.

[Slide.]

Today, I will be highlighting three separate FDA DDRE reviews of antibiotic-associated ALF. All three of these reviews utilize generally similar case definitions. Reports were included as cases if the totality of information could not exclude telithromycin or the suspect antibiotic as a factor in the liver injury, which is typical for FDA case series.

I will highlight inclusion or case criteria and exclusion or confounding criteria used in these case series.

[Slide.]

The first one I am going to highlight is that for telithromycin-associated acute liver

failure. This was conducted this past winter and spring by my colleague, Ron Wassel, and myself and it followed the market appearance in the U.S. of telithromycin in July of 2004.

[Slide.]

This was part of an ongoing review of telithromycin. We had done an earlier review in June of 2005 and we were aware of the cases as reported in the Annals of Internal Medicine letter and of the concern for hepatotoxicity as observed in controlled clinical trials.

[Slide.]

This case series, this consult identified cases of acute liver failure and acute serious liver injury.

[Slide.]

Acute liver failure was defined as a report describing: diagnosis of acute liver failure, or of acute and serious liver injury with encephalopathy, or liver transplant following acute illness, or death in the setting of acute severe liver injury.

[Slide.]

A case of acute serious liver injury was defined as a report of hepatic transaminase elevations, or hyperbilirubinemia, or clinical jaundice leading to hospitalization.

[Slide.]

Reports were excluded if an identifiable patient could not be identified. This is also known as a "hearsay" report. Reports were also excluded if they included a concomitant infectious hepatitis, sepsis, pancreatitis, rhabdomyolysis, cancer, or selected concomitant hepatocytoxic therapies.

[Slide.]

The initial case series that Dr. Wassel and I reviewed included 110 unduplicated, domestic--that is, U.S.--reports, of liver injury in association with telithromycin.

We excluded 31 of these reports as confounded or hearsay reports. We excluded an additional 44 as indicative of only minor liver injury.

That left 23 cases of acute serious liver injury and 12 cases of acute liver failure.

[Slide.]

As I alluded to earlier, in part of this process, we continued working up this telithromycin ALF with the help of some experts on the outside with regard to a causality assessment project.

In case you are concerned about how those numbers were realized, we submitted 109 unduplicated domestic reports of liver injury to Dr. Seeff. He adjudicated 38 of those cases as very likely, possible, or probably related to telithromycin.

To that 38 we added 12 cases that he did not include, he had not included, that were within our case definition of ALF or AFLI and, in addition, we added 3 cases from the DILIN network to result in a sum of 53 cases. Both Dr. Seeff and Dr. Lee will be describing these in more detail later.

[Slide.]

So, the DDRE review realized 12 cases of

telithromycin-associated ALF. The median age of the 12 cases was 52 years. Most of them were female. The majority of them received telithromycin for sinusitis.

[Slide.]

As I suggested earlier, these reports were remarkable for the latency of 4 days with the median time to onset of symptoms from initiation of treatment and 8 of these cases presented with jaundice at diagnosis. These cases were also remarkable for their remarkable serum hyperbilirubinemia and transaminitis.

[Slide.]

In terms of outcome, 4 of the cases resulted in death and 1 patient underwent liver transplant. Dr. Lewis reviewed this patient with you earlier, so I won't go into detail other than to say that this would be considered a very good case and one that was a very compelling case.

[Slide.]

Here is the distribution of these 12 cases that the FDA had received through April of this

year. That is 12 cases through April. We have received a 13th case in June of this year, so that is a second case from the second quarter of 06 and we have received no cases in the third quarter of 06 or no additional cases as of today.

[Slide.]

Now, in assessment of these cases, this case material, in and of itself, was sufficient for the addition of serious liver injury including ALF to the telithromycin label and, because of the severity of the outcomes, and to be commensurate with other products, this would definitely constitute something along the lines of a warning.

But as has been answered earlier today, what is this risk? What is the risk of telithromycin-associated ALF compared to the risk of other agents? To this end, we are sometimes forced to rely on reporting rates.

That is the nature of the beast for these profoundly rare events and I am going to provide you two analyses which we used to buttress our argument for our recommendations for telithromycin.

[Slide.]

But first I want to talk briefly about the concept of reporting rates and that they typically come in two flavors, drug against drug, and an observed versus expected comparison.

[Slide.]

They are calculated by division of spontaneous cases of a selected event or a selected drug over the exposure or utilization of that same drug. They are typically expressed as cases per million prescriptions or, in today's case, per 10 million prescriptions, or as an incidence density as cases per unit person-time.

They are typically restricted to cases that arise during oral or ambulatory therapy, because that is where our denominator data lies.

[Slide.]

Now, as has been highlighted earlier, spontaneous reports data, such as these, offer very limited insight into population risk and reporting rates are not incidence rates. However, reporting rates have been used in addition to other data to

support previous regulatory actions by the agency and large differences in reporting rate ratios may support a differential in risk.

I will give you two examples which offer differences in reporting rate ratios.

[Slide.]

In terms of drug-against-drug reporting rate comparisons, such comparisons require very similar drug products. First and foremost, they should come from the same class and hopefully have the same spectrum of indications.

The second thing to consider is that they should have similar times on market. We also have to assume that reporting practices are similar for similar drug products over the observed reporting period.

[Slide.]

So, the first case series which I am going to highlight is acute liver failure in association with trovafloxacin. The second with acute liver failure in association with the newer fluoroquinolones, specifically, moxifloxacin,

gatifloxacin and levofloxacin.

[Slide.]

This consult was completed in 1999 by my colleagues David Graham and Sarah Singer. It included a drug-against-drug reporting rate comparison for trovafloxacin versus levofloxacin.

[Slide.]

Here is a table summarizing specific data elements as presented in that consult. The first thing I want to point out to you is the two drugs here on the left and their U.S. market appearance, which was about a year from each other and that is about as good as we get in terms of reporting rate ratios.

The second thing I want to point out is what we see here is U.S. cases that were adjudicated or realized in their review, and then the prescription, the utilization data over here.

So when you take this case count and you divide it by that prescription, you get this reporting rate of 1.5 for 10 million prescriptions for levofloxacin in comparison to 58 for 10 million

prescriptions for trovafloxacin, so again that is a difference of 12 to 1 in absolute counts or 58 to 1.5 in counts adjusted for utilization.

[Slide.]

So, as I said before, that is a 12 to 1 absolute ratio and case counts, and 39 to 1 is the reporting rate ratio.

[Slide.]

In large part because of these data, regulatory action was undertaken for trovafloxacin in 1999 and it was restricted to initial therapy for in-hospital use for the treatment of life and limb-threatening infections.

[Slide.]

The second analysis I am going to show you is one that I conducted along with Sarah Singer in August of 2004, and it included a reporting rate comparison between the newer fluoroquinolones.

[Slide.]

Again, here is a table summarizing some of the data elements realized in that study and, to this end, I want to point out that again we have

all three fluoroquinolones, which makes a pretty good match given the spectrum of these drugs.

The window here is a little bit wider. It's about 3 years, 3 years in comparison to 1 year, and that does offer the introduction to some bias especially against the newer drugs, because of secular trends in reporting.

That being said, this consult realized 12 U.S. cases at this point of acute liver failure in association with levofloxacin in comparison to 6 for gati, and 5 for moxi and these, in turn, realized reporting rates of 2.1 per 10 million for levofloxacin and about 6 per 10 million prescriptions for the two, more recently approved, fluoroquinolones.

[Slide.]

So the absolute ratio in case counts, that was a comparison of about 12 cases to 5 and 6 cases, was about 2 to 1, and the adjusted rate ratio--this is a comparison of the reporting rates--was about 3 to 1.

[Slide.]

So we believed that these observed reporting rates, given the inherent variation in spontaneous reporting data, were not consistent with the difference and we believe that these ALF reporting rates were indeed similar.

So DDRE recommended a discrete warning for ALF within product labeling for all fluoroquinolones.

So, with those two analyses as background, that takes us to where we are with telithromycin.

Now, the problem, if there is one with telithromycin, is the fact that there is not a great comparator drug. There were two recently approved, relatively recently approved oral antibiotics but those drugs had small utilization in comparison to telithromycin, so we chose to use, as our comparison, the ALF reporting rates as generated for moxifloxacin and gatifloxacin.

[Slide.]

So here are the 12 cases that I described earlier and, after consideration of their denominator data, their utilization, that realized

a reporting rate of 23 per 10 million prescriptions in comparison to 6 for the two fluoroquinolones.

[Slide.]

We see an absolute ratio in case counts of about 2 to 1, an adjusted ratio in case counts or reporting rate ratio of about 4 to 1 against telithromycin.

[Slide.]

However, we concluded that these were generally similar given the adherent biases in spontaneous reporting data. Indeed these were not consistent with the data at hand when trovafloxacin was removed from the market with an absolute ratio of case counts of 12 to 1 and an adjusted ratio of 39 to 1, not that you have to hit that bar, because remember these data are primarily driven on safety, they are not being driven on benefit. So there is not necessarily anything magical about hitting 12 to 1, or 39 to 1.

If the benefit of telithromycin is such that we can't tolerate any--then, we have cases--but that is a question that is up to the

Committee.

We recommended regulatory action similar to that advanced for the recent fluoroquinolone-ALF review and, as I said earlier, those were realized.

[Slide.]

But we also realized that the cumulative telithromycin acute liver failure reporting rate was increasing, and that rate was calculated to be 12 through December of 05, it increased to 17 through February of 06, and 23 per 10 million prescriptions through April of 06.

We also realized that liver injury was a concern pre-approval and that was to be addressed within a specific study. Study 3014 was designed in part to address that issue. It is not often that a large safety study is advanced for a drug, so that, to us, represented quite a prior, that there was a substantial prior knowledge that this was a potential hepatotoxin.

