MEETING

OF

Public Workshop - Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs That Target a Single Species

Conducted by Edward Cox, M.D., M.P.H.

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8:30 a.m.

Food and Drug Administration

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PROCEEDINGS

DR. COX: All right. Good morning everybody, and welcome to Day 2 of our Public Workshop series here. It's quiet and it looks like mostly everybody sat down. It's 8:30, so I think it's time to go. So we're very glad to see folks back here for Day 2.

Today is a slightly different topic, perhaps a little bit more challenging than what we even discussed yesterday, and I expect we'll have a fairly free-flowing discussion because this is such a challenging area. I will be very interested to see what folks' ideas are on this topic.

We'll be talking about developing antibacterial drugs that target a single species. And as I mentioned yesterday this is a workshop, so it really is just an opportunity for discussion. It's not one to gain consensus. It's not an advisory committee, but that also should allow folks to feel comfortable to, you know, discuss the issue here and try to work through some of the scientific challenges we face.

There's conflict of interest disclosures. I believe they're on the agenda or at the table out front. So if folks are interested in seeing those, they are available.

And we also in the afternoon will provide an open time for public comment. We wanted to reserve some time for anyone who wants to make any either prepared remarks or statements at that point in time. I think we do that in the afternoon, if I remember correctly. I'll bring the agenda up here in just a minute.

Throughout the course of the day, too, we have the microphones. And just like yesterday, if folks want to get up, make comments, ask questions please feel free to do so and when recognized by the -- either myself or Dr. Rex. We'll be moderating today's sessions.

And I thought what we'd do today would be to start out with panel introductions so you know who's up here, and I think we'll start on the far side with Aaron and then work towards John.

MR. DANE: Hi. Aaron Dane, Statistical

Consultant.

DR. BOUCHER: Helen Boucher, Infectious disease, Tufts.

DR. TOMAYKO: John Tomayko. I'm an infectious disease physician, work for Spero Therapeutics as their chief medical officer.

DR. BORIO: Lu Borio, FDA Acting Chief Scientist.

DR. CAVALERI: Marco Cavaleri, European Medicine Agency.

DR. NAMBIAR: Sumathi Nambiar, Director of Division of Anti-Infective Products, CDER, FDA.

DR. REX: John Rex, Internal Medicine and Infectious Diseases, AstraZeneca.

DR. COX: All right. Great. Thanks to our panelists. I was just mentioning, you know, to folks. I mean, there's -- this day took a fair bit of preparation in preparing the case, and hopefully you all had a chance to study it last night. And it was a lot of work to get to something that seemed to be, you know, really as spot on as we could possibly make it in sort of a simulated case.

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So for today, we'll have first an introduction of the case. Peter Kim will walk through some of the slides. And then we'll hear from a series of different folks representing academia, industry, FDA and EMA provide some perspective on the case that we're presenting. And the case will be a particularly development issue for a drug that targets a single species.

We'll also have time for questions, and then John Rex will go into more detail. And we'll sort walk through and sort of unfold the case over time and welcome folks' input during that.

And you know, this is an area where there is interest. There is -- you know, there are compounds out there that folks are trying to develop, and I think if it's a compound that's targeting staph aureus and the goal is to see how it works in treating patients with staph aureus skin infections that's probably feasible, but if you move to a gram-negative rod that infrequently causes any variety of serious infections, whether it be HABP/VABP, complicated intra-abdominal, complicated UTI, it becomes much more

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challenging much quickly -- much more quickly.

And that's really the case that we'll be focusing on today. So just for clarity purposes, we're talking about a drug that is only active against a single species. So this is not a choice that you're only going to develop it for a single species. This is because the drug really is only active against that single species, and you're looking to develop a drug in a serious infection.

Rapid diagnostics -- and we talked about this some yesterday -- could be very important here, not only for identifying patients for a clinical trial, but also for how the drug might be used out there in the real world should a drug, you know, get out there and be available to clinicians treating patients.

As I mentioned, there are compounds and, you know, at various different public meetings over the last so many months, whether it be ASM, the Barn meeting, another bio, I mean, people have talked about these compounds that are really only active against a single species, and they're interested in developing

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such drugs.

You know, one of the ideas here, too, is that if you have a drug that is only active against a single species, maybe it will have less of an effect on your GI normal flora. And, you know, the normal flora that we have are very important to us and prevent, you know, colonization with other less favorable organisms, such as either those that have resistance, fungal colonization of the gut and then C. diff colitis.

So the hope is that if you can target more narrowly maybe you can avoid some of these problems. And you know, how a drug would be used in clinical practice is, you know, still, I think, a challenging question, but we hope it's a question that we can get to.

And what I mean by that is that oftentimes therapy for antibacterial diseases is empiric and you're targeting a range of pathogens that are likely. And you know, with a narrower spectrum agent, you know, how that will figure into the paradigm I think is still something that needs to be worked out. Rapid

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diagnostic certainly can help there, but I think we look forward to trying to solve that challenge if we get there. I hope we do.

I won't say too much about this slide but talked about this some yesterday. And that is, you know, disease characteristics for serious bacterial diseases make them particularly challenging to study. We talked yesterday about, you know, diagnostic uncertainty, the urgency, you know, the start -- the need to start therapy, that you really don't know who these patients are. They can show up at any hospital at any point in time, which can make it really difficult to actually conduct a study.

And here, we're sort of taking it even one step further. Now we're looking at a particular species that makes this, you know, even more difficult to identify a patient for whom the test agent is likely to be -- you know, where you can evaluate the test agent. If you're only looking at pseudomonas aeruginosa, you've sort of cut down your set of patients in whom you can study the drug even further.

So this brings us to the question of what do

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you when the species of interest is infrequent. So you know, it becomes, in essence, sort of a numbers game on the human clinical trials side. You'll -- if you have fewer patients, you just simply can't enroll them. You can't find them. You'll probably end up with less precise estimates of efficacy and greater uncertainty around, you know, what you know about the drug. That's -- you simply have less data. And so you may not really be in a situation to practically be able to achieve the usual statistical conventions that you would expect for a clinical trial.

And this is particularly challenging where the outcomes for serious acute bacterial diseases are variable. And you know, we know some of the factors, but I don't think we know them all. And we seek, you know, cure rates, or success rates that can vary, you know, by plus or minus 20 percent or more depending upon a lot of different patient factors, some of which we know, some of which we don't know.

And we're not -- you know, following this we're not really in a situation where we have lights on, lights off. I mean if you could take something

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where, you know, there was a 90 percent bad outcome and you could drop it down to 10 and you were always at 90 and, you know, you clearly would never get to 10 without some intervention, it would be much clearer.

Here, I think we're in the range of -- you know, it's usually sort of around 60, and maybe we can drop it 40 or 30. But sometimes it may move from 60 to 40 just depending upon the patients that you happen to enroll at a particular center or over time, so lot of variability here that makes this particularly challenging.

