no evidence of antigenicity as determined by an anti-antibody assay. We concluded that TMA-15 was safe and well tolerated at all the doses, ranging from 0.1 to 3 mg/kg.

[Slide]

At that point we moved into a safety and pharmacokinetic study in a patient population, namely, pediatrics.

[Slide]

We conducted the randomized, double-blind, placebo-controlled study in STEC positive children, ranging from ages 1 through 15, although the majority of the patients were under the age of 4. Entry criteria required that they have bloody diarrhea of less than or equal to 72 hours at time of IV infusion, which was given as a single administration, and we studied two doses, a 1 mg/kg dose and a 3 mg/kg dose. The initial 24 subjects were actually administered drug in a sequential fashion for safety. We started off with 1, did 12 and then moved on to the 3. We had independent assessment of the safety data and then proceeded

with assessing both safety and PK for the complete panel of patients, and we also looked at efficacy.

[Slide]

In terms of enrollment, which I think is one of the dilemmas that we are confronted with, we actually had sites in Canada, the U.S. and Argentina and we will talk about some of the difficulties, but we had gone in with the premise that we would be able to enroll 36 patients from our North American sites. We had selected sites that had previously worked with an oral binding agent for Shiga toxin. Unfortunately, we were only able to enroll 8 subjects from the 6 sites. In fact, it was only 3 sites that actually produced patients. Three of the sites did not produce any subjects within that one season.

In Argentina we conducted a study over a 13-month period and we were able to enroll 101 subjects from seven sites. Totally, we actually randomized 110. We were able to actually administer drug to 109 within that 72-hour window of onset of bloody diarrhea. We followed all of

the patients for a period of 4 months.

[Slide]

The pharmacokinetic results indicate that PK was similar to the adult PK findings that we had, and mean plasma concentration remained above 10 mcg/mL, again, for about four days at the 1 mg/kg dose level and for more than 22 days at the 3 mg/kg level.

[Slide]

This is just the graphic of the PK profile where you can see that the 3 mg/kg that is illustrated in blue shows an extended area above the 10 mcg/mL, as represented by the red dotted line.

[Slide]

In terms of safety, we saw few differences in lab values, vital signs or adverse events. There are actually slightly fewer SAEs that were noted with TMA-15 compared to placebo. The 24 percent represents the 1 mg/kg; the 17 percent is with the 3 mg/kg and 28 percent for placebo. There were two deaths that were determined to be

unrelated to TMA-15. One was in the placebo group. The child succumbed to HUS. The second patient, who was in the 1 mg/kg group actually had a Klebsiella pneumoniae pneumonia and actually was in tremendous decline by the time they had actually administered the TMA-15. There was no evidence of antigenicity in any of the subjects that were assessed. In fact, all the patients were assessed using our assay for anti-TMA-15 antibody. Thus, we concluded that at this point there were no identified safety issues with TMA-15 clinically.

[Slide]

Which brings us now to the issue of statistically significant randomized studies.

[Slide]

We have heard today that STEC infection is sporadic. It is infrequent. HUS is uncommon and, from our perspective, there are very few options to enrich the patient population at risk for HUS. In our study we were able to enroll only 8 percent of the patients that were screened, that is, 109 out of 1,368 patients that were screened.

[Slide]

We heard aboutB-what?--84 years today about conducting a study well? I am glad to say that we can do it in about 14 years. But we used a 90 percent power in our calculation, looking at a 10 percent incidence of HUS and we are looking at a 50 percent treatment reduction effect. So, just looking at those numbers, using our calculations, we require over 13,000 screened patients.

[Slide]

So, what did we conclude from this? Very simply, it is not feasible to conduct an adequately powered study to demonstrate a statistical significance in prevention of HUS as the primary endpoint, and that we need to generate data from other corroborative measures of efficacy.

[Slide]

So, what are those? They are clinical outcomes and they are nonclinical outcomes. For clinical these are dose effects, timing of treatment, HUS severity, progression from watery diarrhea to bloody diarrhea, and SLT-2 blood

concentration. Nonclinically we are looking at SLT-2-induced mortality, STEC-induced mortality and SLT-2 blood concentration, as you saw earlier.

[Slide]

What are the potential corroborative outcomes? First of all, it is important to use endpoints that are sensitive to treatment effect that are clinically meaningful. HUS by itself is clinically meaningful but it is not practical to do. If we look at frequency and quantity of stool, it is very practical to do but it is not clinically meaningful for a drug intended to prevent HUS. Looking at composite outcome measures may not improve the sensitivity to treatment and, in fact, it may even introduce a lot of noise and it may be very difficult to interpret.

[Slide]

So, our approach is to use one that integrates data sets from both animal and human studies that provide evidence of efficacy, and blending those data to address the issues of a package insert and prescribing the drug.

[Slide]

Again, the patient population would be pediatric patients with watery or bloody diarrhea, and have a positive 0157 or SLT-2 positive stool sample.

[Slide]

As far as timing of treatment is concerned, based on the animal and the human data, treatment should begin immediately after confirming STEC infection. The limitation is that we don=t know how late in the process we can do that.

[Slide]

As far as dose and dose regimen is concerned, in pediatric patients we use a regimen that maintains effective concentration that was determined preclinically, and that effective concentration should be maintained for a appropriate period of time clinically, and we are saying approximately for at least 10 days.

TMA-15 in culture and in vivo at 10 mcg/mL is shown to be protective and it can be achieved and maintained in pediatric patients for about 3

weeks at the 3 mg/kg dose administration.

[Slide]

In terms of clinical benefit, blending of the animal and the human data should provide evidence of the desired effective, i.e., prevention of hemolytic uremic syndrome. TMA-15 animal data are statistically significant and highly predictive, and the clinical data suggest that the drug has the expected benefit.

[Slide]

What are the potential risks?

[Slide]

The safety profile utilizes a combination of studies in animal models, healthy volunteers and infected patients. To date, no safety issues have been identified with TMA-15 either in the animal models that have been used or in the humans, both the healthy adults or the pediatric patients. The human safety database thus far is over 107 individuals that have been exposed to the drug to date.

[Slide]

So, in terms of risk/benefit, we view that the risk of using drug is relatively low, whereas the benefit would be prevention of HUS.

[Slide]

Our conclusions are such that HUS is a serious and unmet medical need. Traditional statistically significant clinical studies of HUS incidence are not feasible. And, blending of animal data with human data can provide evidence of safety and efficacy needed for appropriate clinical use. And, we would need to follow-up collection of data postmarketing to further define efficacy and safety. Thank you.

DR. RELLER: Thank you, Dr. Brookman. You are doing the presentations for Teijin or do you have other speakers?

DR. BROOKMAN: No, no other speakers but if there are questions I may be able to answer or either our PI, Dr. Lopez or Dr. Cato or Dr. Peterson might.

DR. RELLER: Thank you. Questions for Dr. Brookman? Dr. Kocis?