[Slide.]

So we suggested a bar, granted arbitrary but a bar nonetheless, for further regulatory

action should the ALF reporting rate for trovafloxacin meet that of the one for telithromycin, meet the reporting rate observed for trovafloxacin of 58 per 10 million prescriptions.

Yet, again, we would not wait for an adjusted ratio of case counts, an absolute ratio of case counts at 12 to 1, or an adjusted ratio of 39 to 1.

[Slide.]

Now, as I said earlier, a 13th case was added in the second quarter of 06 and, in consideration of the utilization or exposure data, the current reporting rate for telithromycin-associated ALF is identical to what it was in April of 2006, at 23 per 10 million prescriptions.

[Slide.]

Before I finish I do want to highlight the fact that the sponsor last week submitted two epidemiology studies to us, that completed by PHARMetrics and one completed by I3 Drug safety.

Needless to say, the review of these

studies is ongoing and our comments at this time are preliminary.

[Slide.]

That being said, both studies appear underpowered for serious liver injury and, to that end, are woefully underpowered for drug-associated acute liver failure.

Medical record validation is vital and this was done in the I3 study. It was not, however, done in the PHARMetrics study.

So my last comments pertain only to the I3 study. It is interesting that the point estimate raised for severe liver injury is consistent with an elevated risk for serious liver injury for telithromycin in comparison to clarithromycin, however, the point estimate is above 1 and the confidence intervals are wide.

Also the I3 study did show a remarkable elevated risk, as Dr. Walker said, an odds ratio of around 100 for sequential for serious liver injury following a sequential use of telithromycin and clarithromycin. This was indeed based only on 3

cases but it deserves further attention and further study.

I will now follow the Chair, if you want to go directly to Dr. Seeff? Very good.

Hepatotoxicity

Assessment of Causality in Drug-Induced Hepatotoxicity

Leonard Seeff, M.D.

DR. SEEFF: My name is Leonard Seeff, and as you can see from the slide, I am in the Liver Disease Research Branch at the NIDDK, National Institutes of Health.

A couple of months ago, Dr. Serrano, who is sitting in the audience and is the project officer for a study that I am going to describe to you, and I received a call from the FDA indicating that since they were our sister agency, would we be willing to review cases that they had received of potential Ketek telithromycin hepatotoxicity.

So one never says no to one's sister and we decided we would go ahead and review the cases. However, as I guess everyone here knows, and as

Jim Lewis indicated a little earlier, one of the big issues of trying to identify drug hepatotoxicity is that it is very difficult to diagnose.

One would like to establish with some certainty the phenotype for future genotype studies which are going to be done and which we plan to do in the future, as I will describe. But fortunately, we happened to be doing a study supported by the NIDDK. This is called the Drug Induced Liver Injury Network study, or DILIN, and one of the components of that is to focus attention, in fact, on establishing causality.

[Slide.]

Well, I guess, first of all, I should say that I have no conflict.

[Slide.]

But let me set the stage--you don't need to, but I will--and say Dr. Zimmerman, who everyone here seems to have had some relationship with, and I think I actually started with Hy while Jim was still in his short pants, because I started working

with Hy in 1965.

But that aside, there are two forms of hepatotoxicity, so-called intrinsic toxicity and host idiosyncrasy. The intrinsic toxicity, of course, is not the issue, this is predictable and this is quite common. The problem is the host idiosyncrasy and the issue of how you diagnose that.

[Slide.]

Let me remind you that there are three broad categories of liver injury that are associated with idiosyncratic hepatotoxicity: one that simulates acute viral hepatitis, so-called hepatocellular liver disease, one that simulates obstructive liver disease like gallstones, so-called cholestatic liver disease, and then the mixed picture where you get both hepatocellular and cholestatic liver disease.

But I also remind you that in actual fact, there is no form of liver disease, whether it's acute or chronic, that is not mimicked by drug injury. That is where the problem lies, because

drugs can indeed cause not only acute injury but chronic injury and even neoplastic disease. But the focus of attention particularly in this regard is with the acute injury.

[Slide.]

So how do we go about diagnosing hepatotoxicity? Well, unfortunately, there is at present no biomarker. The study we are doing, which I will describe to you, is one in which we hope in the future we will be able to come up with a biomarker and it is even conceivable that there may be multiple biomarkers for each class of drug.

So, for the moment, because hepatotoxicity can simulate all known causes of liver injury, its diagnosis is a diagnosis of exclusion, and I underline that because this is essential in trying to come up with a diagnosis, to be able to exclude anything else that drug injury can simulate.

So what instruments are there, that are available?

[Slide.]

A little history, but not entirely

historical because it is still being used, and that is there were a couple of instruments that were developed, the first one in 1989 called RUCAM. There was a meeting that was held in Paris in 1989. It was supported by Roussel Uclaf and, hence, Roussel Uclaf Causality Assessment Method, or RUCAM.

For that process, there were 7 points that were awarded, points were awarded in 7 categories in assessing the likelihood that a drug is responsible for injury of the liver.

A little later, in 1997, there was a publication that came out of Portugal from Maria and Victorino. It was called the M & V Scale. It was slightly different. There were some aspects of it that were similar but somewhat different. But subsequently it was looked at and found to be less effective than RUCAM.

In actual fact, RUCAM is a process that is used commonly, and I understand that many pharmaceuticals and others who assess hepatotoxicity commonly use RUCAM. The reason I

raise that is because I will talk to you a little later about our sense of the effectiveness of the RUCAM system, which leaves expert opinion.

[Slide.]

Much of what we have heard today is expert opinion and the experts have spent a lot of time looking at the disease of drug hepatotoxicity, trying to come up with a conclusion, is there a relationship between the drug that was received and the development of the injury.

The other thing that I have got here in parentheses is the Bayesian Adverse Reactions Diagnostic Instrument, is something that we have an interest in and will, hopefully, in the future, be able to use something like that, that may be more helpful in making this diagnosis.

[Slide.]

So, that led us to the development of this Drug-Induced Liver Injury Network, or DILIN, which is a network which is supported by NIDDK to study the issue of drug-induced liver injury.

[Slide.]

Just to let you know, there are 6 investigators involved, names may be familiar to you. Most of these are well-known hepatologists who have a lot of interest in this area: Paul Watkins, Herbert Bonkovsky, Naga Chalasani, Timothy Davern and Bob Fontana from Michigan. These are the clinical investigators and then the person who runs the Data Coordinating Center is Jim Rochon from Duke University.

The NIH folks involved are Jose Serrano, whom I mentioned, who is the project officer, and Jay Hoofnagle and myself, and FDA Advisor John Senior and Mark Avigan have been very helpful in helping us to run the study.

[Slide.]

The study consists of two components. One is a limited retrospective study for which we are focusing on four well-established causes of DILI, well-known drugs that lead to drug injury, isoniazid, valproic acid, phenytoin, and Augmentin.

This is retrospective people who have been exposed in the past and have been reported to have

developed injury. We are going back to them, getting information from them and, as I will show you in a moment, drawing blood and other samples from them and then matching them with individuals who received the same drugs and did not develop injury, in the hope that we can do some genotyping and perhaps define perhaps a basis for the development of the injury.

[Slide.]

But more important is our prospective study. In this case, we are enrolling all instances of drug-induced liver injury that we can come across. I should actually have put in here that includes not only conventional drugs but also herbals. Indeed, we have a number of herbals, as is not surprising, that are in our present database and, at the moment, we have a little over 300 cases that we have collected.

[Slide.]

So what are the objectives of this study? I will come to the reason why I am giving this all to you.

It is to provide a prospective clinical database on unselected cases of hepatotoxicity;

To obtain biological samples for studies on the pathogenesis of hepatotoxicity using biochemical, molecular, immunologic and genetic techniques;

To evaluate susceptibility and genetics of drug-induced liver injury;

To provide the foundation for the development of molecular screening tools to prevent or predict drug-induced liver injury;

To provide a stimulus and resource for research and clinical investigation of all forms of drug-induced liver disease;

And finally, relevant to the present discussion, to develop standardized definitions, grading systems and clinical instruments to identify and assign causality to cases of suspected drug-induced liver injury.

[Slide.]

So we, after getting together with our investigators, decided that we would use two

approaches.

The one approach would be the expert opinion. But we would do our best to refine it, to improve upon the whole process of expert opinion and we decided we would use RUCAM and we would compare the two.

As a quick aside, we struggled with the RUCAM. We didn't quite know how to fill it out even though people have used it. We eventually had to call--one of our investigators had to call one of the people that actually developed it, Dr. Damon, to get some instructions as to how you actually use it, because there are parts of it that are really just not explained.

That, in fact, led to an interesting process that will probably lead, we hope, to a publication in the future and that's a separate issue.

[Slide.]

So what we do in order this will have relevance for telithromycin, is that each case that comes to the attention of one of the investigators

is evaluated in a standardized and formalized fashion with collection of medical history and all--again I emphasize all--laboratory test results because this is critical.

This is actually what was a lot easier for us in this study, because we can do that whereas, with the telithromycin, as the information comes in, we don't always have all the laboratory results we would like.

We are collecting serum, urine, PBMCs and DNA, and they are going into an NIDDK repository for future evaluation.

Each case is evaluated by a panel of experts, and I will show that to you in a moment, to establish an assessment of causality. We are interested in determining whether any of these cases go on to chronicity so we follow up all the cases 6 months later to determine whether the biochemical abnormalities have resolved or not and if indeed we think that they are a consequence of the drug-induced liver injury.

[Slide.]

So we developed a Causality Committee, which is a subcommittee of our Steering Committee, and it happens to consist of one PI or designate from each of the 5 clinical sites, a member of the Data Coordinating Center, and then a member from NIDDK.

