diffusely light kidneys, and the histologically tubular degeneration necrosis, increased tubular casts, and tubular dilatation, cortical tubular vacuolation, and the increased interstitial inflammatory cell infiltration. The severity in the instance of this positive findings increased -- with increasing doses. And many of these findings persisted throughout the 28th day recovery period. Although different levels of reversibility were noted.

All these findings were noted, either doses of 50 milligram per kilo or higher doses. And the 50 milligram per kilo equals to human dose of 8 milligram per kilo. That's below the 10 milligram per kilo clinical recommended dose.

In the 30-week dog study. Renal toxicity was evidenced by increased serum BUN on the creatinine levels. And they increased the urinary volume. And histologically tubular vacuolation, dilatation, and the necrosis. All these findings were noted, either 25 milligram per kilo in the higher doses, and the rats equals to human dose starting upon 5 milligram per kilo.

This table just compares the animal and the

 

plasma exposure to the drug -- to animals and the humans. This animal dose listed here, renal toxicity dose. Out of these doses, possible renal toxicity findings were noted.

Based on the plasma AUC data listed here, we can find there's no safety margin between the animal and the human dose. That's all my presentation. Thank you.

DR. FEIBUS: Good morning. My name is Karen Feibus. I'm the medical team leader on the Maternal Health Team in the Office of New Drugs. And my -- this is not working. Oh, thank you.

This morning my goals are for us to review the role of the Maternal Health Team and its involvement in the Telavancin NDA, to summarize the reproductive toxicology study findings that Dr. Chen just presented, to discuss pregnancy labeling and pregnancy category definitions, and discuss potential Telavancin use during pregnancy, with regards to the risks and the populations at risks, the possible benefits, alternative therapies and their relative risks and benefits, the appropriate pregnancy category, and fetal exposure risk management issues.

 

The Maternal Health Team is a consult team that's located in the immediate office of the Office of New Drugs. And our job is to respond to consult requests from drug review divisions. And these consult requests may be with regards to pregnancy and nursing mother's sections of labeling, pregnancy exposure registries, risk evaluation and mitigation strategies, and pregnancy prevention programs, as well as evaluating emerging data on possible drug associated adverse pregnancy outcomes, and effects in nursing infants.

We support and promote well-informed prescribing and use of medicines during pregnancy. As Dr. Scialli pointed out, pregnant women get sick and need medicines. We work to improve the clinical utility and relevance of the pregnancy and nursing mother's sections of labeling, and the label should be a helpful clinical tool. That is what it's there to do.

We also work on data awareness, the healthcare practitioners and other users of drugs, to know what we do know about the use of medicines during pregnancy and lactation, what we don't know, and what we still need to find out.

 

So, in brief, Dr. Chen presented the reproductive toxicology results with Telavancin in rats, rabbits, and mini pigs. And in rats there were rare, but there were findings of brachymelia and syndactyly. In rabbits there were flexed front paws, brachymelia, adactyly, and an incidence of absent ulna. And in mini pigs there was syndactyly, polydactyly, radial agenesis and an incidence of bilateral absence of the tarsal bones.

And across these three species there were findings of limb anomalies and offspring with Telavancin exposure in-utero. And these anomalies occurred at low incidences, but still at higher frequencies in treated animals than in historical controls.

There was some additional findings as well. In the rabbits there was a drug-related incidence in post-implantation loss, and a statistically significant increase in dilated lateral ventricles and missing intermediate lung lobes.

In rats there was a dose-related increase in stillborn pups, and the number of dams with stillborn pups. And the mini pigs had increased late resorptions

 

compared to historical controls. And a 100 percent increase in post-implantation loss in the high dose group, compared to placebo and the diluent group.

So, the Maternal Health Team was consulted to review the study data and make recommendations regarding the pregnancy category for this product, the labeling language, and the potential need for a pregnancy registry. And the current pregnancy categories for teratogenicity are categories A, B, C, D and X. And I want to take a moment to talk about these categories and their definitions.

Although it is often misinterpreted, this is not a grading system from better to worse like the grades we get in school. The categories each have a specific definition that is based on the source of the data, whether it's animal or human; the study findings, whether they're positive or negative; and the relative clinical benefit versus fetal risk for the drug when it's used in the clinical setting.

Categories C, D and X all require consideration of both the benefit to the mother and potentially to the fetus, as well as the fetal risk with

 

drug exposure.

This slide is pretty close to exactly the regulatory language defining each of these categories. And you can use this slide as a reference as we continue our discussion over the next couple of slides.

So, we tried to take a look at Telavancin from a risk benefit perspective. We have what looks like teratogenicity in three species of animal, with findings that are similar across all three species. We also see increased pregnancy loss or stillbirth in all three species of animal.

Animal teratogenicity does not always correlate with human teratogenicity, but it is more likely when teratogenicity is multispecies, and it's also more likely when the exposure in animals is close to what the human exposure is expected to be in the clinical setting. We have no human data in pregnancy for this product.

So, here are our category options. Which ones are viable here? Category B is not appropriate, because Category B requires that animal studies are negative, and in this case animal studies are not negative.

 

Categories A and D are not appropriate for Telavancin, because both of these categories require human data. Category A requires adequate and well-controlled human data that are negative. And Category D requires human data that are positive. So, the category options we are left with for Telavancin are Category C and Category X based on their definitions. And this slide sort of summarizes or paraphrases the elements that go into these categories.

For Category C, you need to have animal reproduction studies that have shown an adverse effect on the fetus, and no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable, despite the potential risks.

For Category X, studies in animals or humans have demonstrated fetal abnormalities, or there is positive evidence of fetal risk based on adverse reaction reports from investigation or marketing experience -- which we don't have in this case, because that would be human data -- and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

 

For example, safer drugs or other forms of therapy are available. And that's the catch for this product. Because, clearly, if you have a pregnant woman with a complicated skin and skin structure infection, there's benefit in treating her effectively. But in situations where there are safer drugs available that are equally effective, that is a reason listed in the regulations for labeling a drug as a Category X, if it meets the other criteria.

So, what do we have in this situation, with regards to relative risk and benefit? We do have more than eight anti-infective drugs that are FDA approved for the treatment of complicated skin and skin structure infections.

With regards to relative risks, Telavancin appears to be a highly suspected human teratogen based on animal reproductive and developmental toxicity study data.

So, what would be the ways to demonstrate relative benefit that could over -- that could potentially override this relative risk and take priority? Telavancin could show superior efficacy. Now,

 

based on the noninferiority trial data, we know that Telavancin is not inferior to Vancomycin. We know that in the superior -- in the superiority comparison it was not shown to be superior.

In addition, we know that -- I'm sorry, in addition, Telavancin could offer a better safety profile than other therapies as a way to demonstrate a better risk benefit profile compared to other available therapies. So, let's take a look at those other therapies.

This slide shows some of these alternative therapies that are already approved by FDA for the treatment of this indication. The first four that are listed have negative animal studies in two species, and no human data, and are listed as a Category B for pregnancy category.

Now, the four antibiotics that are listed on this slide that are in yellow actually are approved for treatment of MRSA.

The second set of three approved agents that are listed have shown increased fetal loss in two species of animal, but no structural malformations, and no human

 

data are available. And these drugs are listed either as a Category C or D, but I wanted to note that Tigecycline, which carries a Category D, actually has no human data. And, so, technically, according to the definition, should probably be a C.

And then we have Vancomycin. Vancomycin has no data in the label. It has no animal data, and for that reason it is a Category C. Now, my search was not as good as Dr. Scialli's, I only found one negative animal study in Vancomycin and I have not seen the other studies that he presented here to you today.

So, the information we have to support a pregnancy Category X for Telavancin, are that for the current indication, Telavancin does not appear to offer clinical benefit above and beyond that offered by Vancomycin. There are teratogenic findings in three animals species, all with limb anomalies and increased pregnancy or fetal loss. And this makes Telavancin a highly suspected human teratogen.

Based on available data, the eight FDA approved treatments for complicated skin and skin structure infections appear to have a lower teratogenic

 

risk.

And, so, based on this information, it appears that Telavancin does not offer enough clinical benefit to justify the additional fetal risk for this indication. However, there are some things we don't know. And, so, we should look at Pregnancy Category C as well, and what the arguments for and against this category might be.

The arguments for Category C are what is unknown. The relative efficacy of Telavancin compared to other anti-infectives currently approved for the treatment of complicated skin and skin structure infections, other than Vancomycin, is not known. And the potential clinical benefit may be there. Under the IND, there were isolated patients treated successfully with Telavancin who failed therapy with Vancomycin. This is a small number and this was not in pregnant women, but it's something to consider. The arguments against Pregnancy Category C are that healthcare practitioners may not see the risk for Telavancin as different from other Category C drugs that are indicated for complicated skin and skin structure infections. And this would likely increase the likelihood of fetal exposures to a suspected human

 

teratogen.

So, I'd like to take a moment to think about Telavancin and managing risk. What's a -- what is our goal? Who are we worried about? And hopefully this information will be helpful as the Advisory Committee members take this into consideration.

Our goal is to prevent all, or at least unintended, fetal exposures to Telavancin. We are worried about women of childbearing potential. Based on the 2006 US Census data, there are more than 42 million women between the ages of 15 and 44 years in this country. And about 10 percent of them get pregnant every year. That is more than 6 million pregnancies each year in this country, and 50 percent of them are unplanned.

Women of childbearing potential get infections. They need treatment with anti-infective agents. And, so, we need to recognize that prescribing is a possibility for this drug.

So, what do we need to keep in mind with regards to risk management strategies? How Telavancin is labeled for use during pregnancy should determine the type of postmarketing data required on fetal exposures.

 

If Telavancin uses contraindicated during pregnancy, meaning that it carries a Category X, then fetal exposure should be tracked as part of a risk management program.

If the benefits of Telavancin use in pregnancy are considered to outweigh the fetal risks in certain clinical situations, and the drug carries a Category C, then the sponsor should have a postmarketing requirement to conduct a pregnancy registry. A pregnancy registry is a prospective cohort study that enrolls pregnant women exposed to drug before pregnancy outcomes are known.

Here's some additional points to consider. This is an IV drug. Its indication for use requires timely initiation of therapy. And the potential settings for use include hospitals, chronic care facilities, physician offices, and homes, either with instruction or home care assistance.

Avoiding fetal exposure to a highly suspected human teratogen is very important. For all women of childbearing potential, same day documentation of a negative serum pregnancy test should be required prior to starting Telavancin treatment. One pregnancy test will not detect pregnancies within a few days of conception,

 

and this should be recognized. But the acute need for therapy really eliminates the ability to require two negative pregnancy tests over an interval of time, or the use of highly effective contraception for a month prior to treatment initiation, as is seen in some other risk management programs with teratogens or suspected teratogens.