DR. KOCIS: I guess I have been listening to the two talks and really still in my mind I am trying to figure out what the endpoints are and how we are going to separate statistically significant results from clinically significant and meaningful results that are going to want us to move towards using this drug. Certainly the preclinical looks good. All the stuff you described looks good but, you know, we have another series of data that follow a very similar role in sepsis looking at anti-TNF antibodies, and the like. You know, we can show we can block certain mediators where you stop the progression but when we give the drug to patients who have sepsis, again, they get infected, at some point they develop sepsis syndrome at a later data. We didn=t impact the outcome of the disease. So, I would look back at those studies and learn from what we went through with those studies in the >80s and >90s and we are following a very similar path.

I guess my biggest problem is, you know, obviously there are STEC-positive patients aren=t

going to move on; 85 percent are going to be self-resolving that we are not going to need to do anything, and the like, and from my standpoint as an intensivist, and obviously I am biased, for 85 percent of the patients, if they have a self-limited disease whether we give them drug or not, it is going to be unimportant and, given the cost of what this is likely to cost, the lab testing and all this sort of stuff, it is unlikely to become a clinically significant outcome unless we can prevent that 15 percent meaning dialysis, meaning chronic renal failure, meaning other severe consequences. Certainly, looking at the scoring system that we have used, just sort of looking at that as one thing, you know, I am very troubled by the scoring system, its development, its validation and all those sorts of things, looking at the diarrhea as a major component of that and knowing that frequency of diarrhea doesn=t impact, can=t even predict what happens as far as those severe chronic real failure, dialysis requiring outcomes, and then ultimately we get down to the major things

which are the definitions of HUS so we are sort of defining HUS, i.e., if you are anemic, if you are thrombocytopenic and you have renal failure, and that I am not sure we need a surrogate for. We can look at rises. We can look at values. We can measure creatinine which is a continuous variable, and we don=t have to go into this waiting issue that we have described.

But ultimately when it comes down to it, as far as I can tell, at least in the United States a blood transfusion, a platelet transfusion is likely to carry much less risk than anything else we are potentially talking about. So, the only outcome that I can see that you are going to need to look at to change is a need for dialysis. I think anything short of thatB-and chronic renal failure that then would follow from that, and I haven=t heard any of the treatment players. We talked and spent a lot of time on fluids but, you know, thinking about the decisions that go into who gets dialyzed are we going to define criteria that creatinine is going to be two, three, four? Being

in this situation and having gone through those decisions, it is a very nebulous thing. It is one that is going to vary markedly by center. You are going to have 50 centers. What patients are going to move to the ICU? What patients will begin dialysis? What kind of dialysis are you going to do? What are the co-morbidities in doing dialysis in foreign countries? These are going to have impact on long-term outcome and mortality as yet another indicator, which we have all decided you are never going to show with the frequency of change in mortality with this drug. I mean, it would have to be an incredible silver bullet.

So, I am left with a lot of questions about what are we going to measure; what are we going to look at; and the clinical pathways that are going to go into the decision-making to decide on dialysis, decide on the length of stay, and I haven=t heard any of that described.

DR. BROOKMAN: Well, I would like to ask Dr. Lopez to talk about the issue of dialysis and treatment because he has probably treated more

patients than I think anybodyB-I mean the total number of people in this room. I think he has treated over 600 HUS cases.

DR. LOPEZ: Good afternoon. I am Dr. Lopez from Argentina. I received a fee for consultation from Teijin. I work in a hospital that receives 60 patients per year of HUS.

We have conducted surveillance studies with 2,000 kids. In bloody diarrhea, 20 percent of them are STEC infection. In watery diarrhea, it is about 3 to 6 percent, and 70 percent of our HUS cases we can provide that were infected for Shiga toxins.

Our incidence of HUS requires that around 50 percent of our patients require dialysis. We have seizures between 10 to 20 percent which could be another issue to take in mind in order to see other composite outcomes.

We have, more or less, 40 percent of our kids that develop renal sequelae and 10 percent who develop seizures have neurological sequelae. That means this is another important issue to keep in

mind.

We have some data in our surveillance study that show that watery diarrhea, in our setting at least, even though we suspect watery diarrhea is a real event to go through a choice, is only 3 percent. But in the STEC bloody diarrhea the outcome is that 11 to 10 percent develop HUS. This is a huge difference.

What is another important thing is that a shift from watery diarrhea to blood diarrhea is a risk factor. People who from shift watery to bloody diarrhea in STEC infection have more risk to develop HUS than other people.

There is other data that we have which is white-blood-cell count. I think it is another important corroborative outcome that we have to take in mind because we see that such amount of white-blood cell count is at higher risk to develop HUS than other people. What I am talking about is baseline data. Okay?

I don't think the other issue is about could be early enough. For instance, if the

creatinine is elevated, I think it is a late marker. I think, perhaps, proteinuria, some microhematuria could be more useful, really, at least as the bedside for risk factors.

Then the other thing that I wanted to tell you is that our incidence of non-157 strains in our setting is 70 percent, responsible to develop HUS, relying on the data in North America, particularly in Canada and the United States, which is that 0157 is almost 95 percent of the incidence. That means that perhaps it is a different environment for HUS. I don't know if I answered your question.

DR. KOCIS: Can I just clarify because, again, you are saying 50 percent of your patients require dialysis.

DR. LOPEZ: Yes.

DR. KOCIS: That, to me, is an enormous number, certainly compared to my practice which, again, pales to yours. But I think that the numbers we have heard and things--and certainly the nephrologists can pipe in to say what is more likelyB-the question in my mind is, if we are

trying to prevent dialysis, what are your indications for dialysis because now, if you are expanding it to proteinuria or--

DR. LOPEZ: No, no.

DR. KOCIS: What are your indications? If it is load overload and we are going to hydrate them with saline from the ER, then that is going to be one thing. If we are going to look for a creatinine of 3, and we have heard some data that maybe early dialysis may be better dialysis because maybe it shortens their course of outcome, still unproven, but each of these centers--and this is going to need to be well-defined if that is going to be your outcome which, in my opinion, is the only one that is going to be of significance.

DR. LOPEZ: Okay. You know that dialysis has several indications in HUS, not just one. One could be, for instance, hyperkalemia, severe hyperkalemia, that you cannot manage orally or IV. The second point is days of anuric. The third point--well, because usually days of anuric relate very well with elevated creatinine in HUS patients.

Okay?

The third one is hypervolemia. The patient has pulmonary edema is another very clear indication. Well, there is another which is more a result of the nephrologists, but we don't have different indications of dialysis. I mean, all of these results are very well published from Gianantonio to our days about which are the indications of peritoneal dialysis.

I want to tell you that right now we have almost 40 years experience with HUS and peritoneal dialysis. Probably in our hospital, the first peritoneal dialysis was performed in Argentina. This is why I think that there is not a different indication in our state about that.

DR. KOCIS: I would just follow up with the same for platelet transfusions, for red-cell transfusions.

DR. LOPEZ: Yes.

DR. KOCIS: If we are using them, which the score does, as major outcomes, I can just say that in my world of critical care there is vast diverse

opinion as to what number we are going to use and it is always, again, that mixture. That is going to need to be well-defined if that is going to be an outcome.