The cases, I will show you the process in a moment, that are received by the investigators, ultimately are adjudicated by three members.

The Causality Committee meets monthly or bimonthly to discuss the cases and to reconcile any differences that might have existed in coming to a conclusion.

If the three members cannot agree, the full Committee convenes and we vote on the case.

[Slide.]

Let me show you how we do this. A case is identified in one of the clinical centers as a potential case of DILI, the PI identifies it.

The PI downloads a CRF from the DILIN website which has been developed and completes the CRF with all the information, the clinical

information, the biochemical results that we are looking for and we have a whole list of things that we are asking them to fill out.

That form is then forwarded to the Data Coordinator Center that cleans the data, extracts a pre-defined subset from the CRF, inserts the information into specially designed data forms to distribute through the DILIN website to the Causality Committee.

The Committee then that received this information can download it, the data forms, and then they are to review the case, and this is to be done independently. We don't know what the other persons have to say.

There is a Data Completeness Checklist to make sure that all the things that we believe are necessary to exclude other competing causes have been, in fact, checked off. Then, once we have made a decision, we come up with a clinical assessment form, a severity form and we also do the RUCAM, and then later on compare.

The completed forms are then returned to

the Data Coordinating Center, who arrange for a teleconference to discuss the cases. Then all the investigators, the entire group, not only the three but all of us get together, the Causality Committee reviews and, if necessary, reconcile the scores in a teleconference and, ultimately, these results are recorded by the Data Coordinating Center and the PI is notified for later selection of controls, which is what we will be looking for.

The reason I show this to you is that this is approximately the process that we used when we were asked to review the cases of potential telithromycin hepatotoxicity.

Just to again emphasize that the Data Completeness Checklist consists of 24 Yes/No questions for the retrospective and 41 Yes/No questions for the prospective study. We have 1 question that the investigators ask about the degree of completeness, do they think that all the information they needed was in this form.

One question they ask if more information is needed and then, having reviewed the case and

come to a conclusion, the clinical assessment form is filled out--and I will show you the scale that we are using--the Clinical Severity Form is filled out, and I will show you that scale, and then the RUCAM is filled out and sent to the Data Coordinating Center for future assessments.

[Slide.]

So what is the scale that we have decided to use? We decided to have these five different categories. We believe it's definite, highly likely, probable, possible, or unlikely, and we give a figure here. Of course, this appears to be very soft. But we have defined descriptions of each of these.

This is formulated, some of this is using actually legal language, for example, the definite is beyond a reasonable doubt. There are many other things. The highly likely is clear and convincing. The probable is preponderance of the evidence, and so on, and so forth. But we have got a much more defined description of what we believe each of these categories would represent.

[Slide.]

As far as the severity, and this is very important particularly in the instance of clarithromycin, for the DILIN study, we have decided to grade the severity of disease into one of four grades.

Grade 1 are individuals who have raised aminotransferase or alkaline phosphatase with a total bilirubin less than 2.5, an INR less than 1.5, and are not hospitalized for DILI.

Grade 2 are those who have the same thing but the bilirubin is raised. Either the bilirubin is raised or the INR is increased beyond 1.5, but they are not hospitalized for DILI.

Grade 3 are individuals who are hospitalized for DILI or their hospitalization is prolonged because they developed DILI in the hospital while being treated for something else and that will give us Grade 3.

Virtually, all of these will have bilirubins greater than 2.5, and the final category is death or liver transplantation due to DILI.

So these are the outcomes that we are seeking.

[Slide.]

Just as everyone else, we face the problem of multiple drugs and ask the question, is this DILI, that this accounted for hepatitis A, B, C, autoimmune hepatitis, fatty liver disease, et cetera, et cetera, we go through the whole thing and, if we believe it is, then, we try to assess which is the likeliest culprit. If we think that there may be more than one drug is possible, we may grade these, and they will be adjudicated separately.

[Slide.]

Now, let me make one point about RUCAM. We, as I say, struggled a little bit with the RUCAM. This is just the conclusion of an abstract that we have submitted for a meeting that's coming up in May with regard to RUCAM. Don Rockey, who is working with us on this, is the first author and let me just read to you what this says. This is the final assessment.

That causality assessment in DILI is complex and not well standardized. The RUCAM system, although widely used, exhibits substantial inter-individual variability, and correlates in our study rather poorly with either retrospective or prospective identified cases with scores assigned by the experts. We concluded that in routine clinical practice, expert opinion is likely to be more reliable than RUCAM but it requires standardization in definitions and scales of likelihood.

One of the important components of this study is, in fact, to improve on our causality assessment and maybe to even consider the possibility of tweaking RUCAM a little bit.

With that long introduction, let me then move to telithromycin.

[Slide.]

Having been asked to look at these cases, the cases came to us, I guess came to the FDA via the MedWatch process, as we heard, and that 53 cases were selected. We didn't select them. They

were selected for review by the FDA Drug Safety and Rick Management Group, and they were sent to five of us who represented the adjudication committee.

DR. Mark Avigan and Allen Brinker from the FDA were two of them, William Lee, who is going to be giving you the information you really want to hear about the signature that we think we see in these cases, from UT Southwestern, and then Jose Serrano, and me from the NIH. The important thing is that we all looked at this independently and as I showed you in one of the earlier slides, this information is then sent in to the FDA.

[Slide.]

We decided to use as an assessment our probability scoring system that we are using in DILIN and the severity scales, and that is what we are using. I will show you the numbers in a moment and leave it to Will, who will follow me, to describe in detail, what we found in each of these cases.

So, just to reemphasize that the results we evaluated independently, submitted to the FDA,

and then we did have conference calls, and we had long, involved, frequent, and I think Will is going to tell you how long it took us to go over each of these cases.

This was not done quickly. We worked very hard at it. I actually just want to go back for one moment to one slide I meant to mention. It is this slide actually that I want to show you.

[Slide.]

When we first looked this independently, we had not had a chance to conference on this at all. We each looked at this, five of us, and what we came up was the view that 11 cases were very likely, 19 were probable, 14 were possible, for 8 there was insufficient evidence, and that is a very important 8, number of cases, and 1 was unlikely.

You will see we don't have any definites. We decided not to put in definites because our definition of definite is that it has to be a case that is well recognized, has previous information to support this, possibly even individuals who perceive it again and therefore run into trouble.

We didn't think we could do this with a new drug, so, in fact, our top category was very likely.

When we had the chance to then go over them, we modified our outcomes, not terribly much it turns out, which was rather surprising. But I think was for us good news as far as we were concerned, that the 11 dropped to 9, the 19 probables remained, the 17 possibles increased from 14, 8, there was insufficient evidence and there were none now that were unlikely.

I remind you that the insufficient evidence does not mean that these are not cases on drug-induced liver injury, it is just insufficient evidence to be able to come to the conclusion.

[Slide.]

We also then gave scoring of the severity using the scale that I just mentioned to you.

15 percent, 8 or 15 percent Grade 1, which means all they had were elevated enzymes and normal bilirubin and INR, not hospitalized.

One had elevated bilirubin but was not hospitalized.

37 or 70 percent of the cases that was saw were hospitalized, we believe, for drug-induced liver injury and there were 7, Grade 4 cases that had a severe outcome, either death or liver transplantation. That will be discussed in detail by Dr. Lee, who follows me.

[Slide.]

My final slide. We don't have a biomarker for drug-induced liver injury, not yet. We are hoping that the DILIN study that we are working on will ultimately permit us to develop one and it may or may not be a single one.

It may be more than one. But if we are going to assess cases and try to come up with a conclusion, I have done this now, shown it to you three times in different colors, we need complete information, complete information to permit exclusion of competing causes for liver injury.

So we must, when we get cases sent to us of abnormal liver tests and a temporal relationship to the use of a drug, we must exclude all other things that could be, in fact, responsible,

hepatitis A, B and C, auto-immune hepatitis, fatty liver disease, iron overload, and so on, and so forth, and we have a whole series.

Given that, I will stop at this point and turn it over to Will to describe the cases as we actually saw them.

Review of Clinical Cases and Perspective

William Lee, M.D.

DR. LEE: Len, thank you for that kind introduction. It's my dubious distinction to be the closer today, so I will try to give you some data on this very rigorous assessment that we put ourselves and these various 53 cases through over the course of the last couple of months.

[Slide.]

As has been said, I am at UT Southwestern. I am also the principal investigator for the Acute Liver Failure Study Group, and you can find us, should you be interested, at acuteliverfailure.org.

[Slide.]

I have no disclosures.

[Slide.]

Let me give you the overall tenor of this last and somewhat short talk. I think my brief is to discuss the liver safety toxicity issues with telithromycin based on review of these very interesting 53 cases.

Certainly the process Len has reviewed in detail. But we started after the Annal cases came out, and the attention was brought to FDA and to us as expert consultants to look at this data independently.

As you have heard, there were 112 or 113 cases, I guess, and we were given the 53 cases that actually is a very good data set because it has been laundered in a sense for cases where there wasn't enough data or where there was certainly a serious confounding issue.

I think what you will see here is that for the most part, it's never perfect as Len has just told you, the data was there for these 53 cases.

Again, we met a number of different times on two-hour teleconferences. We were reviewing all postmarketing data, both AERS, MedWatch and DILIN,

and we had an individual discussion having all the CRF material that we had in hand. Our task was to develop, not a consensus on each case, but an opinion. What I mean by that is that there was not uniform agreement probably on more than a handful of cases, but we were all within one block from each other. In other words, if most said if was very likely or highly likely, then, maybe one other person said it was probable.