So, here are a couple of additional questions. Will healthcare practitioners check for a negative pregnancy test prior to Telavancin administration or will they just order it? Should there be a role for the dispensing pharmacy in checking for that negative pregnancy test? For therapy in the outpatient setting, should there be a contraceptive requirement, and how can this requirement be defined to suit Telavancin-treatment scenarios so that women can get the treatment they need and still be protected?

This concludes my presentation. And I would like to introduce Dr. Susan Berkman. She is a senior risk management and analyst in the Division of Risk Management in the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research. And

 

she's going to talk to you in greater detail about the risk management considerations for Telavancin. Thank you for your time.

DR. BERKMAN: Good morning. And congratulations to making it to about mile ten in this marathon day for you all.

As Dr. Feibus just said, I'm Susan Berkman, a risk management analyst with the Office of Surveillance and Epidemiology. I've worked with several risk management programs for teratogenic drugs, and I was consulted by the review division to take into consideration the issues with Telavancin and provide to you today -- one moment. I do have additional slides -- and to provide to you today an overview of risk management, discuss possible tools and strategies to prevent fetal exposure based on current risk management programs for teratogens and suspected teratogens, and to discuss some of the practical challenges in developing and implementing a risk management program for Telavancin.

The combination of risk assessment strategies and risk minimization tools comprise risk management.

 

The Food, Drug, and Cosmetic Act established what is considered routine risk management in the postmarketing setting.

The information contained in the package insert communicates the risks and benefits to manage the risks, all spontaneous adverse event monitoring and reporting, provide data to assess the safety over the products life cycle.

Additional measures are considered when these routine measures I just mentioned are not believed to be sufficient to minimize the risks. Providing information to the committee today about these additional risk minimization measures will be the focus of my presentation. This presentation does not advocate for or against implementing these measures for Telavancin, just the facts.

Risk management plans are designed to meet specific goals in minimizing known or potential risks of a product while preserving its important benefits. They may utilize single or multiple elements of strategies, such as medication guides for patients, education to healthcare providers, and other safe use strategies.

 

During the development process, the applicant and FDA develop an evaluation component to assess whether or not the program is achieving its stated goals. The FDA now has new authorities to require sponsors to develop what are called risk evaluation and mitigation strategies, or REMs, when additional measures are determined to be necessary to assure that the drug's benefits outweigh the risks.

For the purpose of our discussion today, I will talk about risk management generally and not focus on the specifics of risk evaluation and mitigation strategy legislation.

Routine risk management measures are appropriate for most drugs. Additional measures should be reserved for drugs with important benefits and serious risks that labeling is not sufficient to minimize. It is important that the label reflect the significance of the risks and support the rationale for additional measures.

Risk management plans work to educate the various stakeholders involved in prescribing, distributing, dispensing, administering, and taking a particular drug product, to empower patients to make

 

informed decisions regarding product use. They can also serve to target use to particular settings, patients, or prescribers; or they may function to encourage or require certain monitoring to ensure safe use.

It is very important to remember that determining if a risk management program is needed, it is done on a case-by-case basis. There is no one-size-fits-all approach to managing a particular risk which may become more apparent as we talk about more of the issues.

For each case we must consider a variety of factors, including the severity of the disease, the benefits of a particular drug treatment, other existing therapeutic options, the commonality of the risk to the drug class, preventability of the risk, and the severity of the risk. Many of these considerations have been highlighted in other presentations this morning.

I do want to point out, that while a special setting is not necessary to prevent fetal exposure, pregnancy detection requires special testing. And pregnancy prevention requires knowledge about and comfort with prescribing contraception. These measures may fall outside of the typical standard of care and thought

 

process when a patient is treated for a complicated skin and skin structure infection.

The duration of exposure is also important. Based on the proposed indication and time to eliminate Telavancin from the body with normal renal function, the period of risk is approximately 16 days, short in comparison to the typical length of treatment with other teratogenic drugs.

Another consideration in particular for teratogens is to assess the potential use in women of childbearing potential. According to the Premier RX Market Advisor, during 2006 nearly 10,000 women, age 12 to 44, were discharged from the hospital with a bill for at least one of eight antibacterials approved for complicated skin and skin structure infections, where the primary diagnosis was related to a serious skin infection. While the potential user population data are relatively small, these data do not account for additional antibacterial use, outpatient treatment, or for uses of these drugs beyond serious skin infections. These data do inform us that women of childbearing potential may need Telavancin, and the need to assure

 

safe use in a way that is least burdensome to the healthcare system.

If a risk management program is deemed necessary for Telavancin, my next few slides provide an overview of the general strategy used to minimize fetal exposure for known or suspected teratogens based on current risk mitigation programs.

These programs all strive for a similar goal, to prevent fetal exposure through pregnancy detection and prevention, as well as to further assess the effects of fetal exposure -- to assess the effects of exposure on fetal outcomes.

The objectives are to ensure that no pregnant woman receives a teratogen, and that pregnancy does not occur while women of childbearing potential are exposed to the teratogen. This can be accomplished by employing pregnancy testing and contraception use.

In addition, these risk minimization programs employ pregnancy registries to both better characterize the risk of fetal exposure, particularly if the drug is a suspected teratogen. And to collect additional data to assess where improvements in the program can be made.

 

More specifically, most teratogen risk mitigation programs require one to two negative pregnancy tests prior to initiating treatment, monthly testing during treatment, and a post treatment pregnancy test as a final measure of pregnancy detection.

Requiring two reliable forms of birth control has become the standard. Usually this consists of one hormonal method and one barrier method, started before or at the time of treatment, and it -- before or at the time of treatment when it's initiated, and continuing until the drug no longer poses an exposure risk.

Telavancin's duration of use is days to weeks, whereas most other teratogens with risk management programs are taken for months to years. This difference in exposure and need to start treatment immediately may impact what the most suitable recommendations for pregnancy testing and contraception should be.

Further, teratogen risk management programs have pregnancy registries to collect data on pregnancy outcomes and fetal abnormalities. Each pregnancy registry attempts to enroll any woman with a possible pregnancy exposure and collect data on the timing of

 

exposure, pregnancy outcome, delivery information, long-term follow-up information of the child, and any ways to improve the program.

Now, that I've briefly addressed the basic methods to detect and prevent pregnancy, I will move on to discuss the additional tools that other programs utilize.

Medication guides help to inform patients when it is necessary to the patient's safe and effective use of the drug. The information may help to prevent a serious adverse event, effect a patient's decision to use or continue to use the product, and provide directions for use, when they are critical to the drug's effectiveness.

Education may be developed for healthcare providers to encourage the implementation of the risk management program and to further inform healthcare providers about any serious risks. The information may be disseminated by the sponsor or through various professional organizations.

The purpose of safe use strategies is to assist healthcare providers in following appropriate

 

prescribing practices, and to target the populations and conditions for use most likely to confer benefit. Safe use strategies typically require prescribers and pharmacists to be enrolled in order to prescribe, dispense, and administer the drug. In addition, drug access may be linked to certain monitoring requirements.

The risk management program in place for known or suspected teratogens, like Isotretinoin, Thalidomide, or the Letaris for pulmonary arterial hypertension, incorporate a combination of tools to encourage healthcare providers to follow appropriate prescribing practices.

These may be accomplished through prescriber healthcare setting, pharmacy, and patient enrollment, linking a negative pregnancy test result to dispensing, completing patient/physician agreement forms, create a formal opportunity for the patient to ask questions, utilizing only specialty pharmacies to dispense the drug product upon appropriate patient follow up, and limiting the day supply per prescription and not allowing refills.

Both the Isotretinoin and Thalidomide programs link the negative pregnancy test result to dispensing of

 

the drug. Programs like Letaris and Tracleer for pulmonary arterial hypertension utilize specialty pharmacies to follow up with patients before dispensing the medication to them each month.

There is some practical challenges to consider with developing and implementing a risk management program for Telavancin. The majority of risk management programs are for drug products that are used in an outpatient setting. In fact, all the programs for teratogens are primarily outpatient medication. So, the tools these programs currently employ may not be appropriate to minimize the risk in an inpatient setting.

For example, patient medication guides are not typically provided to hospitalized patients, so, patient education would require alternative measures. The need for contraception and hospitalized patients would also need to be evaluated, as well as the need for additional pregnancy tests beyond the initial test if treatment is completed before discharge.

While the bulk of Telavancin use is anticipated to be inpatient, in a study submitted to support approval, 20 to 40 percent of patients were not

hospitalized at baseline. The risk management program would need to assure safe use in the inpatient, as well as the outpatient settings, which may require different methods than those employed in the inpatient setting.

We assume the risk of pregnancy to be more likely in the outpatient setting, translating to a possible need for different recommendations for pregnancy testing and contraception, compared to that of the inpatient setting. There would also need to be a plan for patient started on treatment as an inpatient and discharged to home to complete Telavancin treatment, ensuring continuity of care, appropriate patient follow up, and determining who the responsible prescriber is for this scenario, would need to be considered.

Designing a single effective strategy to suit all hospital systems is no small task. It may be more realistic to require hospitals to enroll in the program in order to have access to Telavancin, and then to develop a list of requirements for enrolled hospitals from which the individual hospital creates their own policy and procedures to assure safe use.

These measures could or should include

 

standardized healthcare provider education, along with the development of standardized order sets, order entry stops, prescribing limitations and other safeguards.

Designing a risk management strategy for outpatient use for the entire treatment course, or to complete treatment upon discharge, is also complex. One consideration could be to limit use to Telavancin to the inpatient use setting only. However, this option is not necessarily practical. Beyond educating the appropriate healthcare providers, much more discussion would need to occur to determine the best way to assure safe use in infusion centers, or home healthcare settings, and how to identify the responsible prescriber at the time of discharge.

Teratogenic exposure is a preventable risk. There are no further methods available to mitigate the risk of birth defect once a patient and a fetus are exposed.

Women of child bearing potential may need to be treated with Telavancin. This situation creates a need to assure safe use, without denying effective treatment to those who need it, and in a way that is

least burdensome to our healthcare system.

If it is determined that Telavancin offers important benefits to women of childbearing potential, the question today is whether labeling can adequately reach prescribers to assure safe use. The necessary steps to check for pregnancy and to prevent exposure are not new or unique, but are not necessarily part of the standard of care for treating complicated skin and skin structure infections. Labeling should support the significance of the risk and the need for additional risk management measures.