So some of the options that we'll be discussing here today will be looking at clinical data when, you know, we have smaller numbers of patients. And there will be inherently greater degrees of uncertainty. And the uncertainty comes not just from the small numbers, but also from the challenges of studying an antibacterial drug. You know, concomitant therapy will probably be, you know, what patients need to get, and they'll probably get some pre-study antibiotics, too. So you know, this will be, you know, messy data, messy information. So the question

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is how do we make the best of it.

And then if clinical trials are not feasible, one of the things we'll also be talking about today is the animal rule to evaluate efficacy. You know, in this setting you still need safety data from humans, and there are also within the animal rule provisions for restrictions on the conditions of the availability of the drug.

And Sumathi in her talk will go through more of the specifics of the animal rule, so we're looking forward to some more details on that when she gives her presentation. And we also welcome other ideas folks may have about how to solve this particularly challenging problem.

Just a comment or two about animal models for evaluating efficacy under the animal rule -- and as I mentioned, Sumathi will go through more details and the specific criteria. But just to sort of differentiate these from models where you're looking at activity of an antibacterial drug, you know, really, what we're trying to get at here is an animal model that allows us to predict efficacy in humans.

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So it's more than just showing activity. And, you know, for some diseases, one of the first questions is, is there a good animal model of infection.

And Sumathi will walk through some of the develop efforts that have been undertaken in areas where we have used the animal efficacy rule, and she'll be talking about animal model development for the disease of plague and some of the work that was done for that. And you'll see it's a fair bit of work to really try and understand these models.

And there's a lot of difficult questions, and the questions may not be apparent until you start to get into this and trying to really figure out what you need in order to be able to predict human efficacy. You know, which species? Which species behaves similar to the humans? Some animals tend to be intrinsically more resistant to certain types of infections than others. What's the inoculum? You know, is it -- and you sort of engineer the model, too, so that it works within the model. And then the question is, is does that extrapolate to humans.

When do you intervene with the test drug?

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And you know, there's been enough experience to be able to say that, you know, if you intervene at, say, 48 hours and the drug can, you know, reduce mortality in the animal model of infection, is that the point in time that translates to clinical benefit in patients? And -- or do you need to be able to get out to, say, four days or five days or six days in order to be able to translate that finding in the animal model? Because it's not just activity into human clinical benefits.

So these are really challenging questions that we struggle with. And you know, occasionally we do have some human data, and that tells us something about the animal model. And sometimes we learn that we didn't know quite as much about the animal model as we had thought we did.

And the other thing we run into is that animals may metabolize or clear the drug differently, and there need to be certain interventions to be able to get something that's close to the human exposure. We have and animal rule efficacy guidance document that's out on our web that discusses a lot of these

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issues, too, that is quite helpful.

So today, we'll be talking about the pros and the cons of different approaches, and we'll be talking about human clinical data and also animal data. And this isn't sort of a binary decision. I mean, there is the opportunity to have both of these two types of information. You know, matter of fact, the animal rule talks about utilizing available clinical data. So there is -- I don't want to present sort of a binary decision here. I mean, there is the opportunity to draw off information from both.

And I think, you know, the reason that we're here today -- I mean, we know that folks are interested in developing these compounds, you know, if they can be shown to be safe and effective, utilized clinically in a meaningful way. I mean, the hope is that the narrower spectrum agents will do less havoc on the normal flora that we all need and that keeps us out of trouble. So we think it's important to have a pathway for the development of these compounds so that the potential for these drugs for treating patients can be evaluated.

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And with that, I'll stop. And our next speaker is Peter Kim, if I'm reading -- yeah, Peter Kim will be talking to us. And he'll actually walk us through the case at sort of a high level so you'll know what we're dealing with.

Peter is a medical officer in the Division of Anti-Infective Products. So he'll walk us through part one of the tough case. And we'll continue to build over the course of the session. So you'll see as we unveil more information it'll get trickier and trickier.

So Peter welcome to the podium, and walk us through it.

DR. KIM: Thank you, Ed.

Good morning. I'll be discussing a hypothetical case of an antibacterial targeting a single bacterial species. The name of this drug is X-1.

Overview. Drug X-1 is an injectable anti-antibacterial with activity limited to pseudomonas aeruginosa. It has no activity against gram-positives or other gram-negatives, including enterobacteriaceae.

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X-1 has a new mechanism of action. It acts on a novel ribosomal target unique to pseudomonas aeruginosa.

Non-clinical safety. Hepatic and hematologic toxicity have been identified in mice and dogs. Hepatic toxicity signal is a dose-dependent increase in liver enzymes associated with macrophage infiltration at the mid and high doses as well as reversible focal hepatocellular necrosis at the high does.

Concerning safety margins, the liver enzyme elevations were observed at four times the target therapeutic dose, and the focal hepatocellular necrosis occurred at eight times the targeted therapeutic dose. Regarding hematologic toxicity, there is some evidence of neutropenia and it occurred at eight times the targeted therapeutic dose.

Non-clinical microbiology and PK/PD. Drug X-1 is mainly active against pseudomonas aeruginosa. The MICs have a bimodal distribution of 0.06 to one milligram per liter for wild type and greater than 4 milligrams per liter for non-wild type. Ninety-nine percent of isolates had an MIC of less than equal to 1

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milligram per liter in a recent global survey.
The MIC distribution for wild type is centered on an MIC of .25 milligrams per liter with 5 percent of isolates at the low and high ends of the spectrum. Therefore, both the MIC 90 and MIC 99 equal 1 milligram per liter.
The frequency of spontaneous resistance is low. Serial passage studies have shown no change in the MIC up to 11 passages. Drug X-1 has variable activity against other pseudomonas species and no activity against other gram-negatives, as we had discussed, or gram-positives.
In animal infection models Drug X-1 wasn't effective in treating pseudomonas aeruginosa infections based on reduction of colony-forming units per gram in the thigh, pneumonia and peritonitis models and based on survival in the sepsis model.
The PK/PD index associated with bacterial killing is the percent time that free drug concentrations are above the MIC over a dose interval, and this index was observed in the hollow-fiber model as well as in murine thigh and pneumonia infection

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models.
Clinical studies. The sponsor has completed some Phase 1 studies and one Phase 2 study. In Phase 1, the sponsors completed a healthy volunteer study, a long ELF study and renal and hepatic impairment studies. The sponsor is also planning a thorough QT and drug-drug interaction studies.
Population PK model. Simulations of a population PK model based on Phase 1 data showed that a 100 milligram IV infusion over one hour every eight hours would provide greater than or equal to 40 percent time above the MIC for an MIC of 1 milligram per liter in more than 90 percent of patients using parameter estimates from healthy volunteers and using a 40 percent inflated variance. Drug X-1 is excreted renally, and greater than or equal to 90 percent target attainment is possible for varying degrees of renal impairment based on dose adjustment.
Additional data. The terminal elimination half-life of Drug X-1 in healthy subjects was approximately two hours. No significant drug-drug interactions are predicted. The ELF to plasma

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concentration ratios of Drug X-1 were approximately 40 percent and 25 percent in humans and mice, respectively.
Phase 2 proof of concept study. It consisted of a 14-day, uncontrolled study conducted in patients with non-cystic fibrosis bronchiectasis. Drug X-1 was given as monotherapy in 10 patients. At the proposed dose, the predicted PK parameters were observed. Microbiologic activity was assessed in terms of log reduction of pseudomonas aeruginosa in sputum. Greater than 1 log reduction was seen in 9 out of 10 patients, and greater than 2 log reductions were seen in 4 out of 10. No adverse events of concern were observed.
And now for perspectives on the development program from academia, industry, FDA and EMA.
Thank you.
DR. COX: Great. Thanks Peter
(Applause)
DR. COX: And now we'll walk through a series of perspectives. And first, we'll hear from Helen Boucher. And I think many folks know Helen.