So, again, we were very close in our assessments once we finished. Again, we used the DILIN system and some of the differences in the numbers between Jim Lewis' presentation and our presentation, and the other ones that referred to ALF, of course, have to do with the differences in these definitions.

As you heard, the DILIN definition for a Grade 4 is a case that either dies or has a transplant. Now, there are clearly ALF cases that don't reach that very severe threshold, so some of the differences in numbers, if I say 7 and Jim Lewis said 9 or 12, those are the differences

between ALF and death or transplant as a separate category.

Again, our Grade 3 cases in terms of severity are those who made it to the hospital and that is an interesting group to drill down on, because they are severely ill but, again, don't make it to encephalopathy.

[Slide.]

Just to show you how we came together as a group over the conference calls, this slide categorizes the amount of variance in fractions of a single grade, if you will, between the starting point for each of us having reviewed the case individually and where we got to after we finished the conference call and came to an opinion, again, not a consensus.

We used in our data reporting sheet, both the mean, which would be the aggregate score divided by the number of scores, or the mode, which is the score that was given by the most numbers of people. But, in any event, you can see for the zero category, the insufficient data category, our

variance declined and, in each case, our variance between individual opinions and then the group's opinion was relatively small and certainly diminished by the time we finished 6 conference calls.

[Slide.]

Again, these cases were discarded, for other obvious cause, insufficient data or minor abnormality. Again, we are looking at these cases. I think this has helped me at least, who was quite skeptical about these cases, to sort of see the pattern emerge as we went over the cases in some detail.

[Slide.]

Again, others have commented on this but the first point is that the very severe cases particularly have this very rapid onset. I think that is a signature of the cases and something that hasn't been emphasized as much is that many, but not all, maybe 30 or 40 percent of them have prominent fever, diffuse joint aches, and a surprising number, right upper quadrant pain.

The resolution also can be relatively rapid. I will show you some individual clinical examples of people who came into the hospital with an acute febrile reaction, liver enzyme elevations in the hundreds and then, within a week or two, would be nearly resolved and didn't have a long hospital stay but, nonetheless, had a significant hit to their liver.

Some of the cases were subacute, and again we have discussed that, nausea and the 51-year-old physician's wife, who seemed to have a chronic illness that went on for several months, however, remember that that case at autopsy had a 450-gram liver that showed massive necrosis. So autoimmune it might have been but I don't think so.

The other unusual features, which again haven't been brought up to my mind so far, are that there were about 8 of these cases had ascites, very unusual for what looks like an acute illness.

I think it is not cirrhotic ascites, it can't be cirrhotic ascites in this sense because many of them, they came in the hospital with this

acute febrile illness, the diffuse aches, the right upper quadrant pain, and, within a month, let's say, they would be better and back to health, and they had no previous illnesses.

There were a couple of cases of rhabdomyolysis in this set. Again, in the setting of massive liver enzyme elevations, but also some CK elevations--and we could argue about whether these cases really are an ischemic event or a primary hepatic event and I think we really don't know about that. That is a hard point to come down on.

There were a number of cases that had prominent eosinophilia, again about 8 or 9.l

[Slide.]

Now, I am going to walk you through this sort of grid pattern that I have developed to sort of highlight what the cases looked like, again, just to explain this sort of busy picture.

The severity grade again, 4 is the 7 cases who died or were transplanted. Three is the next grade level, which Len outlined, which is 37 cases

that were hospitalized. Then there are 9 cases that were either Hy's Law cases basically, severity Grade 2, and the one case here that is ALT elevations, the Grade 1, 8 cases, it is the ALT elevations. So we are overall again talking about 53 cases.

Now, across here, is going from "very likely," which again as Len showed you, is 75 percent to 94 percent, to "probable," which is 50 percent to 74 percent, and "possible" is 25 to 50 percent, "unlikely" is 0 to 25 percent, and insufficient data over here.

Again, if you look at this left upper quadrant here, what you see is that amongst the greatest severity cases, we graded only 2 out of the 7 as "very likely" or "probable," but there still were 4 that were "possible," and again this is still a gray zone for sure.

Under the hospitalized cases, we had a total of 19 that were either "very likely" or "probable," and 11 that were "possible." Down here, you get down to sparse numbers of cases and

perhaps less significant.

So, overall, 37 cases hospitalized, a total of 44 hospitalized if you include the Grade 4 and Grade 3 groups here, 28 overall, "very likely" or "probable," and additional 17 "possible."

Again, the case quality was good in that we could come up with an assessment and we only found 8 to have insufficient data.

[Slide.]

Again, I have laid this out already. The mean age was 59 but there was quite a wide range. This is just looking at the ones who died. There were again 5 women and 2 men in that group. Three of the 7 had ascites, not counting 1 woman with renal failure who was on peritoneal dialysis.

Two of the 7 had fever, 3 had abdominal pain. I got a mean AST of 2288, again, in these very severe and fatal cases, the latency was five days.

[Slide.]

There was acetaminophen, there is always mention of it in any patient that comes in with a

febrile illness. I have done a lot of work in this area. I was pretty unimpressed with the amount of acetaminophen in the CRFs. But again this is information that we don't always have particularly in these cases where they come in obtunded or very ill.

There certainly were no amounts given and no inclination in any of the case reports that these were suicidal intent.

Interestingly, there was tissue on 3 of the 7 cases, 2 showed massive necrosis and this 1 showed cirrhosis although I am not sure any of us have seen this biopsy. I would love to see if I had the chance because again massive necrosis with hepatocyte regeneration can give you a nodularity particularly in somebody who has hung around for 6 weeks after the initial insult.

Again, most of our cases had adequate viral serologies that were all negative and had adequate imaging studies that excluded things like biliary tract disease.

[Slide.]

For the overall cases, again many of the hospitalized cases were quite severe. The latency was longer, however, the mean AST was still quite significant. I know Jim and I differ a little bit on those numbers but again it sort of depends on whether you pick the peak level or whether you pick another or admission level.

Again, a number did have concomitant renal failure. There were many that had elevated INRs and, interestingly, contrary to what we usually have, we usually have very few biopsies in these DILI cases, we had 9 out of 53, and that is a lot in my book. Virtually all of them showed severe necrosis or something that was either called chemical hepatitis.

Again, these were not reviewed in detail by a hepatopathologist to my knowledge. These may have been out in community hospitals and we get just this one phrase such as chemical hepatitis, compatible but not necessarily diagnostic.

[Slide.]

Here are some of the cases. Again, some

of them have been mentioned and, in each of these cases, I put out a probability score and our severity score down at the bottom. A 80-year-old male given Ketek for bronchitis. Three days later he comes in and has amazingly elevated aminotransferases, I think in the 3800s, and dies on the sixth hospital day. But we didn't have detailed labs available. Again, I don't remember exactly what the aminotransferases were.

But he comes in with no significant past medical history, no drugs, and no viruses. So this looks like it could be a Ketek case. But you never can exclude ischemic hepatopathy, although there was no known hypertension in this instance.

[Slide.]

Another severe case, and again we often think that DILI happens more often in elderly people. I am not sure that really is the case. I think elderly people are likely to be on more drugs. But, in any event, this 85-year-old woman had taken Ketek for 7 days for community-acquired pneumonia. On the 8th day came in with very high

aminotransferase levels, as well as an increased troponin level.

Now, let me say that you can have acute liver failure due to any cause and have an elevated troponin, so again you would say this could mean myocardial infarct, it doesn't necessarily in this setting.

In our Acute Liver Failure Group, 70 percent of our patients have an elevated troponin, meaning there is a multi-organ failure effect going on. But again in this individual, blood culture is negative, not known to be hypertensive, develops liver failure, and dies. Again, the details of the hospital course were not there.

We saw no confounding issues, gave it a probability score of 3 again, which is probable, not very likely, but probable, and the severity score of 4, because she did die, as well.

[Slide.]

Now, here are some milder cases. Again, these are ones that got hospitalized, clearly had a significant illness and perhaps, because they are

not elderly at least, they might have less comorbid conditions.

A 31-year-old health care executive, I don't know why that is important but maybe it is. URI led to two courses of Ketek back to back. I think this is another theme that comes out a little bit is there are at least 4 in this series where there are repeated courses and probably 3 more where there was multidrug allergies in their past.

Here is two courses of Ketek back to back. On Day 14--I am assuming two, 5-day courses--a couple days after finishing the last course, he developed this high fever, shaking chills, in this instance no right upper quadrant pain, all imaging and serologies negative, medium size aminotransferase levels, no bilirubin elevation and his PCP admits him over two or three days in the hospital, says it is highly probable that this is drug-induced liver injury due to this antibiotic.

Now, again, PCPs are often very timid about making this kind of claim, so this sort of stuck out in my mind at least. Again, we said on

that one, probability score of 4, very likely, and severity was 3.

[Slide.]

Again, another milder case, 27-year-old male, no other complicating features, no other meds. One day after completing a five-day course, develops dark urine, he has already got a bilirubin of 8, again enzymes that are in that intermediate range that Jim Lewis described.

This case has a little bit of a cholestatic flavor in that the enzymes are elevated, but not as high as the alkaline phosphatase or bilirubin. So this is what we would call a mixed case.

Again, the INR is not prolonged. It is not a pure hepatocellular case, nor is it a severe case, but all viruses were negative and again the primary care doctor said there is no alternative explanation to this event and again I think the imaging and the virus serologies had all been pretty clearly laid out.

[Slide.]

Here is an ascites case. Again, if you question whether these patients have cirrhosis, let me show you this case. A 22-year-old took Ketek for one course and then at Day 12 began a second course. At Day 14, nausea, vomiting, abdominal pain and fever, pale and weak. No other history.

She comes in with again moderately elevated enzymes and bilirubin, large ascites, bilateral pleural effusion. This sounds like a serositis.