Historically programs have only been considered if it is determined that pregnancy Category X is most appropriate, and is not sufficient alone to manage the risk.

If a risk management program is needed, practical solutions to all of these logistical issues that accommodate the need to administer Telavancin in different settings must be addressed. Consensus on appropriate monitoring and follow up in women of childbearing potential, with consideration for the use setting, must also be tackled. At minimum, regardless of

 

the pregnancy category, the applicant should seek to further characterize the risk of fetal exposure by developing a pregnancy registry. Thank you.

DR. RELLER: We will now take a short ten-minute break. Panel members, please remember that there should be no discussion of the PMA during the break amongst yourselves or with any member of the audience. We will resume at 11 a.m., please. 11 a.m.

(Pause in proceedings.)

DR. RELLER: To enable us to continue the program, we are now open for clarifications by either the sponsor or the FDA on the presentations made, or any questions you have for any of the members who presented this morning.

Dr. Cross.

DR. CROSS: I was wondering whether or not the drug is dialyzed after hemodialysis. Is it like Vancomycin or not?

DR. RELLER: Our renal consultants, nephrologists, Theravance team, response on Dr. Cross' question about whether or not Telavancin is dialyzed and how much -- how quickly, if so. Thanks.

 

DR. BARRIERE: Thanks. I apologize. First let me apologize to the committee for my late arrival. I had a bit of a medical emergency, so -- but Telavancin is minimally dialyzed. Dialysis clearance is about 25 percent of total clearance. But during a brief intermittent dialysis run there would be less than 10 percent of the drug removed -- excuse me -- removed.

DR. CROSS: And the second question I had, Barth, is: I thought I caught that the vehicle was Cyclodextrin, and if so, is there a problem with prolonged IV administration?

DR. BARRIERE: There -- because of the -- primarily -- primary renal excretion of Cyclodextrin, there is some accumulation, but the dosage adjustment of Telavancin in patients with severe renal impairment minimizes that accumulation.

DR. RELLER: Dr. Kauffman.

DR. KAUFFMAN: Yeah, my question -- excuse me -- my question was similar, because there are other agents, such as antifungals, in beta Cyclodextrins, and there's actually a note that you shouldn't use it below a creatinine clearance of even 50 MLs per minute, which

 

isn't severe renal insufficiency.

So, do you have any data on that?

And the other thing linked to this is: Do -- you must have -- we must have data on levels, serum concentrations of this agent, and are those correlated with renal failure, with development of decreased in creatinine clearance, for example?

DR. BARRIERE: First of all, to address your first question, the other drugs that -- including Cyclodextrin -- I believe have a recommendation to avoid them in severe renal impairment. For example, Voriconazole I believe is the one drug. And I believe that recommendation is primarily because Voriconazole is not adjusted for renal impairment because of its primary metabolism, so, there would be some significant accumulation.

And to your second question, are you referring to Telavancin exposure and correlation with -- we've examined that in a number of different ways, and probably one of the best examples would be illustrated here, which is the percent change in creatinine versus AUC, 0 to 24 Telavancin, in the Phase 3 complicated skin and skin

 

structure infection studies. There doesn't appear to be any correlation.

We've also looked at Cmax, maximum concentrations, and minimum concentrations, and a similar profile is observed.

DR. RELLER: Dr. Paganini had a question.

DR. PAGANINI: Thank you. I have actually several, but I'll just -- let me follow up on the dializability. Just as Vancomycin is, frankly, not, quote, unquote, dialyzed with standard hemodialysis, using different membranes, it's dializability becomes much more prominent.

And also in this type of patient that is potentially hemodynamically unstable, the form of dialysis that's formed is usually a continuous form of therapy, which in effect has a very dramatic removal of Vancomycin.

So, my question to the sponsor is -- are -- has any data been generated in continuous forms of therapy, or the more modern wide type of membranes that are used with intermittent dialysis? The reason why I'm asking this question is, not so much to obtain a piece of

 

information, but there seems to be a disconnect between the renal excretion of the drug. And then as renal dysfunction increases, which would then carry with it a higher concentration of the drug, its effectiveness decreases.

And I -- that seems to be a nonsegrator there. And, so, the only potential there is, as renal decreases, there might have been some dialytic interventions that may have removed drug, therefore, drug inefficiencies.

So, there's a whole bunch of questions, I guess, to -- if you have any information on that.

DR. BARRIERE: To answer your first question, we have in vitro data on continuous renal replacement therapy. And it's very efficient, as it would be for Vancomycin and many other antibiotics.

With regard to the removal of Telavancin, it depends on the flow rate. It depends on the membrane type. But as you can see, with very high flow rates of six liters per hour, with the membranes that were used in this experiment, there's fairly rapid removal and it looks very similar to normal renal function and that --

 

in this particular case.

With regard to the correlation between accumulation of plasma concentrations and outcome, you know, both we and the FDA have tried to examine this in multiple different ways and really aren't able to come up with any firm conclusions as to why this is, other than very small sample sizes, and potentially many other factors that these patients were -- had as a result of their illness. These were very sick patients, older more renal -- obviously more renal dysfunction and many comorbidities.

Why Vancomycin did not decrease in efficacy is unclear. One would expect efficacy of the drug to go down as renal function decreases as a natural phenomenon.

And with regard to whether there was any dialytic interventions, there were only a couple of patients who underwent dialysis. And that would not explain this difference.

DR. RELLER: Dr. Steckelberg.

DR. STECKELBERG: Thank you. With respect to the efficacy analysis, the Vancomycin dose was gram Q12 hours, were concentrations and serum monitored, and was

 

it adjusted, and if so, what were the target concentrations and the achieved concentrations?

And I have a second question.

DR. BARRIERE: The dose that was specified in the protocol was a gram Q 12 hours, and that was because that is the FDA approved dose. However, there were adjustments allowed for that dose at each site. We didn't try to mandate any particular dosing regimen for the -- for Vancomycin dosage adjustment, simply because there was so many sites with different methods of doing it.

So, we allowed each site to monitor and adjust doses appropriately, as long as the study blind was maintained at each site through a blinding plan that we evaluated and approved, Vancomycin serum levels could be performed. And to -- they were performed in approximately 25 percent of the patients who received Vancomycin.

Now, as you can see, there were a small proportion of patients who had fairly low concentrations. The vast majority were between 5 and 15. And, again, small numbers of patients who had levels

 

between -- over 15 micrograms per mill.

DR. STECKELBERG: Thank you. And a quick second question. Dysgeusia was notably prominent. In addition, that's common with Metronidazole, which was allowed in the protocol.

Was there -- was Metronidazole use equal in the two arms, and was there any association of the dysgeusia or the interaction effect with Metronidazole?

DR. BARRIERE: Yeah. We examined that, and the Metronidazole use was pretty even. There was a little bit more in the Telavancin arm, but it wouldn't explain that difference. And it didn't particularly be associated with dysgeusia. So...

DR. RELLER: Dr. Kopp is next.

DR. KOPP: Thank you. I have a couple of questions, and one might follow up on what Dr. Paganini was asking about. You -- there was dose adjustment for renal disease. Is it possible that you excessively reduced the dose and then that question about levels would address that?

DR. BARRIERE: We did have certain concentration monitoring -- not monitoring, excuse me --

 

plasma concentrations in a very limited number of patients with renal dysfunction and -- in the Phase 3 studies. What we did was to compare the area under the curve for those patients who had normal renal function in the study, or mild impairment. And that's represented by the bar -- whisker chart on the left with over 300 patients. There's a lot of variability, hence, the error bars are quite large. In a relatively small number of patients with moderate or severe renal impairment, you can see that the exposure was approximately the same. So, this would suggest to us that the dosage adjustment was appropriate and didn't result in under dosing.

DR. KOPP: Then if I could ask a couple of questions about Slide 50 and having to do with the issue of comorbidities that predict possibly renal impairment. So, the data that I haven't seen before was that the -- the HAP Study showed a much higher level of comorbidity, roughly 80 percent of the patients instead of 50 percent had the specified comorbidities and, therefore, or perhaps logically the amount of renal disease was much higher.

Did you have enough in either study or in the

 

pooled study to look at in a multivariable analysis what was important?

I guess you specifically said comorbidities include, but not limited to heart failure, hypotension, sepsis, diabetes, and hypertension.

DR. BARRIERE: They -- this is -- that was the slide that was in the presentation. These are the comorbidities and the prevalence in the pool population of complicated skin and skin structure infection studies. And, again, approximately half the patients -- it was slightly more in the Telavancin group -- had a baseline comorbid condition. And there were some imbalances here and there between the groups. But generally they are reasonably well-balanced, in terms of the types of comorbid conditions that could potentially have been associated with renal dysfunction.

In terms of multivariate regression, the number of patient and disease characteristics that were considered in the model, including body mass index, sex, age, race, of course, and then a number of disease characteristics, including the site of the infection based on creatinine clearance, the lesion size,

 

nephrotoxic medication use at baseline diabetes, et cetera, all of the other diseases. And there were numerous of these factors that turned out to be independently associated with renal risk.

DR. KOPP: And then I guess a couple of particular questions about that, for example, diabetes. That probably was significant in that 25 percent of your study group was diabetic, about 65 percent of the --

DR. BARRIERE: Correct.

DR. KOPP: -- kidney patients.

Another issue WAS morbid obesity. That appeared to be important, in that 7 out of 15 of those with renal SAEs had morbid obesity.

DR. BARRIERE: Correct.

DR. KOPP: So, the question comes up, are those people being overdosed if they're getting base -- drug purely based on weight rather than BSA?

DR. BARRIERE: We examined the pharmacokinetics and a fairly limited beta set. Unfortunately, very few of the patients who were morbidly obese, or obese, or morbid obese had plasma concentrations obtained during the Phase 3 study. But we

 

didn't perform a formal study in obese patients, but we have looked at it.

The patients were dosed according to total body weight. So, your question that relates to whether these patients then overdosed as a result of this excessive -- as a result of an excessive dose, for example. Population PK analysis based on the Phase 3 data suggests that body weight had no effect on the clearance. And, so, our conclusions were that there were no further dosage adjustments. There was a very small amount of -- I should say there was a somewhat -- not somewhat -- but slightly higher exposure to Telavancin in those patients who were morbidly obese or obese, but not sufficient enough such that we would have associated that with an excess risk.

DR. KOPP: And then back to diabetes for a minute. Did you see if albuminuria or proteinuria was a risk factor within that population?