DR. CATO: This is Allen Cato. Hopefully, I am going to be paid by Teijin!

DR. RELLER: Your name, please.

DR. CATO: Allen Cato.

DR. RELLER: Yes?

DR. CATO: I don=t think we are suggesting using any kind of composite score. I think what we are suggesting is that basically you look at different parameters relative to HUS because it is the only meaningful endpoint, and you can look at high dose, low dose for instance. Well, maybe you see a difference. But at the end of the day you are not going to see a statistically significant difference.

So, the real issue is are you seeing data move in the right direction? I think both presentations agree that if you don=t see data move in the right direction, you know, then you don=t

have a drug. But if you see it moving in the right direction the question is how far does it have to move, in how many different directions of things that are related to HUS, clearly related? Again, if you have high dose, low dose, if you give a drug you can go back and calculate how long did the patient have bloody diarrhea before you gave him the drug?

Well, if you open up the window you may find that beyond a certain time frame you get HUS and it doesn=t work beyond that. But if you get more numbers beyond a certain time frame and less numbers before that time frame, that is a good indicator that you have a drug that is working.

At the end of the day you just have toB-I think what we are saying is you have to look at the data from the standpoint of what is really clinically meaningful, I agree with you there, and make a judgment combined with the animal data because you are not going to get a statistically significant trial.

There is precedence for this in drugs that

have been approved that are orphan drugs for which either you can=t give placebos, in some cases, or which are just so rare you don=t get a chance to get statistically significant trials. But each one of those is unique. While we can say they are precedent, none really is a precedent for the other because every single situation is really unique. I think that is why you all have been called here by the FDA to help this particular unique situation and help us figure out what do we do if you want a drug for this indication.

DR. RELLER: The committee will wrestle with these issues and try to address the questions that Dr. Cox is going to pose to us. Before taking the break and launching into that intense session, there are four people waiting for questions and at the end of those four we will take our break. In order, Dr. Cnaan, Wiedermann, Fant and Tarr.

DR. CNAAN: I have one question and a brief comment. My question is in your PK study in which you have, I guess, by now close to 70 kids on one dose or another, did you look at dialysis and did

you look at length of stay?

DR. BROOKMAN: I will address the last point differently. The length of stay is very difficult to quantify because of the differences from institution to institution, and in Argentina if there is no dialysis they send the kids home pretty quickly. They tend not to hospitalize. Is that correct, Eduardo? In terms of hospitalization, it is only the most severe cases that get hospitalized, those that require dialysis or have some intercurrent complication.

DR. LOPEZ: Patients with HUS are hospitalized always. Okay? Patients with bloody diarrhea, STEC infection bloody diarrhea, will be hospitalized if it is needed. That means that patients that have dehydration or some hemorrhagic colitis symptom, or we have some doubt that it is coming out to HUS, we hospitalize.

DR. BROOKMAN: What was the first part of your question?

DR. CNAAN: The dialysis, the same question. Did you look in your data that you now

have at the rate of dialysis? You do have three groups at this point.

DR. BROOKMAN: Yes, they are comparable but it is difficult to interpret the data because the timing of the treatment varied. For example, in the placebo group it turned out by circumstance that those patients tended to be treated a lot earlier, whereas the patients in the active groups were treated much later in the time sequence up to 72 hours. So, it is hard to interpret that data.

DR. CNAAN: By brief comment was that in using the rule of three that we all looked at earlier, the risk, to me, with the number of patients who have to date is that you can only exclude, if you will, adverse events that occurred at a frequency of more than 3 percent, but anything that occurs less than 3 percent at this point, I don=t see the data.

DR. BROOKMAN: No, we recognize that we are not finished with the development. We are just saying at this point that this is all that we have in hand. We do intend to continue with an

additional study.

DR. RELLER: Dr. Wiedermann?

DR. WIEDERMANN: Thank you. I have three brief questions that I hope have brief answers. First of all, in your slide 29 you say there were no adverse events related to TMA-15. In your briefing document you say headache was the most frequent and, of course, that was a problem with the other product. I would just like to know what kind of headaches are we talking about. Is this minor?

DR. BROOKMAN: Minor, very minor and very transient, short term.

DR. WIEDERMANN: Second question, in your calculation to figure out that it would take 14 years to do this study you chose to do the calculation with 90 percent power. What does it look like when you use 80 percent power?

DR. BROOKMAN: A little bit less, maybe 11 years.

DR. WIEDERMANN: Finally, I agree with you, and others have said that when you look at sort of

the scoring systems or composite outcome measures it could introduce a lot of noise, but also there may be something worthwhile in there and I am wondering, now that you have randomized over 100 subjects, would you take some of Dr. Bitzan=s approach and apply it to that data set?

DR. BROOKMAN: We actually data dredged ad nauseam. I have these long, big sheets of paper with tables and we were looking at changes, for example, in platelets, serum creatinine and thrombomodulin. We tried to even establish a weighting score to some of these, because some are more important than others, and we could not figure out a pattern. After several weeks of working at this, we just threw up our hands and said that is it, it is just too complicated, which is one of the reasons why I said we may be just introducing a lot of noise.

DR. FANT: Yes, I have two questions. One is a general question related to pathophysiology of Shiga-mediated disease. It is a follow-up to the question I asked Dr. Cleary. Can anyone speak to

the recurrence risk of Shiga-mediated hemorrhagic colitis, separate from hemolytic uremic syndrome? That is, you know, trying to sort out the different types of immunity. That is one question.

The second question is probably specific to Dr. Lopez. Argentina seems to be a very important site in any study that is going to try to knock off a few years in terms of being able to complete it, and your incidence seems to be quite a bit higher than in most other places. So, my question is do you have any idea whether the difference is due to some intrinsic biologic difference between the population in Argentina versus everywhere else? Or, is there some environmental difference, or differences, and what efforts have been made in Argentina to try to impact on those differences that might reduce the risk and be a lot more cost effective?

DR. LOPEZ: Well, our ethnicity is the same as the United States. We are 40 percent from Spain, 40 percent from Italy. The third group is Jewish people. That means it is almost the same.

We have not many black people; okay?

But I think that the environment is quite different. When we studied for many years with Tom Cleary this disease, we made a surveillance in 1,400 families asking when you introduce meat for the kids. The meat is introduced usually between 3 months to 4 months. But, at 9 months old, 85 percent of the kids eat meat 3 times a week and 60 percent of them eat raw meat or at least that is juicy. Okay?

I think the environment is quite different because beef is very cheap in Argentina. It is quite different about the chicken which is very expensive, or salmon is extremely expensive. I think that the environment is quite different. In our culture, we are used to preparing meat more red in the center than very well-cooked. I think the environment is quite different. The culture is quite different. Introduction of meat in the diet of the kids is quite different.

We have, more than that, a lot of non-157 strain that can produce Shiga toxin. That means

that we have a different environment to develop this disease. For your information, we have 400 to 500 cases of HUS in the country per year. This is the number. It is an endemic disease, in fact, that takes mainly the center of the west to the east, the center of the province, and the south. We don't have cases of HUS in the north. We don't know why.