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Helen is current an infectious disease physician at the Tufts New England Medical Center but also has industry experience in that she was in both Pfizer and Cubist over the course of her career. So we greatly appreciate her perspective. And she'll be providing the perspective, really, from the standpoint of a practicing physician/academic physician on this situation of developing a drug that's active against a single species and providing us some information about what she's seeing out there as a clinician these days.
So Helen, thank you.
DR. BOUCHER: So much, Ed and Dr. Nambiar and Dr. Rex for inviting me. It's a real honor to be here to talk some more about this really important problem.
So my disclosures are shown here. And I'm also involved with IDSA, as I showed on the first slide, and have been working on this problem for a number of years with many in this room.
So as we sort of start to look at this case of X-1, I thought we could harken back a little bit to some stuff that we talked about yesterday where we

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sort of said that in a perfect world all of us would want, and certainly we in academia would want, the most well-justified, statistically rigorous development program and studies for these new drugs that would help our patients in practice and, you know, answer questions to the best scientific ability possible.

But I think we often learn that we have to work in a world that isn't perfect. And when perfect data is not possible, as Dr. Cox alluded to in his earlier talk, these types of studies may leave us with good preclinical PK and PD as well as animal studies; an ability to understand what the needed exposure is and how to dose these drugs; some amount of clinical efficacy data, which I'm sure we'll spend a lot of time talking about today; importantly, a reasonable safety database -- and we talked a little bit about this yesterday, but I think in this context today we'll probably come back to this -- what is that; what is reasonable; and all of this which will come together to give us enough information to use these patients -- these drugs in our patients who have

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really limited options for treatment.

So I thought, for what it's worth, I might start with a couple of cases, and these are cases that we recently encountered.

So the first one is a 71-year-old lady that who had laryngeal cancer a couple of years ago, and she had surgery and chemo and radiation back in 2012. And she was cured. She has COPD now. She's home on oxygen and was recently in the hospital with tracheobronchitis and came to us transferred from rehab where she was living with a new fever, flank pain and respiratory failure. So her history is complicated.

Back in December of last year, she had sort of a cough and sputum production and acute on top of chronic respiratory failure. She wasn't otherwise apparently ill with fever or other constitutional symptoms. She was evaluated using rapid diagnostic for viruses, and we didn't find any other source of infection. But blood in sputum grew a gram-negative that was ultimately identified as a multidrug resistant Klebsiella that had a metallo-carbapenemase.

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She actually did well that time. She was treated for two weeks with IV tigesycline, IV and inhaled colistin in combinations, so pretty aggressive therapy and quite toxic therapy. She ultimately was switched over to IV minocycline for a period and got out of the hospital.

So she came again, not entirely unexpectedly, in late January and again now recently. And most recently, she came in with respiratory failure and now has a urinary tract infection. So she was seen in the emergency room and discharged on a five-day course of levofloxacin and very consistent with the guidelines. And her sputum and urine both grew this carbapenemase-producing Klebsiella.

Back at the rehab she was doing worse. She was requiring increased oxygen, comes back to the ER, is really failing, very tired, having these urinary symptoms, flank pain, fever now, needs more oxygen. And the urine grows the Klebsiella again with a carbapenem resistant, and it's identified as a multidrug resistant organism.

And this is what that multidrug resistance

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looks like. We got Rs to all of these antibiotics, including the two new kids on the block, the ceftolozane/tazobactam and ceftazidime/avibactam. So were left with very few options for this very sick lady.

So after discussion with her and her family about the limited options and the fact that there would be predictable renal, neural and other toxicities if we embarked on another colistin/combination approach, she and her family decided to pursue hospice care. So this lady who was cured of her cancer was now left dying of this infection, so certainly not something that we hope to encounter in our practice very much.

So another case I thought that was instructive is a case that's actually almost a year old now that came across on the Emerging Infection Network, which is a really great tool that IDSA sponsors whereby everyday people can post difficult cases and look for advice across the country.

And so this was a case of a 19-year-old kidney transplant recipient who had developed

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refractory blood stream infection due to stenotrophomonas maltophilia that was multidrug resistant associated, as it usually is, with a catheter. The catheter had been removed, but this patient, because of their transplant and other reasons, was on steroids more than the usual amount for a transplant patient and had this organism that was resistant to just about everything they tested except maybe colistin. And that's what they were using.

So the question to us was does anyone do any special in vitro testing of combinations, is there any value of testing any other drugs with a fancier MIC test and does anyone know anything about using chloramphenicol, a very old drug that very few of use and most of us don't even have in our hospitals, for treating this kind of a complicated scenario. So this is a 19-year-old patient who's gotten a kidney transplant where we're kind of digging that deep to think about.

So the last patient I'll share with you is kind of a different category of what we might consider

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someone with unmet medical need. This is a 47-year-old lady, schoolteacher, who came with pain on urination and some lower abdominal pain. And she was started again by her -- by the doctor at the clinic on oral ciprofloxacin -- again, totally consistent with the guidelines.

Unfortunately, though, two days later, she came back more ill with chills, nausea, back pain, and she now has a high fever and flank pain on exam. She still has evidence of infection in her urine and has an elevated white blood cell count. So she now has a kidney infection, and she's advanced to IV ceftriaxone appropriately, got one dose of that and then sent home because she looked otherwise healthy enough.

So unfortunately, two days later again, now four days after she first came in, she was much sicker. Now she had a high fever, and she had a low blood pressure. She wasn't able to eat or drink, and she was vomiting.

So now she's in the Emergency Room really looking quite ill with, again, sort of evidence of a urinary tract infection, a kidney infection, and she

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grows now in urine culture greater than 100,000 Klebsiella pneumoniae that is producing an ESBL that's resistant to the drugs to which she was treated -- ciprofloxacin, ceftriaxone and trimethoprim sulfa. So she's admitted to the hospital and treated with intravenous carbapenem therapy, which is the drug of choice of ESBLs.

So I think all these cases, while anecdotal and sort of just individual cases, do sort of suggest that these resistant pathogen infections are serious, and they can happen and are happening. In the world of clinical infectious disease, we often have less data than we want. We do appreciate that the data on infections at standard body sites like a urinary tract infection are often the foundation on which we build. But in our everyday life in clinical medicine, we have to extrapolate a lot, and our patients don't always present with sort of textbook, indication-based infection. So we use data from a variety of sources and a variety of observations to make these decisions.

So that kind of brings us back to where are we and how do we develop Drug X-1. And there's a

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little bit of a catch 22, I would submit, because we hope to develop this drug before we actually have enough drug-resistant pseudomonas infections to do the big Phase 3 program that Ed alluded to earlier.