DR. BARRIERE: Yeah. Unfortunately Telavancin interferes with routine protein assays in the urine. And, so, we're limited to using the microalbumin assay.

DR. KOPP: Uh-huh.

 

DR. BARRIERE: And we only obtain spot microalbumins. And using that kind of data we really couldn't find any correlations. There was no associated -- association that we could find with elevated microalbumin and renal risk --

DR. KOPP: And then one more --

DR. BARRIERE: -- the diabetics.

DR. KOPP: One more question and I'll stop. The foamy urine that was mentioned, usually in nephrology we think of that as heavy proteinuria.

Do you have an explanation for that observation?

DR. BARRIERE: We do. The -- we also examined to see if the foamy urine was associated with either elevated levels of microalbumin, or with patients who had developed renal dysfunction, or baseline renal dysfunction. And there was -- really was no correlation.

The Telavancin itself -- and if you shake it up in the vial -- causes -- it looks very much like the foamy urine. And the formulation of Telavancin, when administered like that, would probably result in the

 

foam.

DR. KOPP: Thank you.

DR. RELLER: Dr. Follmann.

DR. FOLLMANN: If the sponsor could bring up Slide 34 which shows the cure rates for the two groups as a function of baseline creatinine clearance. I had a question about that.

It seemed -- right. So, at the lowest level baseline creatinine clearance, we do see this potential difference in cure rates between the two groups, and depending upon what statistical test you do, you might find it significant or not.

The question I have has to do with your proposed dosing, I guess. Which I think I heard earlier you say that, for those who baseline creatinine clearance greater than 30 we're going to cut the dose in half.

And are -- have you -- are you concerned that that might make the cure rate even lower?

DR. BARRIERE: Well, that was what was used in these particular patients. That wasn't just proposed for the future, that was employed during the study. So, the dosage was decreased by 50 percent, given -- actually the

 

full dose given every other day for those patients with creatinine clearances less than 30. And as I showed a few minutes ago, although the data are limited, the exposure appeared to be very similar to those patients with normal renal function.

DR. RELLER: Dr. Leggett. All right. I'm going down my list. Dr. Katona had a question, and then Dr. Black, and Dr. Goetz.

DR. KATONA: This is a question for Dr. Berkman. There are risk management plans that have been around that the FDA has looked at.

How often have you looked at one that has a three-pronged issue, where we're not only looking at pregnant women, but also a QT prolongation and nephrotoxicity?

DR. BERKMAN: The -- thank you for the question. There was recently a drug approved for idiopathic thrombocytopenic purpura that had about five different risks that we're currently managing. It is true that most the drugs that have risk management programs are limited to one specific risk. And even if there's a number of risks in a product label, that

 

doesn't necessarily mean that that warrants a risk management plan to manage all those risks. So, it is feasible that you could have a program that manages more than one risk.

DR. KATONA: But how often does that come up that you're -- you have one that manages more than one risk?

DR. BERKMAN: There's currently, I think, 18 products on the market and their associated generics, when it's applicable, that have risk management programs. And, I mean, I would say -- I'd just be guessing at the percentage -- but I'd say 90 percent of them are probably limited to a -- well, maybe 80 percent are limited to a single product. Ambersantin (ph) and Bosentan have a liver toxicity as well as teratogenicity managed in those programs.

DR. RELLER: Dr. Black.

DR. BLACK: (Inaudible) everybody's serum creatinine went up, you know, regardless. And these are people with normal baselines.

Did you see anything like that in the Vancomycin studies as well?

 

DR. BARRIERE: Just to clarify, these are the patients -- the 48 patients who developed what we had defined --

DR. BLACK: Okay.

DR. BARRIERE: -- and some the FDA defined a potentially clinically significant increase, not all patients.

DR. BLACK: This isn't everyone?

DR. BARRIERE: No. No. It's not everyone. These are only those 48 patients who developed an increase.

DR. BLACK: And I assume the dysgeusia got better. You hadn't said that.

DR. BARRIERE: Yes, the dysgeusia got better. Yes, it was trenchant.

DR. BLACK: Were the investigators aware of the possible side effect, and the foamy urine possible side effect, and could that have affected the blinding?

DR. BARRIERE: The -- that was listed in our -- has been listed in our investigator brochure for quite some time, because it was observed very early. And, you know, given the fact that it occurred in both of the

 

treatment groups, albeit higher in the Telavancin group, it is unlikely to have resulted in that. Despite that, we examined the cure rates in those patients, removing all of the patients who had a dysgeusia or a foamy urine event, and the results were basically the same. There was no difference between the treatment groups.

DR. BLACK: Thank you.

DR. RELLER: Dr. Bennett.

DR. BENNETT: The last I knew, no one has been able to develop an assay for Cyclodextrin and body fluids. The way that Pfizer approached that with their Sulfa Butyl Cyclodextrin, was to use Carbon 14 labeling, and to use that in a small number of normal volunteers and, of course, in experimental animals.

What this means is, we know of almost nothing about the pharmacology of Cyclodextrins in the human body. We don't know if they're removed by dialysis, or CVVH. As has been pointed out, that's quite different than a regular dialysis. We don't know how much they accumulate in patients with azotemia.

This makes me concerned about Telavancin in patients who are azotemic. We don't have much experience

 

with that, with the Voriconazole or the Intraconozole, because we've tried to avoid using those in patients who are azotemic. So, I'm -- I'd be delighted to be updated on my knowledge about the pharmacology of Cyclodextrin.

What do we know about the metabolism in the human body?

DR. CONNOR: Studies of metabolism in Cyclodextrin in the human body are primarily driven by one of the sponsors who originally developed this. We did develop a biolytical method. But what we do know from their studies, and from ours, that most of the Cyclodextrin that's injected, 98 percent plus, is excreted by renal excretion.

DR. RELLER: Dr. Coleman. From whom did we just hear?

UNIDENTIFIED SPEAKER: This is Dr. Mike Connor, Toxicology Group.

DR. RELLER: Thank you.

All right. Dr. Goetz is next.

DR. GOETZ: A question for Theravance. According to the data that was presented this morning, the MIC 90 for Vancomycin against -- amongst the

 

Staphylococcal isolates was approximately 1.0. As one of the possible benefits of Telavancin might be activity against Vancomycin isolates that -- isolates of Staph aureus with higher Vancomycin MICs.

Do you have -- are there any data looking at the response to Telavancin versus Vancomycin among Staphylococcal isolates of MICs of one, one and a half, or two?

DR. BARRIERE: We examined the response rates in MRSA with -- in patients who had Vancomycin -- sorry, patients who had MRSA with Vancomycin -- Vancomycin MIC. And this illustrates -- this is by microdilution susceptibility testing at the central laboratory. And there appears to be a slight advantage in patients with MICs -- patients who have MRSA with Vancomycin MICs of one. There were very few number -- small number of patients with Vancomycin MICs of two. And you can see the cure rates there.

DR. RELLER: Dr. Paganini.

DR. PAGANINI: Again, a couple of issues. In the animal data it -- I was impressed with the pathology, which was clearly an acute kidney injury type pathology

 

that was there. So, then we translated over into the humans. And I ask a couple of questions. Your serum creatinines, you've based a lot of your stuff on serum creatinine, which is fine. But there didn't seem to be a correlation between creatinine, and weight, or age. It -- it -- was there one?

The reason why I ask that, elderly females, for example, which have very low muscle mass, they actually come in with very low serum creatinines and never reach a higher creatinine, yet still have substantial renal dysfunction. And if you base it only on serum creatinine, or delta serum creatinine -- in fact, there's some studies that show that small delta serum creatinines have worse outcomes, especially in the elderly, creatinine being a surrogate for nutrition. So, the correlation between weight, age, and serum creatinine would be nice to know.

And then the final little statement that I would have, is that acute kidney injury by many say, well, don't worry about it. It will get better. That's actually not quite true. Thirty percent of those people actually never regain renal function. And if you start

 

with CKD, or chronic kidney disease, at a level of, whatever, a level three, a level four, a level five, or even level two, with an acute on top of chronic the -- that, in fact, may resolve, but resolves not back to baseline, but to a worse level of kidney dysfunction. So, a CKD patient who has acute kidney injury tends to come away with that -- with worse CKD.

So, those are issues I think that have to be evaluated. And the rationale -- if I can I'll just sort of make a little statement then I'll stop -- why I asked yesterday about the risk benefit, while you were talking about noninferior, was exactly what the committee picked up on, and that is inferiority of a 10 percent is fine if everything else is the same. But if you start to have an increase in complications, then that risk -- that noninferior limit might want to be narrowed a bit because you are expanding the complications of the drug compared to its comparative. And, so, that's the reason why I think complications are very important to be considered, not only in the toxicology portion of your discussion, but also in the noninferiority limits that you may want to set for drugs overall. And I'd use this as a

 

comparator.

So, the question, I guess, would be age, weight, and assumed creatinines.

DR. BARRIERE: May we have that slide that was on preview, please?

Rather than using serum creatinine for the correlation, we did estimate creatinine clearances in these patients using the standard Cockcroft and Gault equation. And here you see the correlation for each of the treatment groups with age and creatinine clearance. And, as you can see, as you might imagine, they're very highly correlated using creatinine clearance. So, we're combining all of these factors. And there is a very strong correlation with increasing age and decreasing creatinine clearance as you had pointed out.

I'd like to ask Dr. Lewis to talk about the reversibility and some of the other issues you brought up, please.

DR. LEWIS: You covered several issues, and I'll try to respond to them in general. First let me take a moment to put the renal effects received for Telavancin into context. The overall incidence of acute

 

kidney injury in the skin studies was, if anything, on the low side for what we see in reported general surveys of acute kidney injury. So, there wasn't an excessive. In fact, there was even a low end acute kidney injury.

My experience in multiple publications would suggest that 70 to 80 percent of acute kidney injury is due to under profusion of the kidney, sepsis, shock, heart failure, hypovolemia. And, so, the majority of the 35 renal AEs in the Tela group and -- out of 1,029 patients. And the 12 out of 1,000 in the Vanc group are not likely to be due to drug effects. And, in fact, our blinded adjudication of the serious renal SAEs were concordant with what has been seen in the literature and with that drug effect representing a minority of the renal insufficiency, senior renal effect scenes.

I think the sponsors should be commended, having adjudicated these cases, for putting very sick patients in this study, including patients with baseline renal insufficiency. It should be noted, however, that the -- they did not stratify it. It was an ID study for things like baseline renal function. And there was a numerical imbalance in patients with severe, chronic

 

kidney disease at baseline favoring the Vancomycin group.