DR. FANT: Are those differences resistant to modification in your opinion?

DR. LOPEZ: Okay. Well, I don't work in the government but I think this is the responsibility of the government, really. That means that I think that we need to teach people how to learn how to handle food contamination, cross-contamination, all of this stuff. But, really, it is out of my hands to change this.

DR. BROOKMAN: You asked a question also about recurrence.

DR. FANT: Yes.

DR. BROOKMAN: Dr. Lopez actually has some data in over 600 patients that he has treated with

HUS. How much was your recurrence? Recurrent hemorrhagic colitis, Shiga-mediated hemorrhagic colitis?

DR. LOPEZ: It is almost zero.

DR. BROOKMAN: And this is in a country where it is endemic.

DR. LOPEZ: Right. We see with Tom a lot of data, many cases, and we don't have Shiga toxin-related HUS recurrence. There is another issue with this assay. Recurring HUS was a different issue than the typical HUS, bloody diarrhea as a problem. Okay? We don't have recurrence of hemorrhagic colitis for STEC infection.

DR. RELLER: Dr. Tarr, do you still have a question?

DR. TARR: I have one question for you and one question for both groups. I think it is terrific that you have been able to enroll 100 patients so far. That is really good. You were a little oblique in your data. You said that you enrolled almost all of them within 3 days of the

onset of bloody diarrhea. What was the median day of enrollment, and also what was the microbiology on the patients?

DR. BROOKMAN: Eduardo, do you want to take a stab at that?

DR. CATO: I think it is 36 hours, the median.

DR. TARR: You enrolled a median 36 hours of diarrhea?

DR. CATO: No, no, no, from bloody diarrhea.

DR. TARR: What day of diarrhea because most of the occurrence of HUS data relate to the day of diarrhea? When was the first loose stool pertaining to day of enrollment?

DR. CATO: I am not sure what you are asking--

DR. BROOKMAN: You mean to take into account the watery diarrhea that preceded the entry criteria?

DR. TARR: Which was almost certainly after the beginning at least of the toxemic phase.

DR. BROOKMAN: I would say it averaged approximately 2 days, if I remember correctly. Hiro? Hiro Sato actually has the data.

DR. SATO: Hiro Sato, from Teijin America. The mean timing of drug administration in that study was 36 hours after the onset of bloody diarrhea.

DR. TARR: To rephrase it, what day of illness did the bloody diarrhea occur? We can add on the non-bloody interval.

DR. BROOKMAN: The duration of watery diarrhea preceding bloody diarrhea, I think it was about 2 days. We don=t have the slide here but we will look it up.

DR. TARR: The microbiology then and one final question for both groups.

DR. LOPEZ: The microbiology is we make a broth method with the Meridian assay plus PCR. Okay? And we can increase the diagnosis 10 percent with PCR. Around 40 percent of the strain were 0157, 40 percent. And 60 percent are non-157. Right now, we are serotyping these strains. We are

going to see which serogroup it is.

DR. TARR: What was the O-antigen-specific progression rate to HUS?

DR. LOPEZ: What do you mean?

DR. TARR: What product of 0157s went on to HUS and what percent of non-0157s?

DR. LOPEZ: In the patient study?

DR. TARR: Yes.

DR. LOPEZ: I don't have the data because there were very, very few patients, I think, who developed HUS. It is only 3 patients, I guess.

DR. BROOKMAN: No, we had a total of 6.

DR. LOPEZ: But you have some in the placebo group.

DR. BROOKMAN: Yes.

DR. LOPEZ: I think it is 50 percent and 50 percent--I think.

MR. BROOKMAN: We will get that to you.

DR. TARR: Then a general question, now that we are approaching an era of on-the-spot diagnosis of an infected child, which is terrific, if this is going to be funded by a study or at

least engendered by a study what are the ethical considerations of sending a biohazard, such as an infected child, back into the community now that we have identified that they are excreting a potentially lethal pathogen, rather than hospitalization? It is a general question.

DR. CLEARY: Well, I am not sure what the right answer is. You know, Phil, obviously you have recommended hospitalizing all the kids who are found to have STEC and I think that makes a lot of sense currently. What has happened in the past, obviously, is that kids were hospitalized based on how they were doing clinically. That is why Dr. Bitzan talked about 30 percent or so of the kids being admitted to the hospital because of the severity of the enteritis, and why we talked about decreasing the severity of the enteritis enough that it affects hospitalization might be important.

The issue of sending them back into the households is a really difficult question. I don=t know what the right answer is right now. Traditionally, that has been done most places but I

am not sure that what you are recommending or what you have recommended isn=t the right thing to do. It would make judgments about the validity of hospitalization as an outcome difficult to interpret obviously, but there still would be other indicators, even if you admitted everybody, in terms of the severity of enteritis if you used the sort of scoring system that Dr. Bitzan has talked about. So I, personally, probably would feel more comfortable with everybody in the hospital but I am not sure that nationally and internationally that is yet the standard. It makes a lot of sense to me but I am not sure we are there yet.

DR. RELLER: Dr. Brookman, thank you to you and your colleagues. We have much work yet to do to fulfill our responsibilities as an advisory committee to the FDA. I would like to ask that those who need a break take a break. Those who don=t need a break stand up and stretch, and we will try to be back within ten minutes, preferably closer to five. So, we will try to start at 4:20.

[Brief recess]

DR. RELLER: If the advisory committee members could please again take their seats, we will hear the charge to the committee from Dr. Cox. Dr. Cox?

Charge to the Committee

DR. COX: Thanks, Dr. Reller. First I would like to thank everybody for the informative presentations today and all the comments from the participants. I think we have found the proceedings so far to be very helpful to us.

I will just make some brief remarks and then walk through the questions that we would like the committee to address and provide us advice on. First, just to jump back to the start of the day, we had a discussion about the regulatory approaches to addressing the safety and efficacy for a product. Clearly, we recognize that doing human clinical studies is challenging but we believe that the information from human clinical studies would provide necessary and important information in order to be able to understand the efficacy, how the product works and the safety of the product,

recognizing that the safety of the product may be in part impacted upon by the disease state that the participants in the study have.

Over the course of the discussions today we have also heard about the importance of the timing of initiation of therapy, and also the issue of a therapeutic window. Clearly, these issues are also related to the enrollment criteria that would be used to enroll patients into the study.

Then, you know, another component here that is another point I will just mention briefly that came up in the presentations is this issue of number needed to treat, realizing that not all folks enrolled in the study are likely to go on to HUS.

Then, moving to the first question, and I will just read through these, the first question deals with the issue of animal models and what role animal models might be able to play here, what sort of information they might be able to provide. We will ask you to discuss the two elements of the question, elements (a) and (b) and also vote. So,

reading through the question:

While the agency does not believe that product approval for this indication can rely solely on efficacy data from animal models for approval--the Animal Efficacy Rule is what we are referring to there--we would like the committee to consider whether animal data may provide supportive evidence of efficacy.