So you know, we never want to see so many cases of resistant pseudomonas that we can do that, but then that brings us to this tension between the desire for the high quality volume of data and the challenges in generating those data. So the question is how do we interpret murky data. And in these studies that are going to have small numbers of patients with MDR pathogens, how can we best manage that so that we can make any judgments and understanding that there's going to be limited inferential testing?

So again, as we talked about earlier, what's the best path? Well, the best thing is to have all adequate, well-controlled trials. And there are a number of different types of adequate and well-controlled trials that I think we'll discuss today. But there will be a continuum of what those datasets will look like. So the dataset from the standard

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randomized controlled trial with statistical testing all the way down to smaller datasets that might include externally controlled or even uncontrolled data if we come all the way down to the animal rule that Dr. Cox alluded to earlier.

You know, well-controlled, randomized controlled trials will tell us a lot when done on a single indication and give us meaningful effectiveness data and also safety data. I think it's important to remember that, too. We get a lot of safety data from these trials.

Externally controlled and even historically controlled data, I would submit, especially when we study patients with the most severe infections -- those bloodstream infections, other pneumonias with high predictable mortality -- in those cases, we may be able to learn valuable data from externally controlled studies.

Whichever path we go, I think it's important that they all have good preclinical PK/PD and adequate safety data. And I think in however -- again, whichever direction people choose to go, doing these

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studies at sites with really good clinical trials, expertise -- and coming back to that discussion we had yesterday about the clinical trials network, being able to really know that these data were generated in the most rigorous sites by the most rigorous investigators -- will be very helpful. And then diagnostics to help us include patients who really have the disease would be extremely helpful.

And I think we as clinicians have to be prepared to use the drugs developed on whichever type of adequate and well-controlled trials are selected. We have to be prepared to use them.

So let's think about a couple of potential examples. So one example would be to use a Tier B approach, harkening back to Dr. Rex's sort of schema that he presented yesterday. So this is a randomized, active controlled study and standard indication, so complicated inter-abdominal infection, UTI, pneumonia for example.

Those studies allow us to have inferential testing. The patients all have a standard kind of proven infection. We would generate PK data at a key

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site of infection, and that population can be very well characterized. We'll also get safety data again in this kind of standard population. Those are all, I think, great strengths.

The challenges, some of which we just talked about yesterday, are enrollment. These are a large number of patients, huge amount of resources that our industry colleagues showed us yesterday in terms of time and money in trying to enroll these patients. We have challenges about whether we treat empirically or we use targeted therapy. So do we wait until we know it's pseudomonas? Or do we enroll people at the onset of their disease? We'll be left, it appears, with small numbers of patients with that pathogen of interest even in a big trial.

There are concerns and challenges about comparator choice in terms of what's the most effective comparator, what's the most accepted comparator in various parts of the world. And the non-inferiority margins might be wide, wider than we would hope.

So if we contrast this to a more Tier C type

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approach where we look at infection in multiple body sites, there are more considerations here. Is this a randomized study versus best available therapy? Is it versus external controls? Both of those would allow some type of superiority testing. Would there ever be a scenario where you do non-randomized studies? We heard a lot of arguments yesterday, I think, that were pretty compelling for the pitfalls of non-randomized studies, but I leave it here as something to consider.

Here, we could potentially include patients who are the most seriously ill with the highest in predictable mortality. If this route is pursued, it's really important that strict definitions of infection, severity of illness scores, things like that, are used so that it's very clear that every patient has the infection that we care about as well as their outcome is just as rigorously defined. Things like adjudication committees and things may be very useful in this setting.

And I think these studies do have some strengths. So the patients have proven infection. Their treatment course can be well characterized.

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There is the ability to get PK data at these kind of most interesting sites of infection like the blood, the lung, even the bone and the brain. There's the possibility to gain safety data. They might be less resource-intensive, and I will probably spend some time talking about that.

Certainly, there are challenges in this Tier C approach. So there's less ability to do statistical testing and less -- especially if no randomization is undertaken. And we heard yesterday about some of the challenges with external controls. There are challenges in adhering to strict diagnostic criteria, especially in these infections. And I alluded earlier to maybe an adjudication committee would help, but there's controversy about that, too. And then if one pursues this approach, there's likely going to be a need for other safety as well as other kinds of data. So in thinking about a whole program, that's an important aspect.

So in both of those approaches, the Tier B and the Tier C type approaches, I think we're left with some challenges that are shared by them,

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actually. So at the end of day, in either of these approaches, we're left with relatively small numbers of patients with the pathogen of interest treated with X-1. So we're still looking at a smaller dataset. There's a resource intensity in either one in terms of human resources, time and money.

There is probably less statistical power and support than for the skin program that Dr. Cox alluded to earlier. And then very importantly, other factors impact outcome in these patients. So these are patients who are critically ill and inter-abdominal infection. They're having surgery. There are other things. And so I think that those are all kind of in the challenge or risk bucket that we have to consider, whether you chose a Tier B or a Tier C type approach.

And I think it's also important to say, as those examples I presented show, there's also a risk of not proceeding with either because, if we maintain the status quo, we could be left with no options.

So again, where would be like to be? We like the perfect. But I think it's reasonable to think that we could work with a program that ended up

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with well-controlled, preclinical PK/PD in animal studies, a clear understanding of the needed exposure and how to dose, harkening back to Dr. Ambrose's talk yesterday. Even a small amount of clinical efficacy data and a reasonable safety database would all be reasonable, I think.

And so where does that bring us for this Drug X-1? I think the minimum thing that we as clinicians would hope to have in order to be able to use it would be data from a well-controlled study and the label -- efficacy data and safety data; and then pharmacology and dosing information, including PK data and, I would submit again as a clinician, from as many body sites as possible and hopefully from patients who are really, really sick with organ dysfunction and critical illness; some information about age, gender and drug interaction studies to help us, again, extrapolate to the patients we see.

And then there's sort of this notion of secondary data, the data that would ideally be available and easy to find that could come from that less controlled or even uncontrolled data, that could

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include groups of patients or even individual patients who had really severe infections treated with this that could help inform our practice not in the same way as the data from the well-controlled study, but that could still be useful.

So some ways to help do this, again, we alluded a little bit yesterday to the LPAD mechanism. And the PATH Act is the current act that's in the Senate that establishes a limited population antibacterial approval pathway that would be limited to this population most at risk. So it would create an option for the development of agents where only limited data are possible.

This legislation has a lot of safeguards to ensure that the drugs are proven safe and effective and used appropriately. And these include clear, prominent labeling, that this drug is indicated only for the limited population, FDA pre-review of promotional materials and then for strict monitoring of the drug use when it's approved. And we at IDSA and others, many others, have been active in helping to advocate for this legislation. And I think there's

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still good hope that we'll see that happen.

So again, in sort of our efforts to use these drugs in the most effective way possible, stewardship is really, really important. And we're very encouraged that antibiotic stewardship programs have been proposed as a condition of participation for both hospitals and long-term care facilities in the United States. And stewardship programs would be the best vehicle to make sure that we use these drugs in the most appropriate way possible and preserve them for as long as possible and for as many patients as possible.