With that all said, I'll -- putting both the preclinical data that Dr. Paganini referred to, and the clinical data together, I believe that Telavancin exhibits a modest and reversible renal effect. Putting it into context -- and I'll address the reversibility a little bit more in a second -- putting it into a clinical context with other antibiotics, I would put it on a scale like this. I would rank it slightly above Vancomycin. But I would have to comment that Vancomycin, which is generally considered to have a low acute kidney injury risk at the dosage used in this study, there are increasing case reports, due to the resistant organisms of higher and higher doses of Vancomycin being used with higher trough levels. And it may actually rise above Telavancin at some point.

The study had study specified creatinines to be drawn as part of the study in renal monitoring. In the cases that we adjudicated, we found that the vast majority were reversible. And you could see the creatinine coming down from its peak. And there was also follow-up data -- and I don't know if Dr. Connor wants to

 

-- but they went and got -- after the study was finished to look at what happened to these patients who had not completed returned to baseline. And, again, three of the three patients identified, two of the three had, in fact, returned to baseline.

We have to remember that antibiotic nephrotoxicity in the literature and characteristically does have -- is reversible completely to baseline.

Also, Dr. Paganini actually is a author on the paper that I'm very familiar with, and the growing literature, that small increases in serum creatinine are associated with worse outcomes. I think that we have to keep in perspective, that if two patients get a CABG and one comes out and goes to the floor and looks great, and one goes in the SICU is in shock, the one in shock gets acute kidney injury, and that surprisingly also has a worse outcome. So, at least in some of these patients the acute kidney injury is a marker for severity of illness.

I think an important study that speaks to this is from the University of Pittsburgh, looking at acute kidney injury in ICU patients. They compared patients

 

who had acute kidney injury to patients who had ESRD. And, in fact, the patients with acute kidney injury had worse outcomes to the ESRD patients, which, of course, did worse than normals -- or normal renal function. And, again, I think that speaks to at least a component of this being acute kidney injury and being a marker for severity of illness.

But, again, I think we saw in our blinded adjudicated review clear reversibility as is reported and expected in antibiotic nephrotoxicity.

DR. RELLER: Dr. Steckelberg.

DR. STECKELBERG: A question with respect to pregnancy categories for the sponsor. And I welcome comments from our FDA consultants as well. In looking at the C versus X definitions, it really comes down to the pivotal point as whether or not there are other alternatives available. And assuming that we're talking about serious life or limb threatening infections, that's basically going to be Vancomycin or Daptomycin. So, how would the sponsor characterize the population of pregnant women with serious infections for whom there is no other alternative therapy currently, and how big is that

 

population?

DR. COLEMAN: This is Dr. Richard Sweet.

DR. RELLER: Dr. Sweet.

DR. SWEET: Thank you. In obstetrics and gynecology, a little belatedly to other specialties, but we are seeing a tremendous emergence of MRSA infections. For instance, the estimates are that they've increased ten-fold in the pregnant population over the last five years. While many of these are minor infections, more and more we're seeing reported in the literature. And I've seen in my own experience severe life threatening infections in pregnancy. The MRSA infections in pregnancy tend to occur in all trimesters, but predominantly after 20 weeks. Fifty percent are in the midtrimester and 20 percent are in the immediate postpartum period. But they range from necrotizing fasciitis, overwhelming sepsis, and septic shock, secondary to severe cellulitis and abscesses.

So, yes, it's a growing problem in our specialty. And there is a need for alternative as the susceptibility to the current available agents becomes less.

 

DR. STECKELBERG: Accepting all of that, what proportion of your patients would you find are not treatable with Vancomycin and Daptomycin currently?

DR. SWEET: I think currently you're probably talking about down in the one percent type of range. But the problem is, when they come in -- especially ones with serious infections -- you can't really wait in a pregnant woman to ensure that they have it. You have to use an appeared therapy. Not only is the mother potentially at risk, but the fetus also potentially at risk, for not only complications of infection, but with uncontrolled systemic infection, you're at risk for preterm labor. And increasing studies show a relationship between such infections in neurologic sequelae like cerebral palsy.

DR. RELLER: Dr. Fleming.

DR. FLEMING: I have two questions for the sponsor for efficacy. But very quickly, if I could have Dr. Pohlman, first, from FDA, Slide 22. As I'm trying to understand the relationship between the renal failure, renal insufficiency and death, we have in the two pivotal studies, before test of cure, nine deaths against nine after test of cure within 30 days, five deaths against

 

2. And then in the uncomplicated Staph aureus bacteremia 203A study, it's five deaths against three. So, overall it's 19 deaths on Telavancin against 14 on the comparator.

And of the Telavancin deaths, the ones that had had prior indication of renal insufficiency or renal failure were two on Study 30A, four of the five after test of cure, and two of the nine before test of cure. That's eight on Telavancin against one on Vancomycin. So, of the deaths that occurred, the patients that had renal insufficiency or renal failure before death was eight against one.

This slide gives us the three that are coded as possibly related. I think these were all in the nine against nine. These are all on Telavancin, renal insufficiency, in two cases acute renal failure. So, it's called possibly related adverse events resulting in death.

Is there any additional clarification that can be provided about the nature of that causal relationship here, the extent to which these may have been causal for death?

 

DR. POHLMAN: If you give me a little while, I may have more information. Let me just check.

DR. RELLER: In the interest of time, we'll come back to Dr. Pohlman.

Meanwhile, Dr. Shelby --

DR. FLEMING: I had two other questions.

DR. RELLER: Go ahead.

DR. FLEMING: So, I wanted to ask those and come back to Dr. Pohlman.

So, for the sponsor on Page 31, Page 31 is your principle analysis. In the spirit of our discussion yesterday, since this includes all of the randomized patients, what I'd like to see is this analysis in those patients who had wound or ulcer infection, or cellulitis, or syphilis, IE, leaving out those that had only major abscess.

And there are three analyses that have been put forward, the FDA's analysis that's less favorable than the sponsors, and then the CE analysis, and then this one is AT. This one is the most favorable. So, giving you the best situation in which to consider, can you give us these results when we look at those patients

 

that have major abscess only left out of the analysis?

DR. COLEMAN: We listened yesterday and last night created --

DR. FLEMING: Okay. Okay. So, essentially, as we look at each of these, you've left out the major abscess only. And, as we look at this, each of these studies with the targeted population would meet a 10 percent noninferiority margin, and that's actually by even -- with your CE population, which is somewhat less favorable than your AT.

DR. COLEMAN: True.

DR. FLEMING: The second question on efficacy is Slide 33. And you had had hopes at the beginning that you would be superior -- Slide 33 -- you had hopes at the beginning that you would actually be superior in MRSA and noninferior over all.

Once you break people into these subgroups and you look at MRSA infected, then if this group is going to be better than the average, then the complimentary group could be worse than the average. And when the average is fairly neutral, this could be very problematic to your label.

 

Now, actually to your benefit here, because the MRSA isn't driving this -- the complimentary group, probably will be meeting noninferiority.

Could you show us -- whenever you show a subgroup, you need to show the counterbalancing subgroup as well. So, can you show us this slide for the rest of the patients, the ones who aren't MRSA infected? Particularly the clinical cure result.

DR. POHLMAN: Yes. Here's the cure rates baseline MRSA for the CE population, yet with or without MRSA.

DR. FLEMING: Yes. Okay. So, it's fortunate in this case that, because the results are fairly neutral, the MRSA weren't plus seven or something, because then the complimentary group would be minus five and that would be problematic.

So, essentially what this says, is why you don't have superiority in MRSA, at least there is consistent evidence that the rest of the group is getting benefit.

Dr. Pohlman, do you have your --

DR. POHLMAN: Yes. Yes, I do.

 

DR. RELLER: Dr. Pohlman.

DR. POHLMAN: In terms of the two that were recorded during the reporting period, one was based on the original protocol, which was a 7.5 milligram per kilogram dose. The study was started with that dose and then the dose was increased to a 10 milligram per kilogram dose. This was an 82-year-old female with venous ulcers and cellulitis to the right leg and foot. Medical history is significant for diabetes, bilateral leg edema, gout, hypertension, fluid retention, obesity, a concomitant medication Simvastatin, Allopurinol, Metformin, Furosemide.

She -- on day eight of therapy, the patient developed an episode of shortness of breath, and on day 10 developed oliguria. Serum creatinine was elevated at 2.1. Then the patient required transfer to the ICU because of hypotension. Study medication was discontinued that day. Patient was intubated. Serum creatinine was 3.2. It looks like she got concomitant pneumonia. Investigator assessed the events as unlikely or not related to study medication.

The second case that occurred on therapy,

 

70-year-old male, history of unstable angina, congestive heart failure, defibrillator placement, hypertension, diabetes, obesity. This one actually was concomitant medication Natrecor, something that came on line after I was around. Baseline creatinine 1.0. Day four, 1.9. Telavancin discontinued on day six due to renal insufficiency. Day seven, serum creatinine was 2.7 and was progressive. The patient status was changed two days later to DNR. Comfort care, and patient died two days later. So, that one was a little -- they're all confounded. I mean, these are sick people.

And the third one that was reported after the -- after the death reporting period, patient had a history of severe heart failure and chronic renal insufficiency, received an inappropriate or high dose of study medication based on baseline renal function. Creatinine rose from baseline of 4.1 to a maximum of 10.3 one week after starting medication, discontinuation. Patient died seven days after the test of cure from progressive renal failure, refusal of dialysis, and was outside the study reporting period. The investigator assessed the event of acute renal failure as possibly

 

probably related.

DR. RELLER: Dr. Shelby had a question.

DR. SHELBY: Thank you. I've got three unrelated questions. First, the bactericidal mechanism of Vancomycin, is it similar to or different from Telavancin?

DR. RELLER: Dr. Coleman.

DR. COLEMAN: Thank you. Dr. Bret Benton from our microbiology group.

DR. BENTON: Good morning. Bret Benton from Theravance. The Telavancin bactericidal activity is related to its dual mechanism of action. It shares, like Vancomycin, a mechanism that includes inhibition of cell wall synthesis by a substrate targeted mechanism. It also, as we've described by virtue of its interaction with the early peptidoglycan intermediate Lipid II, disrupts the barrier function of the membrane. And this results in more efficient and potent bactericidal activity than what's observed with Telavancin.

In time kill studies where we've compared Telavancin's bactericidal activity to that of Nafcillin and Vancomycin -- as showen on the slide here that's

 

projected -- we see comparable or superior bactericidal activity to both comparator agents.