So, the first question here is does the committee believe that the pathophysiology of Shiga toxin-producing bacterial infection and the resulting complications in animal models are sufficiently understood so that we may conclude a model exists that is predictive of the disease in humans? If so, which animal model? In the presentation earlier we stepped through a number of different animal species so we will ask you to vote on that question.

The (b) part of the question, if the answer to the preceding question is yes, does the committee believe that the animal models may be used to provide supporting data for drug and/or

biologic products that seek to intervene in the disease process?

Moving on to question two, question two gets to the issue of the endpoint and there has been some discussion of this over the course of the day and we will be asking the committee to comment on this. Some of the discussion over the day has touched on the issue of, you know, although harder clinical endpoints happen less frequently, they do provide more persuasive evidence of the findings from a study. I am sure that will be something that will come up in the discussions. The issue is that the harder clinical endpoints happen less frequently.

So, question two asks at this time it is anticipated that any product seeking approval or licensure for treatment of Shiga toxin-producing bacterial infection would be studied in clinical studies of a superiority design, in which the product plus standard of care would be compared to standard of care alone. For products seeking to intervene in the disease process prior to the onset

of HUS, what primary endpoint should be used to determine efficacy?

We heard some discussion of this, and the committee may feel free to expand this but the two examples we have included there are (a), prevention of HUS only and, (b), are there alternative clinical endpoints that the committee considers clinically meaningful that may be included in a composite endpoint with prevention of HUS?

Then, the third question is more one for discussion and comment. One of the topics that we heard discussed over the course of the day is the challenges that are encountered in trying to do a clinical study in patients with Shiga toxin-associated disease and for prevention of HUS. And, we will be looking for the committee=s suggestions about if there are certain strategies that might be able to be employed in order to make these studies such that they may be able to be enrolled with greater efficiency.

So, question three asks, the enrollment of patients in clinical studies to assess the safety

and efficacy of products to prevent the complications of shiga toxin-producing bacterial infections is challenging due to the low incidence of infection and the sporadic nature of outbreaks. In addition, there may be a limited therapeutic window in which an intervention may be efficacious. Does the committee have any suggestions regarding strategies that may enhance trial enrollment?

It is not a voting question but a question for comments, and we will look forward to hearing some suggestions as to what might be used to make it easier perhaps to enroll in these trials. Thank you, Dr. Reller.

Committee Discussion and Vote

DR. RELLER: Thank you. One of the reasons that we sought to have everyone ask their questions earlier was so that we could zero in on the questions now and aim toward a vote to give a quantitative sense from the committee to the agency as to the weight we would give in making these decisions.

So, we will go straight to 1(a), does the

committee believe that the pathophysiology of this disease and resulting complications are sufficiently well understood that an animal model exists that is predictive of the disease process in humans?

We would like yes or no answers on this. We will start at the right and come around the table. After the vote there can be any important discussion that would take place, but we don=t want to re-discuss all the matters that have been discussed at length before. Dr. Griffin?

DR. GRIFFIN: I hope you rotate who has to go first!

DR. RELLER: We are. The first time we are going this way and the next time we are going to go this way.

[Laughter]

DR. GRIFFIN: I would modify the question slightly to say that a model or models exist that together could, and not going further into my rationale for that I would then say yes to (a). If so, what models sort of presumes that that is what

the question intended.

DR. RELLER: I think it would be helpful on this one, the way I consider this is does any single animal model or even components, I mean, does it fully reproduce the disease? If it does, then we can get to which animal model most closely approximates. Then, the second part of this question, (b), has to do with how much consideration, if anything models the disease, should the agency give to animal models in relation to the two adequately controlled clinical trials? Should it be supportive? Is it so good that it could replace one of them? I mane, to give that sense to the agency from the committee. That is what you want, isn=t it, Ed?

DR. COX: That sounds fair, yes.

DR. RELLER: Is there an animal model that mirrors the disease processes that we have been talking about, including what we are going to be coming to in question two, the critical endpoint in your view?

DR. GRIFFIN: For me the devil is in the

details of the exact phrasing of the question. The way you phrase the question, I would say no. The way I interpret how it is written here, I would say yes.

Do you want to start at the other end and go this way?

[Laughter]

DR. RELLER: We must finish by 9:00 p.m. I would like to go on as I phrased the question, does any animal model, not getting into which one but is any model that you have heard presented and discussion related thereto, give you the confidence that performance in that animal model is predictive of what the performance would be in a patient with STEC diarrheal disease and its ensuing complications in 5-15 percent of patients in the worst form? Dr. Griffin, do you want to vote again?

DR. GRIFFIN: The way you phrase it, I would have to say no.

DR. RELLER: That is one no as phrased, and we will capture the exact wording because, again,

clearly there are nuances to these. The FDA questions are always nuanced depending on how they are interpreted, but I think what the agency wants from the committee is, taking everything into consideration like a clinical decision, what is the sense of the committee? Are these, as we understand them, good enough? Dr. Kocis?

DR. KOCIS: I think there are several models that we have heard described and I would defer to the presentation today. I think the mouse model was an incomplete model. It mimics to some degree the human state and we have heard that potentially, at least from the presentation today and from what I gather without knowing more about it, the piglet model seems better. So, in my mind, as in most modeling, to have overlapping models would be preferred. I think the data they presented with the mouse answers one aspect of it. I think it is an incomplete answer and I think personally I would ask those questions to be raised in potentially a better model, a preferred model or an overlapping model, meaning the piglet model.

DR. RELLER: Dr. Daum?

DR. DAUM: So, I am going to interpret the question as are animal data helpful, and I think the answer is yes, they are helpful.

[Laughter]

Well, they might not be helpful because there might be no model that is sufficiently predictive that we would entertain any data from them in terms of thinking about moving this product forward. That is not my view. My view is that the models I heard have some helpful features and none of them are perfect. So, if I were sort of making the rules here I would say that animal models would support potential licensure application but I would like to see more than one because I didn=t see one that was perfect. I think the mice win points for their convenience and we saw mice data today that looked nice to me, from both presentations, and it sounds like the closest one to medical relevance is the piglet and I would suggest that be another one, but I think there are different approaches. So, I would say yes, animal data and more than one would

be necessary, and they would be supportive data. I don=t think they would be sufficient.

DR. HILTON: I will abstain.

DR. RELLER: Dr. Wiedermann?

DR. WIEDERMANN: My answer to 1(a) is yes; to 1(b) is yes, and I agree with Dr. Griffin that the devil is in the details.

DR. REHM: I would say no. I am just not convinced that there is enough correlation between the best animal models, the mouse and the piglet model, that the pathophysiology can be easily correlated.

DR. RAPPLEY: I would say no single model. I would say the piglet is the best model but better than that would be utilization of multiple models.

DR. RELLER: I do not believe there is one comprehensive model and I am very easy with a composite animal model as being predictive of the human condition. For example, the mouse model, to me, looked like a neutralization assay, an animal neutralization which you could get from other

techniques but certainly not mimicking in any way the disease in human beings. So, my answer would be no. Dr. Edwards?