So that sort of brings us back to where we started. You know, I think people are asking have we come to the pre-antibiotic area, and we didn't even get into sort of the most recent kind of scary news about MCR-1 and now MCR-2 and the potential of plasmin-mediated resistance to colistin and other drugs. And I think that is somewhat scary. The cases that we looked at certainly highlight the need for both parenteral and oral agents to treat specific pathogens.

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I think it's fair to assume that we're going to be forced to use these drugs with limited data, and the cases that -- where we have to use IV and inhaled colistin and fosfomycin for ESBL infections, which a lot of us have gotten very good at doing with very limited data -- tigesycline for MDR infections -- have all sort of highlighted this.

It's very important that, obviously, we keep up our efforts on infection prevention and stewardship and surveillance. But for X-1, I think we hope to see adequate, well-controlled data emerge from either small, randomized controlled trials, perhaps with wider non-inferiority margins or even some really small Tier C type studies, perhaps with external controls.

As we mentioned, you know, strong case definitions and the inclusion of the most severe infections, I think, are really important. High quality data, hopefully from clinical trial networks, could advance that.

For clinicians, I think having information about infections at multiple body sites is very

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useful, if possible. The LPAD mechanism can ensure use in this limited population with needed safeguards, and stewardship hopefully will ensure that we use these antibiotics in the best way possible for the patients who need them most.

So with that, I'll thank the committee again as well as Amanda Jezek from IDSA and my colleagues here on the panel for the invitation. Thanks so much.

(Applause)

DR. COX: Thanks, Helen.

And now our next speaker is John Tomayko. I'm sure many folks are familiar with John, currently chief medical officer at Spero Therapeutics and also a long history in the field of infectious disease development and is an infectious disease physician, also, too. John will be providing us his perspective from the standpoint of somebody from industry.

So we appreciate your joining us here today, John.

DR. TOMAYKO: Thank you, Ed.

Thank you, Sumathi, for inviting me to talk a little bit about this important problem.

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These are my disclosures. And this is just my opinion. I don't know that I could represent all of industry.

So the agenda is pretty basic. I'm going to just reflect a little bit on some of the success we've had in the past and maybe why we're successful. I'll review the case, and then I'll give you my perspective on how we might develop it. And the end result that I'm looking for is a regulatory approval. And since this is an FDA workshop, I'm looking for an approval in the U.S.

So the past. I think if you look back you can pretty proud of what we've accomplished. We've had tremendous success in identifying a number of classes of antibiotics. There's two points here that I want to make. The first one's obvious because there's an arrow there. We haven't had a novel class of gram-negatives approved in the U.S., really, since the nalidixic acid story began in 1962 with fluoroquinolones.

The other one is that these drugs were broad-spectrum agents. And you were able to actually

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go out. Maybe the parameters of your trial might have been different, but you could still recruit most of the patients with -- that would be causing infections at various body sites. So they were easier to develop, perhaps, than some of the things we're talking about today.

In the present, we actually have a number of drugs that are soon to be submitted for review and, hopefully, approved. On the right, we have gram-positive antibiotics that also have some respiratory spectrum, such as H. flu and the atypicals. So these drugs could be studied in community-acquired pneumonia and skin infections. They could meet the statutory requirements for approval, but they're not really addressing what's considered an unmet medical need at the moment, so they take in the traditional approach to an approval.

On the left, all of these drugs, for the most part, set out to take advantage of what has been described multiple times, the Tier B approach.

In a not-so-distant future, I suspect novel science is going to bring us a lot of interesting

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approaches to managing infection. I can't go through all of this. I'm sure my slides will be available. But I mean, Spero Therapeutics is working on potentiators. These are compounds that interact with the gram-negative outer membrane and create passageway that allows maybe drugs that couldn't access an intracellular cytoplasmic target access to a gram-negative. So that might be a nice strategy, probably bring some challenges, and we hope to work that out.

But there are others -- single pathogen antimicrobials like our Drug X-1, monoclonal antibodies -- we have license in development right now; therapies that modify pathogen virulence -- the literature is filled with ideas about how to do this; novel delivery systems, including two programs where we are trying to study aerosol antibiotics in VABP. And then perhaps more bold would be can we modify the host response and try to help patients in that manner.

So this leads me to just touching on what was brought up yesterday, the difference between an antibiotic and an antibiotic adjunctive therapy. And the adjunctive therapy really does present a

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challenge, and that's because antibiotics are really amazing therapeutics. The treatment effect is so big. As you could see, you could read any of the guidance documents where FDA has tried to generate supportive data for an M-1. And you could see that the treatment effects are huge. So how much better can you be than cured?

And what you need to do -- and fortunately we could do this with antibiotics. We have great translational models. You need to create a clinical equipoise argument, which really answers the question that -- does the test therapeutic -- could it be as good or better than a standard of care. And if it could, you could conduct a non-inferiority study. And I think that most of us throughout yesterday recognized that a non-inferiority study, like we do in Tier B, is probably the most tractable way to get a drug approved.

Test therapeutics that cannot make an equipoise argument -- like most Mabs, anti-virulence therapies, aerosolized antibiotics for VABP -- have to be considered adjunctive. And although they could

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bring great advances, they might rescue patients who would otherwise fail therapy or die. The development is particularly challenging. You have to study these in a superiority study. So here it's standard of care plus a novel adjunct versus standard of care alone.

And there are a number of compounds that are facing some of these development challenges. The MvfR inhibitor that Spero and Roche were working on has presented a number of challenges, and the work is diminishing there. But this is an anti-virulence strategy. It would require an adjunctive approach as would, I believe, any monoclonal antibodies, although the MedImmune anti-pseudomonas antibody is still looking for a superiority study. I think they're going to pursue prophylaxis.

The aerosol antibiotic therapies for VABP, the studies are undergoing -- ongoing now. So we should soon see whether or not there's any benefit from an adjunctive. I know people use aerosolized antibiotics all the time, and they'll probably continue to use them until we either have one approved with some good data or we have some conclusive data

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that they're not beneficial. The only antibiotic here that I think could really meet that equipoise argument would be Polyphor, the cyclic peptide.

So this is just an illustration taken from the comprehensive regulatory framework, kind of tiered development study that John Rex, myself and a number of industry colleagues published in 2013. And it just seems to me that as we address unmet need or take advantage of some of the new science, we're going to have to become more creative with clinical development and, in general, be conducting smaller studies and relying on more preclinical data and PK data.

So Drug X-1 I don't need to tell you about since you've done your homework and Dr. Kim did a nice job reviewing this. So what I'll basically say is, really, the major weakness of what looks to be a promising therapeutic is how are we going to get it approved. And I don't think that there's a rapid diagnostic that's widely available, but we'll learn more about that in our discussions this afternoon.

So let's look down at the bottom chart here, the frequency of pseudomonas, percent of all enrolled.

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And this is interesting because I think we all recognize that pseudomonas is -- we consider it a common, nosocomial pathogen, and it is. But when you actually try to plan a clinical trial and you look in the literature or talk to your colleagues, you realize that very little pseudomonas is responsible for any single indication.