I could go into more details on the mechanism, but I'm not sure if that's in the spirit of your question or not. I'd be glad to --

DR. SHELBY: No. I just want to know if they're different -- very different. Some are --

DR. BENTON: They're related on a fundamental level --

DR. SHELBY: Okay.

DR. BENTON: -- where both compounds bind, peptidoglycan intermediates and notably Lipid II. Telavancin more effectively targets the Lipid II peptidoglycan precursor than does Vancomycin. And we believe that's the primary reason why it's active against a lot of the Vancomycin intermediate and nonsusceptible strains. And it's interaction with Lipid II results subsequently in a depolarization of the membrane and loss of membrane potential. And that also contributes to the rapid loss of cell viability.

DR. SHELBY: All right. Thank you.

The sponsors proposed a pregnancy registry.

 

Can you speak to how that would work and how the information that accumulates in that registry would be shared and used?

DR. COLEMAN: Our plans would be to follow the examples of the antiretroviral registry -- registries and others that have come before us and learn from their example about how best to construct, and implement, and use a pregnancy registry. The data would be reported in the regular safety summaries to the agency and to all regulatory bodies overseeing the approval of the drug.

DR. SHELBY: Okay. Thank you. And my last question, with regards to the mini pig developmental study. There was mention that these animals were exposed to multiple and various other antibiotics during the course of the study. I don't have a copy of that study, so, I'm curious about what went on in that study.

DR. COLEMAN: Dr. Mike Connor.

DR. CONNOR: Yeah. During the course of this study, the animals are dosed on a daily basis during that period of organogenesis. And this requires people sitting down in the stalls with the pigs and working with them. And over the course of this study, that also

 

provided some degree of stress to the pigs as well. And there was some lameness and skin wounds, excuse me, where the vascular port was. And on occasion topical antibiotics were added to their care as routine veterinary care, but no systemic antibiotic.

DR. SHELBY: No systemic antibiotics?

DR. CONNOR: No systemic antibiotics.

DR. SHELBY: Okay. Thank you.

DR. RELLER: Dr. Alston.

DR. ALSTON: I have two quick questions and a comment. And I can't see you, but I'm sure you're there. I sort of got the sense from reading the materials -- but maybe I'm wrong and you can tell me -- that somehow in enrollment patients with MRSA were encouraged, or I think the word enhanced was used yesterday. And since the hope, especially in a noninferiority trial, is that you enroll patients promptly and get going promptly with treatment, I'm just interested in the mechanics of performing the study of how investigators were encouraged to get MRSA patients into the trial.

DR. COLEMAN: In addition to selecting sites

 

that had higher rates of MRSAs, we first went only to countries across the globe where MRSA rates are high. We then spoke with investigators and looked for documentation of the rates of MRSA within their institution.

Within the protocol; however, in addition to the usual inclusion/exclusion criteria, we asked that the investigators focus in on groups at higher risk for MRSA, and provided a list of the risk factors that have been -- appeared again and again in -- amongst publications as indicating a patient will have a higher risk for MRSA. And that's how we enrich the population for MRSA.

DR. ALSTON: I see. And my second question was about the altered taste. And in a short trial like this of seven days, I would imagine that patients can put up with a bad taste. But as a clinician, I'm sure that if this drug supplants Vancomycin and is used for prolonged periods off label, I can imagine patients becoming fatigued with the bad taste and starting to call us when they're on their home therapy. And I was wondering with the Staph aureus bacteremia trial whether you have experience with patients being treated for

 

longer than seven days, and whether the taste led to discontinuations.

DR. BARRIERE: The metallic and soapy taste is very trenchant. And it led to discontinuation in one or two patients total. So, they were able to tolerate it quite a while.

In the uncomplicated bacteremia study, that was a two-week trial. There was a fairly limited number of patients. And I apologize, I'm not sure I have the data completely in front of me, but there were just, I believe, one or two patients who may have complained of metallic or soapy taste. And that's consistent with what we found in the hospital-acquired pneumonia studies, where metallic or soapy taste was basically not reported.

DR. ALSTON: Thanks. And then just a comment, I think really just for FDA, that in the area of community-acquired MRSA where a lot of these are going to be abscesses and surgery is probably as important, if not more important than the antibiotics. For a noninferiority trial I think we're really going to have to look at subgroups of patients, in terms of whether they required surgery or not, and the adequacy and timing

 

of the surgery. And it would be great to look at a subset of people who didn't require surgery and didn't get preactive antibiotics, because in that sense this would be essentially step-down therapy. But that would obviously be a very small group. But I think we're really going to have to focus on the surgical aspects of enrollment in the area of community-acquired MRSA.

DR. RELLER: Dr. Cragan.

DR. CRAGAN: I had a question for Dr. Scialli actually. I actually had two questions, but one has to do with interpreting the reproductive tox studies. One of the specific limb defects that was reported was absent ulna in the rabbit, and radial agenesis, or absence of the radius in the mini pigs. And presumably those have a similar ideology. And I wanted to know how you interpret those specific defects.

Are these the kind of limb defects that have been seen historically or that you typically see in animal studies? And might absent radius be an explanation for a short limb, or an otherwise malformed limb in an animal that didn't get a skeletal examination?

UNIDENTIFIED SPEAKER: All right. Thank you

 

for that question, Dr. Cragan. Let me show you the experimental animal data again. This is the rat. And, if you remember, there were two control animals with spontaneous abnormalities, and then the two -- the middle and the high dose individual fetus with abnormalities. The middle dose fetus didn't have absent radius ulna or anything else. That animal had a normal limb. The high dose, we don't know.

Let me show you the individual fetuses. This is the one fetus that had a skeletal exam. And you can see that this fetus had other abnormalities beside the external finding of the short limb. There was syndactyly and anophthalmia. So, this is certainly an abnormal fetus, but not with any limb syndrome, other than the syndactyly, which is a spontaneous occurring malformation in the rat.

This is the second fetus, the one that was not examined skeletally. And this fetus, as you point out, could have had anything. We really don't know. I'm somewhat concerned about calling external malformations without internal verification. And, of course, in the prepostnatal study in the rat, there was no short limb in

 

several hundred fetuses.

The rabbit study showed an abnormal fetus in the control. There was also a fetus with multiple malformations at the high dose group, one of which was absence of the ulna. There was another fetus with umbilical hernia. And if we focus on that -- I need the rabbit -- well, let's just go on. If we focus on the rabbit fetus that had the abnormalities -- this is not -- this is the rat -- but that fetus had multiple abnormalities, including diaphragmatic hernia, gastroschisis, absent of gall bladder, as well as the missing ulna.

Now, I don't consider this to be a specific limb defect. To me this is an embryo that's had a disruption of the developmental program and is wildly just not put together well. So, this is not a specific abnormality.

In the mini pig study -- can I get that mini pig slide back, please? In the mini pig study, the incidence of polydactyly is high in many pigs. It's a spontaneous malformation that occurs commonly and -- even in controls. The polydactyly incidence was zero in the

 

high-dose group. The absent radius was present in a middle dose animal that also had other abnormalities. That absent radius was described by the study director as a radial rate abnormality, or radial rate deficiency, which is somewhat different from missing -- other than missing lungs, radial rate deficiency, as you know, in humans is a specific defect.

In addition, in the pig study we heard about the increase in resorptions -- in late resorptions. Interestingly enough, in these animals in the high-dose group, there's only one resorption per litter. It occurred in four out of the five litters. And that resulted in a elevation in the litter incidence of late resorption.

But the key thing about the mini pig study is that none of these animals reproduced very well, including the controls. So, this is a study that's difficult to interpret. So, because of the individual -- the sort of sporadic nature of the malformations, the lack of a dose effect, the general poor reproduction, the study director in this study -- for the mini pig study, concluded that there were no Theravance -- Telavancin

 

associated abnormalities, either malformations or other developmental abnormalities in this study.

One of the difficulties that we have with studies like this with sporadic and not reproducible abnormalities being interpreted as showing that a drug is a teratogen, is that, if you assign Category X based on sporadic malformations, Vancomycin would be Category X. And, of course, Category X says that the label writer has decided that the clinician and the patient play a role in making a risk benefit determination. Whereas Category C, which this drug clearly is, says there are adverse vex in fetus. In this case fetal weight reduction. And that the benefits and risk decision are made by the clinician and the patient.

DR. CRAGAN: And my -- along that line, I guess my second question is: Given the difference in interpretation that you and Dr. Manson had versus the FDA review, are there, in your opinion, additional studies, repetition of animal studies, things that might help clarify that difference in interpretation and have a more uniformed resolution of how the situation --

UNIDENTIFIED SPEAKER: It's an excellent

 

question. And actually we considered that question. The rat and the rabbit study were well-performed, standard, teratology studies, that to us gave very clear results, and that was the decrease in fetal weight. We can argue whether the fetal-weight determination or the litter-based determination is the appropriate one, but either way it's an adverse effect.

The teratology findings, the malformation findings were very similar to every other study that you see in these drugs. And I showed you some examples of Category C drugs. I showed you Vancomycin. These are very similar data sets. These are adequately done studies. This would be sufficient, in my view, to determine what the labeling ought to be. I don't see any reason to do additional experimental animal studies.

Now, the sponsor plans to put the limb findings in the label, although Dr. Manson and I considered them to be sporadic. But I think that to do anything further regarding categorization of this drug would be unwarranted and out of keeping with other data sets for other medications.

DR. RELLER: We have consumed the 45 minutes

 

allotted. I realize we started 15 minutes late, but we picked up 15 minutes in the open hearing. That was a draw.

There are eight persons who have already raised their hands. And what I would like to suggest is that we hear from each of them, but that -- after those eight -- and not all may ask the questions -- that we then go to a charge from the committee regarding the questions. And there will be opportunity for discussion during that period. Therefore, we will go to Dr. Lesar who has been patiently waiting for some time.

DR. LESAR: Yes. I'd like to ask questions right to the response with varying renal function. And I just want to point out the difference between the analysis of the FDA, which was FDA Slide 18, and then manufacturer Slide 34, in that there was a difference certainly in the CE evaluation. But what that apparently did is magnify the difference as the creatinine went down. And I'd like to have some comments by one or both related to how we should be considering that, because it would appear that that might have some issue related to the question, how we should label this drug. And also it

 

has to do with the noninferiority discussion of yesterday. I'd be interested to see if the analysis was done of just lumping all the patients who had serum -- were using the FDA numbers, everyone who had serum creatinines less than 50, and what those confidence intervals were.

DR. RELLER: While that reply is being assembled -- and please raise a hand when the responder is going to present the material -- we'll go to Dr. Weinstein's question.