DR. EDWARDS: I echo the concerns about the phraseology of the question, but I would interpret the word Amodel@ to imply lack of perfection of precise representation in the human, also the word Apredictive@ also is an implicative word. So, my answer would be on the basis of the data we have seen, yes, with the piglet being the most representative model. I also favor the baboon model and would raise the question of perhaps extending studies in the baboon because of the difficulties that are going to be encountered in the clinical studies. So, the answer is yes.

DR. RELLER: Dr. Smith?

DR. M. SMITH: I guess how I interpret it is I am not happy with the mouse model so I would say no, and I think I don=t have enough information to know that the piglet model is the best model but it sounds very promising and I just think we don=t have enough data.

DR. ROSENTHAL: I feel like there is insufficient data to say yes to part (a), although I agree with what has been said regarding the fact that there may be various facets of this question that can be answered by different animal models. I am wondering whether the greyhound isn=t going to be an important contributor in the scheme of things because the clinical manifestations in that model seemed similar, from what I heard.

Regarding 1(b), I do think there is a role for animal data to support and inform our decisions in this regard.

DR. TARR: While the piglet data produced a reasonable histopathologic lesion, there were insufficient data supplied with it to enable me to say that the pathophysiology that led to those lesions resembles what we see in humans so I would have to say no to 1(a). I would like to qualify it by saying I would like more work, more data on that model.

DR. RELLER: Dr. Acheson?

DR. ACHESON: I think the answer to the

question is that a model, I would say no. But, again, I would support the notion that a composite model is the way to go here, and I agree with the comment about the greyhound. I think the greyhound, from a renal perspective, was really very interesting but it didn=t follow the oral challenge model.

DR. TOWNSEND: I would actually echo the sentiments of Dr. Edwards. You know, we are not going to get perfection with any animal model. I think we can, you know, just sort of get the best data we can and I think the piglet model is probably close enough that we can at least use the data to make some predictions about what would happen in the human. So, I would say yes.

DR. RELLER: Dr. Moxey-Mims?

DR. MOXEY-MIMS: Based on the way you phrased the question in terms of a single model, I would have to say no to 1(a). However, with the possibility of using some composite I would say to 1(b) that data would still be useful despite not having one single model.

DR. RELLER: Miss Dokken?

MS. DOKKEN: I am a little confused about which question we are answering, but if it is the one that the chair phrased at the beginning my answer is no to 1(a) and then I don=t have to answer 1(b).

DR. KASKEL: I would say no to 1(a), with the hope that a better model would be developed. Certainly we would like to look with transgenics and knockouts and silencing at what might happen in a mouse, why it is protected from the glomerular lesion. As far as the piglet model and the greyhound model is concerned, they hold promise. I would like to know what happens to their kidney function over time. Thank you.

DR. FANT: To the first question, with the status of the models as they exist now, I would have to vote no for part (a). But I think as that work progresses they would be useful to provide supportive information.

DR. RELLER: Dr. Wong-Beringer?

DR. WONG-BERINGER: I think as a single

model I would say no and, again, I would echo the points that were made. I think that multiple models together could be useful as more work needs to complete the picture. Single model, the answer is no but with more work multiple models could provide useful information.

DR. RELLER: Dr. Gorman, we missed your vote.

DR. GORMAN: For 1(a) the answer would be no. I think that we have models that mimic disease injuries but I am not sure they are predictive of disease processes in humans. I would, again, echo some of the comments made about further study of these models to see if they really do follow the processes, not just the injuries that we see in humans.

DR. RELLER: Dr. Daum?

DR. DAUM: I have to apologize, I really like what Deborah said perfectly because I said yes to 1(a) because I wanted to answer 1(b)--

[Laughter]

-Bno, the way it is worded you wouldn=t.

So, I actually don=t think there is a single model, because that is what it says Aa model@ and I vote no. But I want to answer 1(b) anyway because I think that there are data from learning about these models, as many people have now said around the table, that would be useful in helping understand this disease and would be useful potentially in a licensure application in understanding these products.

DR. RELLER: I would like to summarize for Dr. Cox and for Lt. Mosaddegh. I think the sense of the responses here is that there is currently no single model that mimics the disease in humans that could be studied and extrapolated to the human condition in its full manifestations. There are components of several animals that may mimic pieces of the human disease and that, at most, what one could do with further work is to provide supportive evidence for efficacy of a potential intervention.

Question two, and this has to do with trial design and endpoints for the products that we have heard about and ones that may come

subsequently, what primary endpoint should be used to determine efficacy?

For 2(a), prevention of HUS only? Let=s get a sense of whether this is the principal endpoint that one would want, yes or no, and then we can come to alternative in part (b). So, this is 2(a). As promised, Dr. Wong-Beringer?

DR. WONG-BERINGER: I think this is one endpoint that could be used, although I am looking at how daunting this could be in terms of trial patient enrollment so I guess until we get to the alternative I will say yes, this would be an endpoint that could be useful.

DR. RELLER: I think it could be phrased that in your view should prevention of HUS be the primary endpoint?

DR. WONG-BERINGER: Yes.

DR. RELLER: Dr. Fant?

DR. FANT: As the question is written, prevention of HUS only, I would have to say no. I mean, the setup of the study is going to be very complex. Timing is going to be critical. The

number of sites is going to be numerous. I think hanging our hat on HUS only will sort of increase the burden of the work that needs to be done to answer any question. So, I think more of a composite endpoint, outlined previously, is probably more realistic and relevant.

DR. RELLER: Dr. Kaskel?

DR. KASKEL: I would agree. I would say no for (a). Can I answer (b)? Composite endpoints would be variable depending on whether renal failure progresses to eating replacement therapy, whether it is permanent renal injury left with risk factors for progression.

DR. RELLER: Miss Dokken?

MS. DOKKEN: No for (a).

DR. MOXEY-MIMS: I would say no for (a) for all the feasibility reasons that have been outlined previously.

DR. RELLER: That was Dr. Moxey-Mims and now Dr. Townsend?

DR. TOWNSEND: I am not sure I can answer (a) without answering (b) as well, or at least give

a stab at it. I think it is probably impractical to design a study, as we have discussed ad nauseam, to look at prevention of HUS as the only endpoint, but I don=t know that we have another endpoint that we could use as a surrogate. I think if we had something identified that we could use either singly or as a composite, and that would be the only practical way to approach this but I don=t think we have that either. So, frankly, I think the answer to both questions is no.

DR. RELLER: Dr. Acheson?

DR. ACHESON: I think to answer, as written, I would say no but, as always, it is nice to add a caveat and I think if it comes that this is the only measurable endpoint and that essentially it goes by the board if you can=t come up with anything else, then I would want to reconsider that but, as written, I would say no.

DR. RELLER: Dr. Tarr?

DR. TARR: I need a little bit of elaboration here. If we are going to give something we want it to be medically, clinically,

short-term and long-term relevant. An intervention that I would be willing to give to my patients on the GI service should really be targeted to preventing HUS and most particularly anuric HUS. So, what should be the primary outcome in that situation, anuric HUS or HUS not otherwise specified? I need some administrative clarification.

DR. COX: I guess you can answer the question as you see fit here as far as whether it would be HUS not otherwise specified or anuric HUS.