Perhaps the most pseudomonas we'll see is in a nosocomial pneumonia, and that's even probably skewed towards VABP. And that probably ranges between 10 and 20 percent, and it gets even lower as you look at this illustration.

I've always loved this slide, and I think it first appeared as we were preparing that document. John Rex had presented this in several form, and I like the title, "The Painful Math." But it illustrates what we're up against.

And I guess I should just digress for a second and say that if you follow my logic here, you might even come to the realization that I did, that a Tier C program could actually be bigger than a Tier B program but generate less substantial evidence. So

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that's -- that was an enlightenment that I had as I put this together.

And this kind of illustrates the situation. You know, if you have a typical endpoint with a 20 percent failure rate and you use the typical parameters that we would like to use, 90 percent power in industry and you're stuck with a 10 percent margin, you've got a pretty decent study on your hands to conduct, 335 patients per arm. But now, if you have to only consider the evaluable population, culture-proven pseudomonas, if the rate's 22 percent, that goes up to 1,500 an arm. And you can see that it just gets progressively worse.

So you might get a good safety database out of a study like this. But is it actually feasible to conduct? And that's a question that I'm going to come back to multiple times today because that's part of the thesis of our discussion this afternoon -- feasibility.

So for Drug X-1, what are some of the issues we should consider? I already said that this was a very drugable molecule, and there's clearly evidence

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for clinical equipoise versus a standard antibiotic, albeit this only has a narrow spectrum. So non-inferiority is possible. But where would you study it? What site of infection? Or would you pool?

You have to recognize, though, that if you're going to enroll patients empirically, you might not be right. Even with a diagnostic, they're not 100 percent sensitive or specific, so you're going to have to provide coverage for the spectrum gaps that this agent has. What are your choices? You don't want to combine it with something that has activity against pseudomonas, which would further confound your analysis. So you're left with a few things. Tigesycline doesn't have good reliable pseudomonas or any, nor does ertapenem. So maybe those would be good things to combine it with.

But you also have to face the reality of the VABP guidelines, which say you need to double cover patients that have VABP. And typically we use an aminoglycoside. So now you've compounded your analysis with some confounding coverage.

I want to also point out that patients with

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pseudomonas infections, it's not -- often not their first nosocomial infection but their second. And they get progressively debilitated in the hospital. So there, they're typically sicker. They have higher comorbidities. But as they become sicker and have higher failure rates, that could lead to the need for a larger sample size to really measure a treatment effect. So maybe in the Analysis section, is inferential testing even possible? I think we need to really answer that question today.

And about enrollability, you know, how long will it take? How much will it cost? Would a rapid diagnostic help us, and is the design going to be something that investigators will actually be willing to accept?

So here, I'm going to provide just some standard parameters, and I'll explain a few of those. I think you heard a little bit about this yesterday, but roughly speaking, a UTI and IAI study costs about $50,000 per patient. And a HABP/VABP is over 100. And the costs are amplified as you have to go to more centers. You could imagine having to visit those

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centers, audit those centers, monitor those centers. So the costs are amplified.

The time is even more worrisome than the cost. And I'm -- I'll just focus on HABP/VABP. It takes, on average, about 12 centers actively screening to recruit one patient per month. So you could turn that around. And what does that tell you? That if you have a good center, you might be lucky to get one or two patients a year from that center.

This leads to investigator fatigue. The site staff has to work hard. And as Helen said, we want to go to the best sites, sites that have a good staff. But a good staff requires -- you know, the fundamentals have to be in place. You have to be able to pay for that staff. So these studies typically compensate the sites when they recruit patients, when they actually enroll a patient.

So these sites that have good staff typically do more than one study, and your study being very, very challenging may actually get less attention than a study, just because they have to pay the bills, that is easier to enroll.

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Nobody's really mentioned investor fatigue. And I'm actually going to emphasize this quite a bit because, as I said, these are expensive studies and they have to be paid for. And I've had two experiences. Now I work for a small venture backed company, but before this, I worked for GlaxoSmithKline. Actually, at GlaxoSmithKline, maybe it was a little easier to make the argument. There were so many layers of management that at one point somebody says do you really think we should do this. And maybe somebody like Lynn Marks would say, yeah, I do, and it would get funded. Maybe it's not the experience that others have had.

But with a venture group, you actually have to explain what you're doing, and I don't think they're going to be sensitive to or excited about a three- or four- or five-year study. And they have other choices to invest.

Rapid diagnostics to the rescue. We all -- we've mentioned this a lot, and I have actually had some firsthand experience trying to use a rapid diagnostic, which was approved in the United States.

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And I'll tell you that that experience isn't worth getting into too much detail, but I think we have to be careful about what we -- I think we'll accomplish there.

And I'll start with my aside. You know, I do think a rapid diagnostic, if the economics get worked out and if people use it, will be very valuable with antibiotic stewardship and should lead to improved outcome in patients that are in our hospitals.

But we have to remember diagnostics don't create patients infected with the target pathogens. Therefore, we could use them for enrichment. They may allow us to save costs, but it's unlikely they're going to help us save the time. And I pointed out that time and risk is really what I'm focused on here. I think that those are the elements that don't always get the obvious attention. Cost -- you know, we have a fairly good sense of what that is.

Why do I feel that diagnostics aren't a panacea? Well, they require hardware, and you have to train people on how to use that hardware. You have to

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get that hardware to the sites that you're doing your clinical work, and then you have to service it. I talked to a few diagnostic companies who feel that their machines need servicing at least twice a year.

So you could imagine that if only a few people can use that diagnostic, even if it's relatively simple, that could impede your ability to recruit patients who might present when those few people aren't there. And the other thing I should point out is the companies aren't working to your clinical trial timelines, which means that they might not be available to initiate your center, train them and make sure everything is in operational condition when you want that.

So moving forward, Drug X-1. I'll point out, first of all, that no standalone Tier C programs have been submitted for review, but we're going to see standalone -- we're going to Tier C-like work in Tier B presented. And I'm not saying that those aren't important studies to conduct. But small samples may not contain sufficient numbers of the target pathogens to allow inferential testing even if we take advantage

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of wide non-inferiority margins and one-sided significance testing.

Also, small samples from a sick population may have this sample variability that we talked about. With many comorbidities, we could get unpredictable results, increasing our risk of failure. We've already talked about what you can do, and I think you need to do everything you can even for a narrow spectrum drug. There's -- there is no reason to skip the easy stuff, but what we're talking about is the study required to generate the substantial evidence of effectiveness.

So here's where my thesis comes in, that with these feasibility challenges highlighted for Drug X-1, can one expect that a clinical trial will meet the requirements of substantial evidence of effectiveness with any predictable certainty. Remember, when you go ask for the funding, you're going to have to say -- everybody's used to risk. But you're going to have to tell them how you're going to manage it and get people to believe that, you know, what you're going to do is going to be successful.

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So where does this substantial evidence come from? I think we all know this. In Tier B, we rely on a non-inferiority study against the usual drug-resistant pathogens and the target pathogen study, which I think is very important -- and we should find ways of including that information in the label -- becomes supportive evidence.