DR. WEINSTEIN: I just had a quick clarification question for Dr. Barrier. When you -- when Dr. Alston asked you about the dysgeusia, you replied that it was transient. But do you mean transient associated with each dose, or did it only last in the initial period that the drug was being given and then no longer occur?

DR. BARRIERE: It often occurred during the infusion, and when the infusion was over it would fade away. There was some patients -- very few patients who would have repeated dysgeusia, and I believe very small numbers of patients who had dysgeusia just -- they could

 

not get rid of the taste. And those were the two Telavancin patients who discontinued. And actually there was one Vancomycin patient who discontinued due to dysgeusia as well.

DR. RELLER: Mr. Levin.

MR. LEVIN: Thank you. Two things. One is I would take exception, I think, to the statement that a Category X would eliminate a discussion and an informed decision-making process between patient and doctor. It creates a very structured process. For example, as we have with Accutane, where there is a formalized, informed consent, and a formalized providing of educational materials to the patient. So, I see it as actually an enhanced relationship, rather than the elimination of the relationship. Elimination of the relationship would be if we don't approve the drug, then we've taken it out of the hands of a patient and doctor to make a decision. Category X does not do that. It creates a set of management tools to try to mitigate the risk where appropriate. So, that's a comment.

On Slide 79 the sponsor and demonstrated benefits said, no emergence of resistance seen to date in

 

clinical trials. And as a lay person I was wondering whether any sponsor for any of the competing products could have made the same claim at this point in the development process.

In other words, when preapproved -- coming to an Advisory Committee for approval, given the small numbers involved in clinical trials prior to approval, is that likely to have been said by everybody, we didn't see any resistance? Is this something unique to this drug that is defensible in terms of the evidence, or is this simply sort of the reverse of lead-time bias?

DR. COLEMAN: Dr. Corey, you want to speak to that?

DR. COREY: All right. I think that during -- what we've seen in the last several years is a gradual emergence of resistance in other products. At this stage of the game, did -- was there resistance noted in Daptomycin in the studies? Absolutely. If you look at the bacteremia trial, the -- and endocarditis trial we did, there is emergence of resistance during therapy in seven patients. So, I think that that claim could not have been made at the same stage we were for it.

 

And I'm not sure about Linezolid. We know that since then there have been resistance. There may have been resistance in other Staph species, and I just don't know whether there was Staph aureus resistance during their initial consideration.

DR. RELLER: Dr. Cross.

DR. CROSS: I was wondering whether or not there are any other antibiotics that attack the Lipid II precursor, and if so have any of these developed resistance over time?

DR. COLEMAN: Dr. Benton.

DR. BENTON: The portion of the Lipid II molecule that's recognized by Telavancin is the diala diala (ph) peptide -- dipeptide terminus. That's the same structure that's recognized by Vancomycin. The place where the two antibiotics diverge is that Telavancin is more effective at targeting the Lipid II molecule for Vancomycin. Vancomycin binds to the diala diala sights on immature and mature peptidoglycan equally well as it does to that of Lipid II. Telavancin targets Lipid II primarily.

The -- to my knowledge there are no other

 

antibiotics that specifically bind Lipid II, approved antibiotics. There is Niacin, which binds to a different structure of the diphosphate cage on the Lipid II molecule. It's not an antibiotic. It's used a food preservative. There are other compounds, Ramoplanin, that binds to a different region of the Lipid II molecule. That's not yet approved for human use.

So, to answer your question, any other antibiotics approved for clinical use, no, other than Vancomycin there are not.

DR. CROSS: So, if I understand you, the Telavancin targets the exact same mechanisms of Vancomycin and -- which means both peptidoglycan and the cell membrane effects are also true for Vancomycin?

DR. BENTON: The cell membrane effects aren't true for Vancomycin. Could I have the table depicting the IC 50 values that was in our briefing document? I believe it might be Table 1. Thank you.

This table displays the inhibitory -- 50 percent inhibitory concentrations for the two cellular targets for Telavancin, and by comparison Vancomycin against the reference Staph aureus strain. And you can

 

see the cell wall. The IC50 for cell wall and the MIC correlate nicely. The membrane mechanism is approximately -- the IC50 is approximately 10-fold higher in this particular strain. And when (inaudible) in parallel, Vancomycin does not detect a producible effect on the membrane. You -- we cannot detect an IC50.

And this -- can I get Figure 1 from the briefing document as well, please? Another way to visualize this differential is -- was performed by conducting experiments were we derivatized Telavancin and Vancomycin with fluorescent tags and used those in microscopy studies to study the localization of the antibiotics on the cell surface.

Sorry. Figure 1 from our briefing document. And when that slide comes up, basically what it shows is that for Staphylococcus aureus cells -- Figure 1. That's the -- there we go. Thank you. And, so, we're labeling Staphylococcus aureus (inaudible) type cells with fluorescent antibiotics, Telavancin on the left and Vancomycin on the right. And the -- the side of active cell wall synthesis where the majority, if not all of the Lipid II, is localized in the cell was at the division

 

septum. And you can see that while -- on the right, while Vancomycin stains the septum, there's quite a bit of staining on the mature cell wall as well. And that's where a lot of the unproductive binding of Vancomycin occurs. Telavancin has limited binding characteristics to the mature cell wall, binds primarily to the division septum.

DR. RELLER: Excuse me. Dr. Septimus.

DR. SEPTIMUS: Real briefly. I want to get back to a subanalysis, specifically on the MRSA infected patients, did you do the same subset analysis looking at lower creatinine clearances, and also in patients who had underlying problems, such as diabetes, large lesion sizes, or other comorbidities, to which you stated the drug was less effective. How did it look for just MRSA or enough patients to do that subclass analysis?

DR. COLEMAN: Dr. Barriere.

DR. BARRIERE: The -- we did examine the -- and that's not the slide. We did examine the -- oh, I'm sorry. Put that back. That's -- that answers one of your questions. I apologize.

We did examine by comorbid conditions, such as

 

diabetes. And this is overall by a diabetes. And I'm not sure that we have the analysis broken into creatinine clearance in diabetic patients, but we did look at this in patients with MRSA by renal function.

And if we could have the slide up. The pattern for MRSA was very similar to -- was very similar to those patients with other organisms. No. That's not it. Oh, I'm sorry. Yes, this is it. These are in patients with normal or mildly impaired baseline renal function, where the results actually were significantly greater for Telavancin than Vancomycin in the patients with MRSA. And consequently the response rates, as I have just mentioned, in the patients with moderate or severe renal impairment were lower by about eight percent or so.

DR. RELLER: Dr. Mirkes.

Dr. Paganini, you passed?

DR. PAGANINI: Yep.

DR. RELLER: Dr. Smith.

DR. SMITH: Thank you. I just want some clarification, I think, from FDA on their animal studies for the teratology. I found it somewhat confusing that

 

they used the word significant. And I wasn't clear if they were using that in terms of statistically significant. So, I'd just like to ask, if the findings -- which findings were statistically significant. Dr. Chen, I think it was in your study -- in your presentation.

DR. CHEN: Here we don't seek for the statistically significancy. Here we just compare the positive findings with the control group, in the placebo control group. And as this point that we may use the clinical statistical significancy but we may not. We just -- based on the judgment -- the scientific judgment. Also we compare with histological database compared with that of finding to see if that's higher or lower this -- based on this. Not necessarily significant. Right.

DR. RELLER: And a final question or comment from Miss Thomas.

DR. THOMAS: This is a question to the sponsor. I'm very concerned about the nausea and vomiting side effects that were very high, much, much higher than Vancomycin. Can you tell me the duration

 

experienced by patients?

DR. BARRIERE: The nausea and vomiting that was observed was, as noted, was about twice as frequent in the Telavancin group as the Vancomycin group. Again, it was trenchant. And notably less than one percent of the patients discontinued for nausea, and about one percent discontinued for vomiting. Actually slightly less than one percent of patients discontinued. So, the nausea and vomiting was -- the vast majority was mild to moderate in intensity and very well tolerated by the patients.

DR. RELLER: And Dr. Pohlman's response to Dr. Lesar's question.

DR. POHLMAN: Yes. Since a little bit of time has passed, too, can I -- can you just clarify what it is you wanted to know and -- or repeat it for my sake so I -- now that I have all the numbers?

DR. LESAR: Yeah, the question had to do with the difference in the analysis by the FDA and the sponsor related to changes in response rate as creatinine clearance decreased. And the FDA analysis magnified those differences. And if one looks at the FDA analysis,

 

it -- individuals it become -- for let's say as a group with creatinine clearances less than 50 mills per minutes, the rate appears to be over 15 percent -- minus 15 percent compared to Vancomycin. And mine was the comment of, why that appeared -- urine analysis appeared to magnify that difference, and also how we should assess that in terms of thinking about labeling.

DR. POHLMAN: I can explain it now. I think there was a difference in terms of the population definitions for clinically evaluable, in terms of, as I mentioned, test-to-cure windows, compliance factors, some center effects played into that, although that should be taken out of -- that shouldn't be a difference between the two analyses.

In addition, the patients -- when I was trying to explain about the case report forms and the outcome assessment -- or the investigator assessment at end of therapy, when investigators assess people as indeterminate, they could go on to have a -- an assessment at test of cure and be cured, even if they got concomitant antibiotics. So, what -- instead of going through each -- what I did -- what I ended up doing was

 

doing an algorithmic type approach. I looked at the antibiotic that the patient received, what they -- what organism they had, why they were, you know, being considered -- whether I agreed with the assessment. And I think clinical evaluability status changed on some patients. Outcome assessment changed on some patients. Patients who got concomitant antibiotics were considered to be clinically-evaluable failures.

In addition, that was the -- in terms of the late surgical procedures there were some changes. There was no one predominant thing. But I think those -- that did contribute to the change in numbers -- or the difference. But I don't think it was all any one thing in particular.

DR. RELLER: Dr. Cox will introduce the charge to the committee before we deal specifically with the three questions on which we shall vote.

Are we okay with regards to the open public hearing?

There were no presenters at the open public hearing.

DR. COX: Thank you, Barth.

 

DR. RELLER: And for this afternoon and tomorrow, if there will be open public hearing, we will have that open public hearing at the time designated, even if it means coming back to questions.

DR. COX: Yeah. Thank you, Dr. Reller. I'll keep the charge brief. I know we're tight on time. I just note I want to thank all the presenters for this morning's presentations. Throughout the sessions we've covered a number of issues for the committee to consider. We've talked about information on efficacy, information on safety, including renal adverse events, animal Reprotox studies, information on QT studies. And we've also provided an update regarding some of the regulatory history on this application, and talked about some of the inspectional history, and then also the regulatory status with regards to Europe.