DR. TARR: If I was testing an intervention I would really want it to prevent primarily anuric HUS, secondarily HUS not otherwise specified.

DR. RELLER: Dr. Rosenthal?

DR. ROSENTHAL: Well, for 2(a) I would say no, but I agree with what has been said earlier, that we don=t really have very good alternate clinical endpoints, or at least we haven=t come across them in the discussions today. So, I would just support a recommendation to do more research to try to understand elements of the

pathophysiology of the progression to either HUS or anuric HUS which would be relevant and help us to get an answer on this.

DR. RELLER: Dr. Smith?

DR. M. SMITH: I wrote down a long time ago no, but now that I am sitting here, thinking about this, I think HUS is the only hard and fast thing we have. Whether it is anuric renal failure or non-anuric renal failure, it is the only hard thing I think we could all agree is what we don=t want to have. So, I guess I am answering yes.

DR. RELLER: Dr. Edwards?

DR. EDWARDS: I am going to need a little elaboration, I am afraid. To me, the answer has to do with the practicalities of doing this study and if we were to try to get a yes or no answer on HUS in a U.S. population with enrolling or screening as many as 5,000 patients per month almost, I don=t think we would ever reach that endpoint. Alternatively, if the epidemiology of the disease were similar to that described by Dr. Lopez, where there are 400 to 500 cases of HUS per year in a

single country, that kind of a hard endpoint could be reached. At the moment, not having other substantiation of the epidemiology being in other locations similar to what Dr. Lopez has described, be of the lack of feasibility, my answer would be no for HUS only.

DR. RELLER: My answer is yes, I think it should be the primary endpoint. In fact, the clearest progression that I saw for possible efficacy of interventions is in Dr. Tarr=s presentation of incipient anuric renal failure with the alterations in creatinine and platelets. You know, once it got to that point there was evolution and I think that is what is the primary thing that needs to be presented. Now, whether or not there are, or could be, or someone would develop other indices that would be predictive of that is another matter. But if an intervention doesn=t prevent the spectrum of HUS, that is, the entity of HUS, then I don=t think we have a reason to intervene. So, I would clearly answer yes, that should be the primary endpoint.

DR. RAPPLEY: I answer yes as well. I think it should be the primary endpoint. I think that in order to call a particular drug a preventative it must prevent the disorder of concern in its essential elements. Given that, I also think that it is worthwhile to explore other surrogate markers until we find things that are better and appropriate to study.

DR. REHM: I am going to say no, with the idea that HUS is a spectrum of disease. Although anuric HUS is the thing that we are most concerned about preventing, in a trial situation I think improvement on the other pre-anuric HUS manifestation, if the product was proven to reduce the incidence of some of the other parameters that we see and that Dr. Tarr so nicely outlined in the picture from his chapter, then we could also imply some degree of efficacy there as well. So, I would say that HUS only is no.

DR. RELLER: Dr. Gorman?

DR. GORMAN: As the primary endpoint I would say yes, HUS has to be the primary endpoint,

and I give the companies and other developers full license to come back and try to change their indication for a disease-modifying agent and, therefore, having different risk/benefit calculations to be made.

DR. RELLER: Dr. Wiedermann?

DR. WIEDERMANN: I would answer yes with the same caveats about feasibility and vagueness in the definition of what we are calling HUS.

DR. RELLER: Dr. Hilton?

DR. HILTON: I am in favor of HUS as the primary endpoint.

DR. RELLER: Dr. Daum?

DR. DAUM: So, I vote yes, that it should be the primary endpoint and I think that the practicality of it is the main concern. I think that we heard that it may be possible to really do an efficacy study using mostly Argentine patients. If that were done I would be enthusiastic about it. Then, I guess the next question would be how to bridge the results from Argentina to the United States. I would not just extrapolate them one for

one. I have the same concerns people have alluded to all afternoon. The biology of the organisms may be different. The biology of the folks who are getting infected may be different. The epidemiology may be different. But I would still be very impressed if the product worked. So, I guess my main issue in voting yes would be to construct sufficient bridging information, and it may be pharmacokinetic; it may be some safety data; and it may be endpoints that some of the folks in the room that are really experts can help with that would be more practical to do. So, I would like to see the primary efficacy be yes, that it be done mostly with Argentine kids, and that the U.S. kids have different outcome parameters that are carefully chosen to convince everybody to a reasonable degree that we have bridging information.

DR. RELLER: Dr. Kocis?

DR. KOCIS: I would vote yes, to show safety and efficacy of the drug we would need to show prevention of HUS. But as a physician, once a

drug was approved I wouldn=t use it unless it showed a decrease in anuric HUS.

DR. RELLER: Dr. Griffin?

DR. GRIFFIN: I guess I am the outlier. To 2(a) I would say no. My feeling is that the purpose of the treatment is mainly to prevent HUS, but the purpose of the study is not to prevent HUS but to show whether the treatment ameliorates the disease. And, my concept of the pathophysiology of this disease is that you start out with a healthy person, they get sick, they get sicker, they get sicker, and then they develop what we define as HUS. So, if you can show that the drug ameliorates the disease, then my concept of the pathophysiology is that you have shown an effect on progression to HUS, and I think the numbers are such that it would be hard to have HUS as the only endpoint.

My answer to (b) about alternative endpoints is that I would not use an unvalidated composite endpoint. However, I do think that there are other endpoints. I think that anemia is an endpoint. I think thrombocytopenia is an endpoint.

I think that evidence of renal injury is an endpoint. And, I think it is possible to use those as endpoints and then to combine those in some way, possibly in the statistical analysis.

DR. RELLER: Many committee members have commented on 1(b) [sic]. Is there anyone who has not commented on 1(b) who wishes to add further about alternative clinical endpoints that might be included in a composite endpoint for prevention of HUS, particularly those members who voted no, that HUS was not, to them, an obligatory primary endpoint? Dr. Rosenthal?

DR. ROSENTHAL: Sorry, I was just noting that that was question 2(b) and not 1(b).

DR. RELLER: I am sorry, you are correct, question 2(b). Yes, Dr. Acheson?

DR. ACHESON: I would just like to endorse what Patty Griffin just said and for the record point out that half the room answered the question Aonly@ and half of the room answered the question Aprimary,@ and they are very different.

DR. RELLER: Yes, Dr. Fant?

DR. FANT: Yes, I believe I answered the question as HUS only in the context of the word only. Just to clarify my statement about alternative clinical endpoints, I alluded to using more of a composite endpoint and that was making the assumption that HUS is not HUS is not HUS, I mean that it takes many forms. So, having a system that kind of distinguished the severity of HUS among the patients--Dr. Tarr mentioned anuric versus non-anuric is sort of a simple break point, but some measure that sort of distinguishes severity of disease I think would be useful.

DR. RELLER: Dr. Cox, do you want us to further clarify this differentiation between primary and HUS only? The way the question was phrased is that HUS only should be the primary endpoint but, again, it was trying to get a clean, you know, whether these other composite or other surrogates would be possible. Do you have sufficient clarity? Do you have what you want from the committee or do you want to have us say that HUS should be the primary, yes or no?