In Tier C, we don't have the UDR study, the non-inferiority study. So now suddenly we have to make that target pathogen study our substantial evidence, and I think that that raises a lot of questions.

So you know, fortunately, there's the Tier D, or animal rule. And here, the target pathogen study could remain your supportive evidence. It still should be done. It'll generate the PK. It'll be very important, but the statutory requirements could be met by demonstrating substantial evidence of effectiveness from animal studies.

So I'm really saying that I know that pseudomonas is an important problem. It may be more common than KPCs and NDMs in the U.S. and parts of

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Europe. There is strong supportive data for a drug like Drug X-1. But I really think that the challenges of recruiting a single pathogen Tier C-like study carries a high degree of unmanageable risk. And I don't know how I could put together an argument that the results of a Tier C study, no matter how carefully conducted, will favor a chance of supporting approval versus condemning the drug to failure.

So we do need an alternate approach. At least that's my thesis. And this is in the -- since we're going to hear a lot more about the animal rule, this is just a review of what you need to consider and what the animal rule's all about.

But here, I've highlighted the word feasible. If you cannot conduct an adequate and well-controlled clinical study because it's infeasible and you need to generate substantial evidence, could it be -- could it come from an animal study? And first of all, we have to agree that it's not feasible and unlikely to work to do the clinical route. And then we have to determine whether or not there's a validated pseudomonas infection model that could

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provide substantial evidence. And I'm not prepared to tell you that there is or there isn't.

I'll just point out that there is this requirement for a field study. So if you're -- take advantage of the animal rule, say, for plague, when you submit your NDA, you have to provide a protocol that talks about a field study in the event that there's a plague outbreak. And you should be prepared to conduct that. I would argue that if you were to take an animal rule approach here, that there are questions that could be answered after approval and there are enough pseudomonas isolates out there that you might be able to do a selective study that might improve your benefit risk.

So in conclusion, I think that we'll see promising narrow spectrum agents and that the -- but the development path is unclear. As the basic science advances, we'll see more translational changes. Adjunctive therapies will continue to be challenging to develop. I think the blending elements proposed under Tier C with the animal rule may allow FDA approval for select narrow spectrum therapeutics.

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And I guess I'd hate to see us slip backwards to the -- a point where we don't have antibiotics to support important medical advances like bone marrow transplant, solid organ transplant and other things that have been mentioned. And I don't think we should rely on or hope for only broadly active, easier-to-develop antibacterial therapies. We're going to have to solve this problem.

But thank you.

(Applause)

DR. COX: All right. Thank you, John.

And now Sumathi Nambiar, who's the Director of the Division of Anti-Infective Products, will provide information on potential clinical pathways, some background information about the animal rule and then also describe some of the experiences with development of animal models that have been utilized in the area of plague.

So Sumathi, thank you.

DR. NAMBIAR: Good morning. So I think some of this was touched upon by Ed in his introductory talk. So we do recognize that there's a potential

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clinical utility for antibacterial drugs that are active against a single species. But we also recognize that such drugs are very difficult to study when the single species that the drug is active against occurs infrequently.

This has been stated earlier. Pseudomonas is not really a rare cause of certain infections, but it just doesn't occur frequently enough. And so enrolling such patients in a clinical trial becomes particularly challenging. Certain infections like hospital-acquired pneumonia or ventilator-associated pneumonia, you're more likely to encounter pseudomonas aeruginosa. But such infections tend to be polymicrobial, necessitating the need for concomitant therapy. And this concomitant therapy often has overlapping spectrum of activity, which means it covers pseudomonas as well. So that really confounds our ability to assess treatment effect. You've heard a lot about rapid diagnostics, how they could help some but certainly will not solve all our problems.

Again, Ed mentioned this this morning. So in contrast to other rare human diseases, we have

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unique challenges when we are trying to study acute bacterial infections. There is an urgent need to start therapy. Patients are sick. They need to lay an initiating effective therapy can impact outcome. There is diagnostic uncertainty at the time of presentation. Therapy tends to be empiric in most instances.

It's difficult to identify such patients a priori ahead of time. So a lot of the other rare diseases, you can maintain a registry. You sort of know who your patients are and you can plan and conduct a trial. It's very different in this particular setting.

And lastly, patients present at local healthcare facilities rather than at a special facility, and I think this, too, had come up in Dr. Rex's presentation yesterday.

Some of the characteristics of X-1. I think overall, as was mentioned, by John Tomayko, this seems to be a promising candidate, appears to address an unmet need, has a novel mechanism of action.

In vitro studies do not suggest a high

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likelihood of resistance development. Safety profile seems reasonable. We have identified hematologic and hepatic toxicity, but both of them appear to be monitorable. And at the proposed dose, we have a safety margin for both toxicities.

There is evidence of antibacterial activity in animal models of infection, so these are the routine models that we do to assess if there's activity. And they really don't rise to the level of being efficacy studies that we'll talk later today.

There's a proof of concept study in a small number of patients with non-CF-bronchiectasis. There was evidence of log reduction, so there is some evidence that the drug actually does impact the organism.

Dosing rationale appears adequate, and dosing has also been evaluated in patients with renal impairment. So this will allow for patients in the trial with renal dysfunction and, again, highlights the importance of trying to enroll patients with comorbidities, which tends to be more common in these kinds of patients.

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So we've certainly had a lot of discussion on this within our group, and we've come up with four options. Again, I'm sure there are other options out there, and we look forward to the input during our discussion period this afternoon. So this is not meant to be an all-exhaustive list.

And I'll go through each one of them. But broadly speaking, the first option hinges on doing a non-inferiority trial. The second one is in superiority trial. The third one is trying to do a trial in a population that's at a high risk of infection due to pseudomonas. And the last option, again, has been discussed in earlier presentations, is establishing efficacy under the animal rule.

So this is a first option. And here, I have A and B which is an NI trial either at a single body site or an NI trial pooling across body sites. So if you look at an NI trial at a single body site, it's potentially feasible if you're willing to accept a greater degree of uncertainty, which translates to a wider non-inferiority margin.

In such a trial, there is no need to enroll

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patients who only have pseudomonas aeruginosa for specific phenol types. And all-comer pseudomonas aeruginosa population would be acceptable.

You know, we'll go through some numbers, but I think we all understand that it is difficult to enroll an adequate number of patients with pseudomonas in a standard non-inferiority trial. Availability of the rapid diagnostic might help some, but really helps with enrollment. It's really not going to change the frequency with which the organism causes infection. Again, this has been highlighted previously.

I touched upon this a little bit, and I think it's going to come up a fair bit for discussion this afternoon. I mean, two real difficult issues to deal with -- one is the need for concomitant and antibacterial drugs that treat other gram-negatives because HABP/VABP is polymicrobial and X-1 is rarely targeted only against pseudomonas.

So we've talked about ertapenem as a potential option, and John mentioned this earlier. I do want to note that it is not indicate it for HABP/VABP. It has an indication for CAP. So we will

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need to do some work to find out if it will be accepted or considered clinically okay to treat a sick patient with HABP/VABP with ertapenem.