Hospitalized briefly began to improve, labs returned to normal within a month. No underlying liver disease before, no apparently liver disease after.

[Slide.]

Another ascites case. 37-year-old male with one week of Ketek. Admitted with fever, right upper quadrant pain, nausea. Again, moderately elevated enzymes, INR starting to go out. Prominent ascites. This man had an ultrasound showing the same thing, had 800 ml of clear fluid removed, documenting that it wasn't an

insignificant amount.

All the tests were negative. Again, we ought to try in the future to get the paracentesis data, not just the fact that it was "negative," but what the cell count was, and so forth.

Hepatitis serologies all negative. Hospitalized briefly, began to improve and again, one month later, he was seen eventually at Ohio State University and he resolved. They were sort of threatening to do a biopsy, but his tests continued to improve.

Again, these are ascites cases that have no grounding in underlying cirrhosis that we can determine.

[Slide.]

Again, these cases have been mentioned, I won't go into them except to say again that these are the Annals cases that both explant and autopsy showed massive hepatic necrosis. So these very severe cases typically had this short latency once again.

[Slide.]

I come back to this slide and just again emphasize that maybe the flavor of these cases is a little bit different than what we have seen with some other drugs. If you have acute liver failure, and we talk about something like Rezulin with a 1 in 30,000 likelihood of acute liver failure, we don't have as many acute liver failure cases here as that for sure. But what we have is a higher number of these hospitalized cases.

What I would suggest, and this is just conjecture on my part, is that because this is not a drug that you take continually but that you only take in little bursts that you may get these cases that would have progressed to something worse had they been on a 20-day course or a 40-day course rather than a 5-day course.

So I am wondering whether we have--again, I don't have the data to support this--a smaller N for ALF cases, but a bigger N for these hospitalized cases. They are not transaminitis only, it is coming in with fever and ascites and jaundice.

So, again, there are 21 hospitalized cases in this group that were very likely or probable. I think that is what I take home from this whole analysis.

[Slide.]

So, again, to summarize, careful adjudication of 53 cases, most of which had enough data. Five experts showed that we had good documentation for the most part, but I have shown you where some of the gaps were.

The confounded cases that we sometimes are wrestling with, and I have had to deal with on other Data and Safety Monitoring Boards, had been excluded at least for this evaluation, and yet 44 out of 53 were hospitalized and more than half had been considered very likely or probable.

[Slide.]

So what is the take-home message? I think there is certainly a clear-cut signal of hepatic necrosis with this agent. There are certain cases, but not a preponderance of cases, that have these unusual features, fever, bodywide joint aches,

ascites. I think the severity is of concern, as is the short latency in this small fraction of cases, and the severity in some instances may be limited simply because the drug exposure is quite short.

There is not many confounding issues that I could see in review of this particular data set. Now, again, this is a skewed data set from what we have sometimes struggled with in these other cases where we have this, as was pointed out earlier, hearsay information.

Again, what I would conclude is that a causality assessment by a panel of experts, despite its shortcomings, suggests that more than half the cases here are due to Ketek.

My thought is that, you know, we are never certain about causality. But, out of 53 cases, there are at least 30 or 35 here that are very, very likely to be in the final analysis if you just put in the cases where you don't have enough data, and put in the cases that you can't prove, but you have strong suspicion of.

So what is the final likelihood or numbers

that we come up for reporting rate? I am not certain. It is certainly less than Rezulin, and it is certainly quite a bit less for acute liver failure, but I am wondering whether it's more for hospitalized cases.

I would guess that for hospitalized cases it may be in the 1 in 20,000 to 1 in 30,000 range. But maybe for ALF, it is more likely 1 in 150,000 or 1 in 200,000 range.

Thank you.

DR. EDWARDS: Thank you very much.

We are at the time now for an open question period, and I would like to invite the members of the Committees to proceed with their questions.

Dr. Norden.

Committee Questions & Discussion

DR. NORDEN: We have heard an amazing amount of data today and for, an Infectious Disease person, it's a lot of hepatology. But it was extraordinarily well done, I thought.

I would like to make two quick comments

and then ask a question about the power of the sponsor's studies.

I think the stimulated reporting has bias but it may not be all bad and I think that sometimes reporting becomes stimulated because there are things going on. To show my age, I would just like to cite INH, which certainly wasn't considered a hepatotoxin for years. I took it as a resident when I converted my PPD and nobody ever talked about liver toxicity. This was 1964.

Yet, when there was an outbreak on Capitol Hill among Congress staff, it suddenly became apparent that it was a hepatotoxin and we found out, not by good epidemiologic studies, but simply by reporting.

The second comment is Dr. Jones's excellent summary. But I think the last slide, the question about risk-benefit, an unqualified yes may have to be rephrased, the question has to be rephrased for each of the indications of Ketek, which is what Dr. Cox talked about before.

The question I had was for Dr. Brinker and

perhaps the Sanofi group. Could you comment further about how underpowered are these studies, because they certainly with 12 million in each base, sounded very convincing at first blush.

DR. BRINKER: I will turn this to allow all my colleagues in pharmacoepidemiology to comment after me. My opinion is that these studies probably rule out, probably cap the risk at definitely 10-fold, maybe even less than that, maybe around 6-fold--that is, the relative risk.

But that is all I will probably give them in terms of their power.

Dr. Walker.

DR. WALKER: You are quite right in terms of relative risk. The upper limits on the attributable risk was about 1 per 100,000.

DR. EDWARDS: Dr. Gutierrez.

DR. GUTIERREZ: I have a question for Dr. Lee about these 53 cases and the virologic diagnosis.

As an infectious disease specialist, we always want to make sure that we have looked for

every single virus possible, so in addition, when we see cases of hepatitis, we do the usual hepatitis serology. But there are also a variety of other viruses that can cause hepatic injury like adenoviruses and all of the members of the herpesvirus families.

I was wondering if, in your opinion, you felt that in most of these cases that you have looked at, or in all of them, that the virologic diagnosis has been adequate to rule out the large variety of viruses that could cause hepatic dysfunction.

DR. LEE: A great question. We have looked in the ALF Study Group at a number of other viruses, HEV, HSV, B19, SEN virus. We can't find any of these viruses to be prominent except there are always a couple of cases of HSV and they are the ones that you are familiar with that have the rash and often have immunosuppression.

CMV, EBV don't as a rule cause this severe a disease but, in theory, probably in this data set weren't looked for.

DR. EDWARDS: Dr. Morris.

DR. MORRIS: I have a question for either Dr. Lee or Dr. Lewis or both.

In looking at the reporting rate after the Annals articles, compared to the cases reported prior to that time, did you find any difference in either the severity of the probability differences pre-post?

What I am concerned about is obviously there is an increase or spurred reporting rate. I know the quality of the cases we have heard are not as good afterwards but what about the probability or severity, are there more false positives?

DR. LEE: I am not sure that quality is necessarily worse. If somebody sees a pattern, then, others later on may say, oh, my goodness, yeah, I did see that pattern. I would sort of take a little bit different slant on this.

I think in the first year that a drug is out, it may get a free ride until somebody says whoa, we had a case, and then everybody says, oh, yeah, I had a case, too, so you could play it

different ways.

I don't know whether we should say that after the Annals article there was overreporting or there was certainly enhanced reporting. But maybe there was underreporting before because the drug was assumed to be safe until proven otherwise.

DR. MORRIS: It is not so much the rate. I am just looking at the cases.

DR. LEE: The quality of the data? I have no way of--

DR. MORRIS: Not the quality, but the probability, using your rating system, the probability or severity, was there any difference in those two indicators pre/post?

DR. LEE: We could probably look at that, because the 53 cases were over the whole span of two or three years, but we haven't specifically looked at whether they were mild or earlier.

DR. LEWIS: I would tend to agree with that. We are probably very close in the cases that we have looked at and I just want to say I mean it's like two ven diagrams coming together, not

exactly sure which cases were the 53 that Will and Leonard looked at, the 54 that I mentioned are from all the same data set.

We probably differ in some of the 12 acute liver failure cases that came in. Reasonable people can disagree on the possibility of those cases.

Regarding what cases came in after the Annals, I am not sure we can say to what extent we saw better quality cases. Some of those are the acute liver failures and some of them have been retracted as you saw.

We would have to look closely at when they actually came in and got reported, and I am not sure that I can tell you that today.

DR. EDWARDS: Thank you.

Dr. Proschan.

DR. PROSCHAN: In the background materials, and the FDA mentioned this today, the reporting rate going up over time, and they mentioned that as disturbing or some term to that effect. But, to me, I look at that and I say,

well, that is suggestive of the reporting bias, and I would say that that's--if anything, why would you expect that rate to change other than by reporting bias.

DR. AVIGAN: Could I answer that just very briefly since I was involved in this process and struggling with the problem of uncertainty. Here the uncertainty was how it was going to play out over time, because we were at a point when we were writing that review and, coming to our landcrafted language about how we saw this, where we were at an inflection, where it would rise rapidly, or where it would perhaps plateau, we just didn't know.

But there was a trend upwards in a system which is, as we have heard, spontaneous data driven, so that we have such an overlay of secular trending that we wouldn't know exactly what that reflected as an incidence problem.

So that is why we were concerned but we were also sort of holding back in terms of making a definitive regulatory decision to do something completely different. But we were concerned.

So that concern was basically an expression of the need to monitor carefully and then be prepared to act if we saw that it was getting out of hand.

MR. MARCO: I had a couple of questions but I think I will just ask one. This was related to the sponsor's presentation and it was Slide 09-17. It was looking at the crude and adjusted risk ratios for severe hepatic injury.