DR. COX: I think we have enough on this. I mean, important to us is not only the answer to the question but also the rationale behind it. If people would want to go around, if you want to answer the question specifically that HUS is primary only, we could do that too. I know we are running out of time too.

DR. RELLER: The distinction is understood but I think the elaborations probablyB-because there are different perspectives on this. Some are strict constructionist and others are not.

DR. COX: Right. And, what we will do too, you know, we not only look at the answers but we also look at the rationale people provide.

DR. RELLER: Lastly, and this is not for a vote and we will not go to each person for the sake of time, but any committee member who would like to comment on question number three, having to do with what you would do to enhance trial enrollment or any other comments about what is in question three, depicted on the screen. Dr. Rappley?

DR. RAPPLEY: I don=t know the answer to

this and I am raising this for consideration, whether or not a registry would be an appropriate vehicle to study this.

DR. RELLER: Dr. Kaskel?

DR. KASKEL: Based on experience with the current NIH multicenter study in pediatric nephrology, I would survey the community to let them know that this is something on the horizon and get an input from the community of the primary care doctors and specialists who will first see these patients.

DR. RELLER: Dr. Tarr?

DR. TARR: I would suggest that you focus on children on or before the fourth day of illness for two reasons. Number one, that is probably the window where a therapeutic is going to have the highest efficacy. Two, paradoxically-Bmaybe not so paradoxically, children who present early have a higher rate of developing HUS than children who present later. So, this may end up being a smaller N but a higher rate of HUS. It is not easy. In our four-year pathophysiology study where we looked

at prothrombotic indices for example, we enrolled four states, 46 participating laboratories, 16 children on or before day four of illness prior to the development of HUS, population base of eight million.

DR. RELLER: Dr. Edwards?

DR. EDWARDS: The big problem we are having here is the low incidence of this disease and the sporadic nature. There are other problems but those are the central problems. In an ideal world it would be wonderful to have the opportunity to review Dr. Lopez= experience in great detail and to get an assessment of how representative it is to what we may be seeing in the United States, and if the conclusion were that it were highly representative, then his experience sort of negates the low frequency of occurrence of the disease and doing a study in that setting to establish proof of principle of the activity of the agent would be highly desirable in my opinion, and would enhance the overall amount of data that is going to be generated regarding the efficacy of a monoclonal.

So, in summary, I am saying that if the disease nature, incidence and pathophysiology were deemed to be similar to what we think of it in general, in Dr. Lopez= setting it would be an ideal place to establish proof of principle.

DR. RELLER: Dr. Hilton?

DR. HILTON: Two thoughts, one is that an alternative outcome could be time to failure with various types of failure defined in advance. Secondly, thinking about ways to restrict the eligibility criteria to higher risk patients, for example, those who are 0157 positive, if they could be identified at enrollment, in that subgroup those are the only patients who had HUS in the Klein study.

DR. RELLER: In the U.S. disproportionally but not necessarily, as we heard from Dr. Lopez, in Argentina. Dr. Tarr, please continue.

DR. TARR: I would like to take exception to that. I don=t think we know what the serology is in Argentina from the data we were presented today and, in fact, data from Dr. Rivas suggested

it is predominantly 0157 in Argentina.

DR. RELLER: Thank you for that clarification. I was just, you know, repeating what was stated but we don=t know for sure. That is an important point to get sort of out. Dr. Griffin?

DR. GRIFFIN: Yes, I would have to begin my remarks by saying in any place where the cause of HUS has been rigorously sought it has been, by and large, predominantly 0157. So, my suggestion would be to look at ways to enrich the study population for patients that have 0157 disease, and one could do that by choosing only patients who have bloody diarrhea. Another way to do that would be choosing patients who have infection with the Shiga toxin-2 only producing strain, a strain that does not produce Shiga toxin-1.

DR. RELLER: Dr. Wong-Beringer?

DR. WONG-BERINGER: I would like to see some additional variables that might impact severity of disease, mainly in the biology of the infecting strain and the patient, i.e., looking at

the quantity of toxin produced by the infecting strain and also obtain DNA samples for genotyping studies in the future, that is, every parameter that will be identified.

DR. RELLER: Does any other committee member wish to provide comment on question number three?

DR. KASKEL: Can I get a second chance here?

DR. RELLER: Of course.

DR. KASKEL: I just want to say that to see one of these children come in, in a storm, critically ill and have to go through the process that many of us do to keep them alive and, hopefully, be successful every effort, no matter how early on or premature, that can be developed to prevent this storm from coming should be supported. So, with all the fall-backs and some of the criticisms that we have heard about today, I want to make it clear that I think any effort at a defined study, proactive, looking at factors that put these patients at risk and any interventions

that may prevent it, should be encouraged. Even if it is a pilot study, obtaining samples in a biorepository for DNA and biomarkers can yield useful information in the future, even if it is a short-term pilot study. I just wanted to put that down.

DR. RELLER: Dr. Acheson?

DR. ACHESON: Yes, just a brief comment, I think given the criticality of early intervention, raising awareness among both parents as well as health professionals is going to be key. But you have to combine with some of the technology that we have heard of rapid, sensitive, specific diagnostic tests. But in terms of the strategic approach, just approaching health professionals will be part of it. I think it would be worth investigating raising awareness among parents if this comes to reality.

DR. RELLER: Dr. Griffin, does the CDC have initiatives along those lines, like other public health education methods about bloody diarrhea in your child can portend serious complications. Seek

medical care straightaway?

DR. GRIFFIN: Sure. I mean, we try to give that sort of information but, you know, if you think about how many people are in this room and how many of you have had a child with bloody diarrhea, that sort of learning is hard to convey. It is easier to convey learning about, you know, don=t give your kid a rare hamburger. Can I make one other comment?

DR. RELLER: Sure.

DR. GRIFFIN: That is that if one or more of these studies is done, as we have heard, it will be a massive undertaking that would probably only happen once and, as you have heard, we are doing a cohort study of 0157 and that is a huge undertaking. We, and others, have done studies of HUS and they re a lot of work. So, this would be an incredible database of people with Shiga toxin-associated illnesses, as well as illnesses due to other causes of diarrhea or bloody diarrhea, and I would strongly suggest that the companies take a collaborative approach with academia, with

public health officials in the countries to mine the data and design the study in such a way that it could be used for many purposes.

DR. RELLER: So, in conclusion, I think we could say that this is an important issue to be pursued, intervention, but it is a daunting task. I want to thank all of the committee members for their endurance, their forthrightness and I hope, Dr. Cox, that the deliberations have provided at least a portion of the balance that you would like to hear from us.

DR. COX: Yes, thank you very much, and thank you, everyone, for the discussion over the course of the day. I think it was very helpful to us.

DR. RELLER: The Anti-Infective Drugs Advisory Committee meeting in joint session with the Pediatric Advisory Committee, and I thank Dr. Rappley who was with me on this meeting-Bthe meeting of April 12th is now adjourned. Thank you.

[Whereupon, at 5:10 p.m, the proceedings were adjourned.]