We've also heard discussions on approaches to risk management. So, this is, you know, information for the committee to consider. The questions that we have for you, number three, that we'd like to get your advice on. And if I could have those questions up, Janie.

The first question asks the question with

 

regards to safety and efficacy for Telavancin for the treatment of complicated skin and skin structure infections, asking whether the data presented demonstrate the efficacy of Telavancin for the treatment of complicated skin and skin structure infections. After your discussion we'd like you to vote yes or no.

And if your answer is yes, are there any specific issues that should be addressed in labeling, and whether you would recommend any further postmarketing studies to further evaluate nephrotoxicity.

And if the answer is no, what additional data or trials are needed?

The second question addresses the issue of use in pregnancy and asks, are there any clinical situations when the benefits of Telavancin use in a pregnant woman would outweigh the risk? And we're -- we'd ask that you vote yes or no on that.

And if there are situations where the benefits would outweigh risks, we ask you to describe those situations.

And then question three, we ask about risk management strategy. Is a risk management strategy

 

needed to prevent unintended use in pregnant women or women of child bearing potential? And we'd like you to vote yes or no on that.

And then also if your answer is yes, what elements should be included in the risk management program? And those are the three questions.

Thank you, Dr. Reller.

DR. RELLER: Question number one is now open for discussion among the committee members. Dr. Lesar. Yes. Please. I'm sorry. Go ahead.

DR. NELSON: Nelson.

DR. RELLER: Nelson first.

DR. NELSON: I know we look a like a little.

DR. RELLER: No. No. No. No. the signs were switched a little bit. Dr. Nelson then Dr. Septimus.

DR. NELSON: Yeah. I appreciate that. I actually thought I was going to be one of the eight that was waiting in the last session. I was a little disappointed.

But I actually want to bring up a topic that hasn't been discussed, which actually morphs into this

 

very well, and it's the question about QT. And one of the questions I actually had and I hadn't really seen addressed was the question of metabolism of this drug, and, you know, whether or not that metabolism may have any relationship to QTs. It does with many other drugs. We know that the parent comp may or may not produce QT prolongation, and the metabolite may or may not. And they're not necessarily related.

So, I don't know if this is a question for the sponsor or if it's just a question to just think about as we move forward. But along those same lines, I know that the sponsor in its labeling request had asked that this drug not be combined with other agents that are known to be QT prolongation -- that are known to cause QT prolongation. But what's not addressed is whether or not we should mandate the obtaining and checking of an electrocardiogram for QT prolongation before and during the time the drug is being given.

We know that in the world of QT prolonging drugs, the vast majority of people with most drugs do not develop QT prolongation. And there seems to be a uniquely susceptible population of patients who you can

 

identify by having a prolonged QT syndrome, although most don't, and many of them only develop QT prolongation when they're challenged with a certain type of drug. Many times those drugs are not picked up in premarketing circumstances, and many of them wind up getting black box warnings or getting removed from the market postmarketing because of QT prolongation. So, it's a long statement, but I think the question really is going to come down in my mind for the QT, as to whether or not we're going to be able to make it clear enough in the labeling that this is a real risk, something we have to be incredibly cognizant of as we move forward. Because it's going to happen rarely, but when it happens it could be very consequential.

DR. RELLER: Dr. Septimus.

DR. SEPTIMUS: I guess one is a point of clarification of what the charge is in that first question. Are we looking at the risk benefit ratio of safety and effectiveness in that question in being able to answer yes or no? Because clearly I think there's been a fair amount of data shown about the effectiveness, in terms of noninferiority trial. I have some concerns

 

about the efficacy about renal dysfunction and certain underlying diseases. But then there's the toxicity issue, which relays to the dysgeusia and the fetal problems -- potential fetal problems, and potential for nephrotoxicity and increasing nausea and vomiting. Do we consider all of those issues in answering those questions?

DR. COX: Yes. Yeah, it's a question of looking at safety and efficacy, so, it would weigh all the risks and all the benefits.

DR. SEPTIMUS: So, theoretically -- I'm not saying this is how I may or may not vote -- if you felt that the efficacy issue was not strong enough, but the toxicity issue was -- had greater weight, you would vote no on this question?

DR. COX: Yeah, because you would be considering all the risks and benefits --

DR. SEPTIMUS: Okay.

DR. COX: -- as you wait -- make that balancing.

DR. SEPTIMUS: I appreciate the clarification.

DR. RELLER: Dr. Kauffman.

 

DR. KAUFFMAN: I just had a small question. The sponsors can easily answer I'm sure. I was surprised not to see anything about red man syndrome. And also is there cross reactivity in patients who are hypersensitive to Vancomycin? Can you actually use it in those patients or not?

DR. BARRIERE: Sorry. The -- we looked at all infusion related events in the complicated skin and skin structure infection studies. Could we have our slide up, please? And this included, not only what would -- the investigators call red man syndrome, which didn't occur that frequently, but also any other reevents that might be considered infusion related; or typically like Vancomycin, if you will, including itching, and flushing, et cetera, et cetera. And the incidence was twice in the Vancomycin group, about 10 percent for -- 11 percent for Telavancin and 20 percent for Vancomycin.

DR. RELLER: Dr. -- Mr. Levin.

MR. LEVIN: So, I mean, following up on Dr. Septimus' comments. I mean, I think we're sort of in a difficult spot, because we -- yesterday we did a lot of work, but we didn't address Dr. Paganini's challenge,

 

which was we found a margin that we sort of said was okay, but we didn't deal with whether that margin would change if we were getting a lot of safety problems, signals on the drug under consideration, whether 10 percent was sort of all things equal, and 10 percent was too high if all things weren't equal. And in this case it seems maybe things -- all things aren't equal. We've got a lot of safety signals from a lot of different directions, QT, the fetal stuff, and renal. We don't -- you know, we don't have overwhelming evidence, but we have a lot of signal, a lot of stuff coming at us. So, I mean, I think it's -- we're sort of in a tough spot, because we did the work yesterday, but we sort of didn't do the next piece, which you suggested we need to do.

DR. RELLER: Dr. Fleming.

DR. FLEMING: So, these are really key issues as we do talk. As Dr. Septimus and Levin had pointed out, we did talk yesterday about margins, and we were very explicit about how the margin is very specific to the setting. And one of the aspects that it is sensitive to is safety. And if one has an anticipated favorable safety profile, that gives one more confidence to justify

 

using a 10 percent margin. When the reverse is true, it's very problematic.

We've had significant discussion about nephrotoxicity, QT prolongation, and safety risks in pregnant women.

If one is -- I guess it's leading to a question to Ed. In many settings it's not easy to characterize where the risk resides, what types of patients can you categorize where the risk resides, and if you can, then you can use it in others. When you can't, it really becomes especially problematic in the spirit of what you're saying.

So, Ed, if we think we can characterize the nature of patients who should be separated here, in terms of nephrotoxicity risk, QT risk, and pregnancy risk, and we think once you've separated those out in the remainder of the population, then benefit to risk would be favorable, then would we be voting yes?

DR. COX: Your question is a fair one. And that is, are there things that can be done to effectively manage the risk? And if there are things that can be done, should you consider that? And my answer to that --

 

excuse me -- would be yes. If there are things that can be done to manage the risk, then, in fact, when you're making your assessment, your assessment would be on the assumption that those things would be in place and that they would be part of managing those risks. So --

DR. RELLER: Dr. Black.

DR. BLACK: There's one thing that's been bothering me most of the morning is the concern -- which I'd like some support from others who do this and I don't -- is there really going to be more Vancomycin resistance? Is there really going to be more MRSA that's going to be Vancomycin resistant? We'd be approving a drug with that possibility, so it's available should that happen. And I'm not really sure where I go right now with that. If there isn't going to be anymore, or there isn't going to be anymore intermediate resistance where you need another drug, then I think the safety signals bother me.

I don't know who to address that to. There are a lot of people who are infectious disease experts here, and I'm not, so --

DR. RELLER: Dr. Septimus, and then

 

Dr. Goetz. And we'll have the -- and after those two we'll have the question.

DR. SEPTIMUS: I'll attempt to address that. I think we are seeing MIC creep. And we are seeing VISA and heterogenous resistance, a very little bit of VRSA, but I think the potential is out there.

So, I think the answer is yes to that question.

The other question I think that -- I think you didn't ask was, are there alternative agents to Vancomycin that are currently available that will give approximately the same efficacy that may be safer than the drug that's under consideration. I think that's really what the discussion is going to be about in making the determination on this drug.

DR. RELLER: Dr. Goetz. Oh, excuse me. Go ahead.

DR. SEPTIMUS: Well, there are, I think as has already been stated, and I just didn't want to -- but there are some other drugs. But to answer your first question, yes, there's increasing MIC creep, and other issues with Vancomycin.

 

DR. RELLER: Dr. Goetz.

DR. GOETZ: Briefly. I will endorse everything Dr. Septimus said. Looking at national databases, there's no question but Vancomycin MICs have been increasing. Looking at our own experience in Los Angeles, I'm frankly surprised by the fact that there were so few isolates with an MIC of two in the studies that were performed. And, yes, we also have concerns about the alternative antimicrobials. I endorse these statements made by the sponsor that there are concerns about nasalide resistance and that Daptomycin may be an imperfect drug for many of the patients with rising Vancomycin MICs.

DR. RELLER: The fundamental purpose of the Advisory Committee is to deal with difficult, complex questions.

It's time for voting on number one, many analogies to clinical decisions.

Please vote. You have 20 seconds --

UNIDENTIFIED SPEAKER: No, they don't have 20 seconds.

DR. RELLER: Oh, you have some time. Is

 

everyone sure they've pressed the right button?

UNIDENTIFIED SPEAKER: It's the last one they hit that counts.

DR. RELLER: The last one pressed is what counts.

Everyone is certain about the button that they pressed?

The vote is locked in. We'll see shortly the results.

The results of this vote are 21 yes and 5 no. We'll start at the left side this time and go around to those who voted and why they voted as they did.

Dr. Katona.

DR. KATONA: I voted no. Looking at all of these problems, the renal, the QT, the fetal abnormalities, in and of themselves I didn't see them as problems, but put together as a whole, together with a -- some data integrity problems, I felt uncomfortable giving it a complete yes. I was most bothered by this less response to baseline renal impairment when levels are expected to be high. I didn't quite have a good explanation for why that was.

 