We keep hearing about confounding and whether these cases of hepatic injury, there is confounding involved. I think Dr. Seeff and Dr. Lee and Dr. Brinker had said that they do not believe so in their analysis but I am not really seeing a great difference between the 1.37 crude and the 1.44. If you could sort of help me out with that.

MR. MOYER: So your question is there is a difference in the studies?

MR. MARCO: I am just not seeing a great evidence of much confounding there at all and, if it is, was it age, was it sex, or was it prior

liver history.

DR. DAI: In this regression analysis, it is GEE model. In fact, the history of liver disease and Charlson Index, as well as gender, are significant predictors of the outcome.

You don't see much changes in the risk, because this is a risk ratio versus Augmentin, and the age, gender and covariate distribution were similar between Augmentin and telithromycin, therefore, you don't see really a big adjustment after putting all these cofactors into the analysis.

MR. MARCO: It just sounds like the sponsor has been claiming a great deal of confounding as the reason behind all this hepatic injury.

DR. DAI: I think you are probably talking about other factors may be a reason for liver injury, such as alcohol intake or acetaminophen intake, maybe that is what your question is about, some other factors.

In fact, in this database, you definitely

do not know whether there was patient exposed to acetaminophen, which is highly likely because underlying condition but, since it's over-the-counter medication, it is not recorded in the database.

However, what we did do--slide on, please--we actually reviewed this computer profile. We did not really have the medical record access to review this medical record in detail. But what we do have is what appears in the computer profile of diagnosis associated with this outcome and we found there were cases with cholelithiasis, cirrhosis, chronic liver disease, et cetera, listed below.

So we used computer program in those cases and ended up with much less cases, about half the cases left, and the risk now for telithromycin is 3.6, is still very similar as compared with other comparator anti-infectives.

DR. EDWARDS: Dr. Seeff, I am sorry, you wanted to make a comment a moment ago.

DR. SEEFF: There have been a couple of

comments about the fact that once these three cases were reported, there was a sudden increase in the number that were identified subsequently.

I think that that is true. I think that that is a phenomenon of the prepared mind. I think that the diagnosis of drug-induced liver injury is very difficult, even the experts here may have difficulty in coming to this conclusion, so that out there in practice, many of the physicians haven't the faintest idea when somebody gets jaundiced or gets an abnormality what the cause is.

But if something is brought to their attention, and I think then this is the time when they begin to think, could that be the case.

An example of that I think actually is seen in the DILIN study. We have, as I mentioned, five investigators, each of whom are based at a primary hospital, a university hospital, But they have also got the surrounding hospitals in their orbit.

It has been surprising to me that most of the cases they have identified have been found in

their hospital, but not in the other hospitals, and it is because they are asking other people, please let me know if you see a case of drug-induced liver injury, so I can put it into our database and people don't identify them.

I do not believe that there is any reason to believe there is a difference in the frequency of drug-induced liver injury among the various hospitals. Are they all receiving a drug that is potentially hepatotoxic, that can happen just as frequently in a hospital that is not the hospital of the primary investigators.

So I think it is the prepared mind that leads you to make this decision, to come to the conclusion and that is perfectly appropriate and I think acceptable.

DR. EDWARDS: Thank you.

Before we go on with the other questions, I just wanted to take a moment to come back to an issue to make sure we don't run out of time to cover this, which has come up several times today.

That is the issue of our not having a

prospective study, such as the 3014 study was designed to be and the issues with relying on the voluntary reporting data.

I wanted to ask Dr. Dal Pan and/or Dr. Graham, who has been mentioned and cited several times today if they would like to elaborate on those issues for a moment.

DR. DAL PAN: Maybe I could elaborate first and then Dr. Graham is here, I think he would like to elaborate, as well.

Dr. Graham wrote a letter to the New England Journal of Medicine that was published a few weeks ago in which he did an analysis that basically looked at the amount of data that would have been available via the foreign postmarketing data relative to how much data was actually available to FDA at the time it made its labeling change in June 2006.

I am not going to belabor you with the details of how he did it but, basically, it's a projected method. He derived some metrics of population reporting using WHO data by country on

numbers of reports and then he had the populations of those countries and was able to get a population-based rate of reporting.

It's different from the kind of reporting rates you heard today and he had that for a number of countries. He also had that for the United States, so he was able to get a factor by which reporting rates in the sense I just mentioned differ from those in the United States.

Not surprisingly, he found that most countries had less reporting per million population or per 10 million population than the United States. New Zealand, which has an active reporting system, actually had more per capita than the United States.

So, with that he then said I know how many prescriptions there were in the country, and I know how many prescriptions there were in the United States at the time the action was taken, and I know the reporting rates.

He was able to look at the number of prescriptions in that country and then determine,

using this factor he developed, how many prescriptions would have been needed--rather, he knew the number of prescriptions in the United States and he multiplied that by the multiple factor he determined to say if their system rate, to get their system up to ours in terms of reporting, what it would be. Then he divided that into the number of actual prescriptions and he came up with rates around 5 to 10, 12 percent that would have been available to FDA at the time it approved Ketek.

That was a novel way of looking at this and it was, in the absence of a lot of other information, not a bad way to compare reporting rates in this population-based sense across countries.

The reporting rates are for all reactions, it is not specifically for hepatic or anything, just all reactions, and because he didn't do it for a specific drug, it's for all drugs, so it's really an average of drugs for which there is a lot of reporting and drugs for which there is not a lot of

reporting.

When we actually looked at the number of cases we had from the foreign postmarketing data versus the number of cases that we had when we made our June 2006 labeling change, we found that the fraction was actually higher than he predicted based on his model.

That is probably because Ketek is a relatively new drug, so it would have had more reporting than the average drug, which is a mix of newer drugs and older drugs. But that is just a technical methodologic issue.

I think the conclusion was that there was less available data available to FDA in terms of numbers of foreign postmarketing reports when it made the June 2006 labeling change versus when it approved Ketek in April 2004. About 50 percent was the number we came up with based on actual data.

I think these numbers sort of obscure the larger issue of what postmarketing data actually tell you versus what clinical trials actually tell you.

As we have heard before, postmarketing data, be it here or in Europe or in some other part of the world, is based on spontaneous reporting. People see something, they observe something, they decide to tell someone about it and, at least in the United States, there is no obligation for anyone at the point of care, physician, nurse, pharmacist, patient, to actually tell either us or the company about a suspected adverse drug report.

So we get what we get and we rely on that largely when we see something. So clinical trials are different, clinical trials have a protocol, they have an objective, they have inclusion criteria and exclusion criteria. They have a defined length of follow-up and, if they are properly done, you can really get near complete ascertainment.

I think one of the big problems with spontaneous reporting, or I wouldn't even call it a problem, it is just a fact of life with spontaneous reporting, is that there is woefully inadequate ascertainment of what is happening out there.

So, in the clinical trial, if you power it for a certain observation and you don't see any cases, you can make some conclusions about how likely it is that you have excluded a phenomenon. We don't really understand how the postmarketing system works in that regard.

We don't have any data to tell us, if a product has been on the market and there have been a million prescriptions and we haven't seen a case of something that we haven't previously seen, how likely is it that we will subsequently see a case of that.

Similarly, if a product has been on the market for a year and we haven't seen a case of something, how likely is it that we will subsequently see something of interest. We don't have those metrics, we don't understand the dynamics of that system.

It is something of interest to us but we simply don't understand how that works. We use the spontaneous reporting system really to generate signals to tell us things that we didn't know about

before.

So a good example is the myasthenia gravis exacerbations came up in postmarketing data, we were able to look at those data and do something.

A lot of the hepatic cases you have heard about today really that formed the basis of our discussion came up in a spontaneous reporting system. We speak a lot about the problems of a spontaneous reporting system, it does have some benefits for rare events that you are not likely to find in individual databases, because it covers the whole country, it can bring in events for which a few cases can be clinically important.

So, if you have new drug come on the market, and you get a flurry of cases of, say, 5 or 8 cases of aplastic anemia, which you hadn't previously seen, that is important, and it is the only system we have for doing something like that.

I think Dr. Brinker sort of alluded to that, as to what this system is really good for, and it serves the purpose of telling us about serious, unexpected events that change our opinion,

that can change our opinion of a drug's risk-benefit profile.

I think that is where I see the strengths and limitations of a postmarketing system. I think despite all its problems, it does play a purpose. I think it's an important purpose but I think there is limited inferences we can make from it.

I just want to say we have talked a lot about reporting rates. That was the main point I think of Dr. Graham's letter and we will hear from him in a minute.

He also spoke about a rate for telithromycin and hepatotoxicity of acute liver failure. I think it was quoted as 167 per some person-year metric. I don't know if it was a million person-years or what. It was a rate that we discussed internally and that from a methodologic point of view, I think a number of us had a problem with it.

Just to back up, Dr. Brinker explained the standard reporting rates we used and Sanofi-Aventis also used them. That is where you take the number

of cases of a given event and divide it by the number of prescriptions.

So, again, it's not an incidence rate, there is problems with the numerator, some problems with the denominator. When you do person-time, you take those same two elements and add a third element to the denominator and that's the length of time somebody is treated for the disease. That is how you get, quote, unquote, "person-time" here.

He compared this to three other drugs that were removed from the market because of hepatotoxicity. One was bromfenac, a drug used to treat pain. The other was trovafloxacin, which you have heard about in some of the presentations, an antibiotic. The other is troglitazone, you have referred to as Rezulin for diabetes.

At least two of these, the bromfenac and the trovafloxacin had at least a component of their hepatotoxicity that was delayed.

In the case of trovafloxacin, to actually account for that in the analysis, we can have Dr. Graham explain this more, he actually had to add on

some time to the actual period of the prescription to account for the time course of hepatotoxicity.

With telithromycin, it is a very rapid onset. One of the assumptions of this method is that events occur uniformly throughout the interval, and I think I and some others felt that that wasn't really the case here.

To add to the confusion, the standard reporting rate for telithromycin that Dr. Brinker quoted as 23 per 10 million prescriptions, for these others it is somewhere between 70 and 76, so using the standard reporting rate, it is actually those three drugs are higher.

When you do the person-time, they are lower and the reason is, is that the period you are using, treatment 5 days, is shorter, and so that makes the denominator for the telithromycin rate smaller, so it makes the overall number higher.

When you do it for the other drugs where the period of treatment is longer, your denominator is larger, your overall figure then is smaller.

So that's why you get this inversion.

But that having been said, we differ in this methodology, though. I think we both feel that based on everything we know now, it is still important for us to address the hepatotoxicity of telithromycin and, even though I disagree with the methodology here, I don't disagree with the conclusions we have heard from Dr. Lee that this is a hepatotoxin.

So, with your permission, could we have Dr. Graham come up?

DR. EDWARDS: Dr. Graham, would you care to comment, please?

DR. GRAHAM: Thank you, Dr. Edwards.

I have just a few remarks. As Gerald was speaking, I just jotted down a few notes.

I will start off with what was my motivation in writing the letter that I wrote. It was, one, to challenge the premise used by FDA to support the approval of Ketek, actually, basically, upon which the approval was based in my logic, and I will explain that in a moment if you care to hear it, was that foreign postmarketing data could be

used to establish the safety based on the absence of an apparent signal in that data.

First, the question was asked earlier, and Dr. Cox and Dr. Jenkins gave an answer. But I didn't think they answered the question. I think the question is how many other occasions in the history of FDA has postmarketing data from a foreign country been used in lieu of, in exchange for a clinical trial to basically provide the evidence that was needed to say we no longer have to be concerned about, in this case, hepatotoxicity, which if you recall, as we saw this morning, was the basis upon which the approval of this drug was held up for a number of years, because there was a lot of concern expressed by the Committee, enough concern that the company should go out and do a study, which turned out to have a lot of data integrity problems.

So it was to challenge that, because if that's the case, then, why do clinical trials in the future, we will just get postmarketing safety data, we don't see something, so you are

establishing a precedent and I wanted to challenge that precedent because I don't think that it is scientifically valid.

I would encourage the Committee to ask FDA for the documentation of other examples where they have done this, because in my view, it's an example of lowering the bar, so that there wouldn't be disincentives for the future development of anti-infectives.

So, in any event, the second point is, is that I wanted to place in the public domain that there is a difference in adverse reaction reporting between different countries around the world.

The countries that were shown before, many of those countries don't even have postmarketing pharmacovigilance systems, they are Third World countries basically, when it comes to pharmacovigilance, and they were contributing to that denominator of 5.3 or 6 or 7 or whatever million prescriptions we were talking about.

Even the most sophisticated countries that provided the most data, France and Germany, if you

look at the efficiency of reporting from those countries, it is far less than the efficiency here in the United States and I could cite you references that document the much lower reporting rates in France and Germany than in the United States.

Related to that is the fact that--and in relation to the first point, is that I am sure many of you have heard Dr. Temple and others from FDA talk about the AERS, our spontaneous reporting data, as basically being garbage, and the question is why would you take data that you consider to be garbage and use that in lieu of a clinical trial for the approval of a drug where there was a major safety question.

The third reason why I wrote this letter was to remind my colleagues that there is another way to look at risk using reporting rates and that is to factor in time. Actually for the other three drugs that Gerald mentioned, trovafloxacin, troglitazone and bromfenac, I was the epidemiologist who worked on those drugs. I also

worked on pemalin, which is no longer on the market and had problems with hepatotoxicity, as well.

In each of those instances, time was factored in to computing that reporting rate. And why is that important? It is important because you want to be able to (a) compare what you observe with reporting to what you would have expected if nothing was happening, like the background rate.

The background rate that we heard mentioned earlier of 1 per million per year was actually a rate that I developed in my work on troglitazone. So, if that is the background rate of 1 per million per year, and then I have a drug that has a reporting rate of 100 per million per year, I already know, causality has been established, because you have gotten far more than what you would have expected before you even go out and do a formal epidemiologic study, so there is value in that.

The other point to be made is, is that the statement was made I think by Dr. Jones that it was inappropriate or it's misleading to use time

because the exposure to Ketek is so short.

What I would argue is, is that if you think of the time during which a person is on a drug as a time of running a gauntlet, okay, you are onboard some ship and you are running the gauntlet. This is the War of 1812 and you are in the British Navy and how long are you going to be running the gauntlet. The gauntlet here is your risk of liver failure.

With Ketek what we have is an enormously elevated risk over a short period of time. The only way you see that enormous elevation of risk over a short period of time, and this enormous elevation of risk is a relative risk, is by factoring in time. When you do that, what you see is that Ketek keeps bad company, that its reporting rates are virtually identical to those with trovafloxacin, troglitazone and bromfenac, three of the drugs that were withdrawn from the market in the United States because of hepatotoxicity.

Now, there was a fourth reason why I wrote the letter and that had to do with the benefit side

of Ketek. In my view, for acute bacterial sinusitis and for acute exacerbation of chronic bronchitis, we have no evidence of efficacy whatsoever.

The non-inferiority design and some of the confidence bounds on that showed that it went down to like minus 15 percent or minus 14.7 percent. We have no basis to conclude that for those diseases, for spontaneous recovery is so high, that the drugs are actually adding anything.

In that situation where you don't have actual certainty that you are doing something useful and beneficial, what level of harm is actually acceptable?

In any event, thank you for allowing me to speak and address the Committee and, if you have any questions about my methods, I will be happy to talk about those, as well.

DR. EDWARDS: Thank you very much.

Dr. Jones, do you have any comments?

DR. JONES: No.

DR. EDWARDS: Is there any other discussion about these points that have just been

raised, that members of the Committee would like to bring up? We are going to go on with other questions.

Dr. Leggett.

DR. LEGGETT: Dr. Brinker, in one of your slides, I think it was Slide No. 31, I am not sure I knew what the final number of prescriptions was before trova got pulled. Was it the 2 million that was quoted there? I sort of vaguely remember like 8 million or something of people that have received trova before it got yanked.

Then, that sort of also pertains to the statements that have been made about people, if they don't know what to look for, they don't see it, so that's why you don't get reporting for over a year after the drug is on the market. But I seem to remember that trova ran into trouble within weeks.

I don't know that I can generalize from one drug to the other.

DR. BRINKER: Slide 31, can you bring up Slide 31.

There we go. So these are the data that I know of and that is that trova came off with about 2 million prescriptions and about a year and a half after marketing.

I don't know of any remarkable publicity associated with trovafloxacin either. I think there was a bolus of reports that came in towards the end of the first year but I know of no remarkable temporality with regard to that.

DR. EDWARDS: I believe, Dr. Proschan, you are next.

DR. PROSCHAN: We are obviously in a difficult position, you know, because a clinical trial is the best way to get an answer to, you know, an efficacy answer. It is not a great way to get an answer to a question that involves a very low event rate.

Much has been made--well, Senator Grassley made a lot out of the fact that this clinical trial was not being considered, so why not do another clinical trial. The problem is for the event rates we are talking about, a 24,000-patient trial isn't

going to show much.

In this case, we have to rely on other kinds of data like this FDA database. Yet that is causing problems, because I do think this reporting bias is a big issue. I think notwithstanding the comment that it is something to the effect of, well, this is informed judgment being made, I think the only way to figure that out, whether that is real or not, is to have a placebo or a controlled New England Journal of Medicine article, where you report that clarithromycin has increased liver toxicity and see what happens to the reporting rate there.

DR. EDWARDS: Thank you for those comments. It is going to be a little impractical but we may suggest it, though.

This is sort of a difficult area but let me go ahead anyway. I am certain that in everyone's mind on this committee, well, let me put it this way.

It would be of benefit I think to the Committee members to hear from the FDA, some of

their thoughts about the issue of not, let's say, asking for a clinical trial similar to the 3014. Now, I am not sure that the Committee has a clear understanding of what the trial design was for 3014. Is that a fair statement? Would it be of benefit for us to have a clearer notion of that?

Could I ask someone to help us with that, and then that may help us with this area.

DR. COX: The study was a study of approximately 24,000 patients, so 12,000 per group, done in the usual care setting, and patients were randomized to receive either Augmentin or telithromycin, and the patients who enrolled in the study had community-acquired pneumonia, acute bacterial sinusitis, or acute bacterial exacerbations of chronic bronchitis.

They were followed and had laboratory testing a couple times over the duration of the study. That is sort of the broad outline of the study, if you will.

I will just make some other comments for the Committee's consideration. If you are thinking

about this 24,000-patient study, 12,000 per group, essentially, where we were at the end of the first review cycle was the case of the Finnish man, some elevations in the liver function tests.

We were looking for an incremental, you know, additional information that would help us to get more information about the potential for hepatic toxicity, recognizing that there is limitations as to the size and how many patients you can enroll in a clinical trial, taking the database that we had, somewhat over 3,000 patients, we thought another incremental step here would be to get data from approximately 12,000 patients. That would give us more information about the potential for hepatotoxicity.

As it turns out, we couldn't rely on Study 3014. We have to recognize the limitations as to what a study of that size would show, and Dr. Proschan has commented on that.

If we saw zero events in 12,000 patients, by the rule of 3, that would cap the risk at 1 in 4,000 patients.

It seems here for the presentations that we are hearing today, Dr. Lee's estimates, we are hearing estimates of acute liver failure of the 1 in 150,000, 1 in 200,000 range. Hospitalized cases, I believe--and please correct me if I am wrong--a potential rate of 1 in 20,000 to 1 in 30,000, so I think it gets back to the point of knowing what we know about serious events that occur infrequently, how much power would a study of 12,000 patients exposed to telithromycin compared to 12,000 patients who had received Augmentin be able to tell us about liver injuries that are occurring at these very infrequent rates.

It may bring us back to I believe it was a point that Dr. Proschan is making, that to get at these low frequency events, you need larger numbers.

No question, I mean some of the issues with spontaneous adverse event reports, their limitations, that all needs to be taken into consideration. But, with low frequency events, it is very difficult to do much with a controlled

clinical trial of the specified size.

One last point, too, I want to make that I think is important, is that we did have safety data at the end of the first cycle on 3,200 patients, a pretty considerable size database. At the time of approval, there was safety data from the Phase III studies of 4,780 patients.

So it is not that we didn't have safety data, we did have safety data. We also had studies looking at GT prolongation and mechanistic studies looking at the effects on vision. So there is a lot that goes into this. 3014 was one component. We couldn't rely upon it but there was other information that we had from the foreign postmarketing data. I will stop there.

DR. EDWARDS: Dr. Proschan, do you have any other comments about the difficulty in doing a prospective clinical trial?

DR. PROSCHAN: Not really, just that it would have to be so huge, it's not practical.

DR. AVIGAN: I just wanted to make one comment as a hepatologist about clinical trials and

the problem of very rare events. There is an iceberg phenomenon that the hepatologist tries to build a case around and the question is, since you know you will get more frequent, less severe injuries that are self-resolving, and that was actually potentially seen even in the 4,000 patient database that set this whole thing into motion.

The question then was what is the tip of that iceberg and what is the shape of that iceberg for the more severe end of the spectrum.

One important concept, we talked before about Hy Zimmerman, who was sort of one of the founders of this field, was the observation of an intermediate form of severity called the Hy's Rule patients. Those are patients who get both transaminase elevations and hyperbilirubinemia as a consequence of liver injury.

When you see that in a drug development program, that is often a signal that in a larger exposure population, you will, in fact, run into trouble, perhaps at a much more rare rate for bad clinical outcomes.

So one way of thinking about a clinical trial design, if that were to be entertained, would be that the endpoints would not necessarily only be liver failure, which would be, of course, very rare and maybe undoable but so that there is this phenomenon of intermediate level severity which is a harbinger at a population level for a problematic drug.

DR. EDWARDS: Dr. Morris.

DR. MORRIS: I wanted to get back to trying to match up some of the definitions that we are using in terms of some of the spontaneous report reviews and some of the larger studies that Dr. Walker and Dr. Dai have done.

I guess my question, generally, is to what extent did the diagnostic codes used by Drs. Walker and Dai in their studies cover the range, because I guess what we are hearing is that it may not be that the tip of the iceberg but the next level underneath it and to what extent did their studies actually look at that level of injury.

So I guess it is a question for the

sponsors.

DR. WALKER: When you are looking at insurance claims data, it is not looking at the CRF. You have lots of bites of the apple. Every time somebody submits a charge for something, there is a new opportunity for a diagnosis to come up. Every time somebody submitted a charge related to liver failure or hepatic coma, that person, individual, would come on to our radar screen.

We didn't include the nonspecific hepatitis codes because, as we were looking for outpatient disease, they would have just been overwhelmed in a way they couldn't have possibly have a report ready for this advisory committee.

The assumption that we made was that, at some point in the course of somebody with serious level disease, there will be a code of either liver failure or hepatic coma.

DR. MORRIS: It looks like you included two codes, acute and subacute necrosis of the liver and hepatic coma. I am not an expert in the area but it seems to me those are fairly narrow codes

for a very serious injury and you might have missed some of the less serious, but still hospitalized, patients.

DR. WALKER: We certainly would have missed a patient who had an incident elevation of transaminases who would have met the definition but was, indeed, in the hospital for something else.

DR. DAI: I think informatics analysis is different, that we did include all nonspecific hepatitis codes--that means, it is non-viral--these are included. In addition, we also looked into other codes such as cholelithiasis or even Jompers[?] kind of codes as long as the resulting hospitalization was as broad as we can use. Even, when we are looking at that, still, the risk following telithromycin use is comparable with the other antibiotics.

DR. MORRIS: So do you feel that you would have picked up a lot more of the still-hospitalized but I guess less serious injury or less acute than Dr. Walker did?

DR. DAI: Actually, we did. Actually,

once we included all the other codes that were also required on hospitalization, the rates actually increased about 10-fold. So, definitely, it is much more higher.

DR. MOYER: Did you have a follow-up question?

DR. WALKER: May I just say that a transaminase elevation in passing in somebody hospitalized for something else wasn't what we were looking for. The notion of serious is people hospitalized for their liver disease.

DR. EDWARDS: Dr. Norden.

DR. NORDEN: One other comment. We have been talking about doing clinical trials. I think this is one other major limitation to clinical trials in terms of safety data and that is that the majority of clinical trials done by all sponsors across the board don't enroll very sick people in general. They usually enroll patients, for example, in CAP who have mild to moderate disease, not the kind of people John Bartlett talked about, for example, in an ICU.

I think trovofloxacin is a good example where, despite a large clinical database, there were very few reports of hepatic injury that raised a flag during the clinical trials but, as Jim said, after the trial, suddenly it was being given to sick people, diabetic patients, and, lo and behold, we had a lot of liver disease.

So I think there are, unfortunately, limitations to doing clinical trials besides the one you pointed out, Dr. Proschak.

DR. EDWARDS: Dr. Wong-Beringer.

DR. WANG-BERINGER: Thank you. I have a question for Dr. Lee and Dr. Seefe. On the 53 cases that you reviewed, it appears that several of the representative patients that you described had received repeated courses of Ketek. In the context of Ketek having an approved indication for 5-day treatment versus how it is prescribed in the community, I wonder if you could comment on those patients who showed up with Grade 3-4 severity, what Ketek was prescribed for and what was the median treatment duration.

DR. LEE: I don't think we have that detail at this point. We can certainly get it to you. We have a whole big spreadsheet of all 53 cases. But we have been sort of rushing to get this distilled to the extent that we have done it so far.

I would say, as I said earlier, that, out of the 53 cases, and this is just purely from memory, there were probably six to eight that had had either a prolonged course--there were one or two that were taking it, like, for three or four weeks at a time. And, as you heard, there was the health executive who took two back-to-back courses.

So there certainly were, I would guess, sort of an over-representation of these kind of cases. But I would also say, as you saw, that the bulk of the cases were the hospitalized group. I would have to parse it out to see which were in which group. But the bulk of them would have been in the hospitalized group.

DR. EDWARDS: Thank you

DR. JOHANN-LIANG: I can just respond from

Dr. Brinker's Slide 20 which was a breakdown of the 12 patients who had acute liver failure. The indications for use were 5 for sinusitis, 2 for pneumonia, 2 URI, 1 bronchitis pneumonia, 1 bronchitis and 1 respiratory-tract infection. So it looks like all respiratory-tract.

DR. EDWARDS: We are coming to our last question and that is for Dr. Shapiro.

MS. SHAPIRO: Oh, oh. Well, this is a follow up on I guess much of what Dr. Graham said as well as what we have been struggling with which is, while clinical trials may not be perfect, may have problems, we are left at the end of the day to weigh and balance risk and benefit.

I am hoping we are going to hear more about benefit tomorrow because I didn't hear enough. We have been focusing on risk and what we have, in large measure, is the European data.

I very much enjoyed the talk from our European colleague but I didn't get any more clarity, really, on my initial questions which were what is the nature of the practice and the

requirements and the culture with respect to being able to have confidence that that data means much at all.

So I was wondering if we could get some of the articles that Dr. Graham was talking about that will talk about some of the limitations and the different--we know our limitations and they are significant about the reporting system here.

If the situation is even more tenuous in Europe, I would like to know about that.

DR. EDWARDS: I think we are going to have to hold that for tomorrow, Dr. Shapiro, if that is all right.

MS. SHAPIRO: Or next month or whatever.

DR. EDWARDS: Yes. There is just one other thing I wanted to take care of. At the break, someone from the sponsor mentioned to me they had a point they wanted to clarify with a slide. I am not sure I see that person here. Oh, yes. Would this be something we could do sort of quickly?

DR. S. JENKINS: It will take about 30

seconds.

DR. EDWARDS: Okay. That would be great.

DR. S. JENKINS: Something came up this morning after my presentation, were there any differences in the evolution of resistance in the various countries in the EU from which we were garnering data.

So we, at the lunch break, went back and actually looked at the resistance rates over time for six countries in the EU.

[Slide.]

Unfortunately, the n's are relatively small. The highest rates that we saw were in France where it ran from 1.3 to 1.6 percent. But, in each case, that represented one resistance isolate.

But the country with the most prescriptions that had actually been used was Germany. In fact, no resistance isolates were detected in the Protech study. The n's for those were 500 to 600 isolates in each year.

So the resistance rates in Germany, so

far, are essentially zero.

DR. EDWARDS: Thank you very much. Dr. Marco had a comment, again referable to what we need in the future.

MR. MARCO: This is just actually for tomorrow, possible. This is regarding Dr. Rullo's presentation. If the sponsor could go into detail their risk-communication strategies. I know we are eager to close and we do need to close. But. tomorrow, I know, we are talking more safety.

So if they could sort of elaborate on Slide 0614, that would be great. Thanks.

DR. EDWARDS: Thank you.

If there are no objections from the committee, then, I would like to adjourn for today and thank everyone for their presentations and participation. Thank you.

[Whereupon, at 5:50 p.m., the meeting was recessed, to be resumed on December 15, 2006 at 8:00 a.m.]

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