The second big issue that we have to deal with is the dual therapy for pseudomonas aeruginosa. Typically, for treatment of this condition due to pseudomonas, a dual therapy is used. And again, this has been -- has come up earlier. Now there -- the treatment guidelines that were published just a few days ago do suggest that monotherapy is acceptable. They identify certain situations either based on the local antibiograms and your institutional antibiogram or the presence or absence of risk factors.

And if you go through the risk factors, it's really hard to come up with too many that these patients will not have by the time they develop HABP/VABP. But still, there is some role for monotherapy in a few patients. Again, we look forward to discussing that this afternoon.

The other issue is, even if patients are started on dual therapy, there is the option of deescalating once you have the susceptibilities. And

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what we've seen from clinical trials that have been conducted in HABP/VABP, there's a great reluctance on the part of investigators to deescalate. So in effect, what happens is most patients get dual therapy for just the entire duration of treatment.

So I'll just walk you through some numbers. We looked at what a sample size might look like for a HABP/VABP trial that uses all-cause mortality as a primary endpoint with the following assumptions -- a 20 percent mortality rate, two-sided alpha of .05, 1-to-1 randomization, 80 percent power. And I'll go through a table review. The NI margins can go from 10 to 20 percent, and the prevalence of pseudomonas can go from 10 to 20 percent.

And John Tomayko showed you some numbers. In recent registrational trials, the prevalence has been in the order of 10 to 15 percent. There are some publications that do suggest that it may be closer to the 20 percent or the low 20s. So we've tried to put in some degree of variability and look at what sample sizes might look like.

So if one is to do a standard NI trial with

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a 10 percent non-inferiority margin and a 10 percent prevalence of pseudomonas, you can see that the sample sizes are fairly large for the total number of patients just to get about 500 patients who have pseudomonas alone. The widest non-inferiority margin would be, really, what M-1 is, based on what's in our guidance with M-1 of 20 percent. And you're at about 1,200 patients.

If you're truly able to go to sites that have a higher prevalence of pseudomonas and you're more in the 20 percent range, it cuts your sample size in half. And certainly, if you're willing -- if you or we are willing to go with the wide non-inferiority margin of 20 percent, which is all of M-1, then the sample sizes seem to be in the feasible range.

The other body sites that we've considered for where one can conduct a non-inferiority trial was complicated UTI. It's certainly easier to study in this indication because pseudomonas can be -- can cause monomicrobial infection. However, the incidence is still low, and we think that such a trial might not be feasible.

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And the other issue is -- again, it was discussed yesterday -- is if you have efficacy only in cUTI, how much comfort does that provide that it might work in other body sites, especially the lung.

We've also thought it would burn some surgical site infections because these tend to have pseudomonas infections more commonly than other organisms. But I think there are a lot of challenges. These indications are very difficult to study. They're not very common. We really need to figure out what the endpoint or the trial design might look like.

Another option to do a non-inferiority trial we thought is maybe pooling patients who have HABP/VABP and/or bacteremia and use all-cause mortality as the endpoint. It might help with the numbers than if you did a trial in HABP/VABP alone. But again, this was discussed. It's very difficult when you combine a type -- different types of infections and different sources of the bacteremia. It might be difficult to discern if there's a deficit in efficacy at one or more body site. And again, this was mentioned yesterday. Decisive treatment effect

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does vary across the different indications.

So moving on to the second option, which is to conduct the superiority trial, so here, we will assess the superiority of Drug X-1 over best available therapy. In such a trial, to be able to demonstrate superiority, one would need to enroll patients with pseudomonas aeruginosa, which is resistant to currently available therapy.

You could enroll patients with different types of infection. In such a trial, again, the shortcomings of that we've already gone through. Certainly, we wouldn't challenge the findings from superiority trial. It's easy. It provides direct evidence of treatment effect.

However, determining superiority over existing therapy can be difficult. We saw some -- went through one example yesterday from Dr. Friedland where the challenges of doing such a superiority trial were very clear. I think we've touched upon that, the impact of pooling. And then it's also an issue of sheer numbers which we will go through in the next few slides.

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So this was a recent study from JMI Labs where they looked at the prevalence of these different organisms. And they used the term PHP pneumonia in hospitalized patients, which essentially is everything other than VABP. So it's VABP and non-VABP patients.

So of about 8,000 isolates, 21 percent was pseudomonas. Twenty-two percent of them were meropenem non-susceptible. They used a definition of MIC of four or greater, though the label breakpoint to the best of my understanding was eight.

Among the meropenem non-susceptible pseudomonas, the incidence Amikacin resistance was 13 percent. We're trying to do this, really, to see what is the likelihood of encountering a multidrug resistant, a band-resistant (ph) pseudomonas because that's the only opportunity you have then to demonstrate a superiority.

And if you look at the incidence of what meropenem and Amikacin resistance in the overall population, so the first numbers are really if you're -- if you're only studying pseudomonas. Going into the study, you know, everybody has pseudomonas. But

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if it's an all-comer HABP/VABP, the numbers are really, really small. So to find one patient with pseudomonas where the organism is non-susceptible to meropenem and resistant to Amikacin, you would need 122 patients.

And I just have to acknowledge, you know, we sort of average the numbers, but you can take a look at the paper. You know, there are differences whether you do U.S. sites versus X U.S. sites. There are differences in non-VABP and VABP. Certainly, in a VABP population, the prevalence of pseudomonas will be slightly higher, and the prevalence is also higher in X U.S. sites. In this study they did -- Europe, Mediterranean was one group; China; and then U.S.

So what would the sample size look like if one were to try to do a superiority trial given some of these numbers I've shown you? These are our assumptions -- 1-to-1 randomization, 2-sided alpha .05, 80 percent power. We've estimated the control group mortality rate of 40 percent. And I'll go through numbers. I won't go through every one of them, but we've tried to provide three sets, you know,

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if -- depending on what the mortality rate and the test control are ranging from 20 to 30 percent. So obviously the greater your treatment affect, the smaller your sample size would be.

And the frequency of MDR, we range it from 5 to 25. Going by the previous numbers, I think five would be your best-case scenario. But again, there are -- you know, that's one data set. Maybe other data sets will speak otherwise. But we just had -- needed something to work with to go through this example.

So if truly the frequency of MDR P -- pseudomonas is only 5 percent and you have a 10 percent improvement in the mortality rate with the test drug, your sample sizes are pretty impressive, whereas if you have a really good drug and your treatment benefit effect is at least 20 percent, even so you're in the 3,000-odd range.

And we've heard over and over again just to do one all-comer HABP/VABP trial. The rate of enrollment is dismal and doing these trials is very challenging. But if your frequency of MDR PA is

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really high, you're in the 25 percent range and your drug really works, then you might have a number that you can live with.

So then moving on to the third option is really targeting a patient population where the prevalence of pseudomonas infections is much higher. So that could include patients with either cystic fibrosis or bronchiectasis. And we know that these patient -- this patient -- these patient populations tend to have pseudomonas more commonly than some of the other patient populations.

But again, there's a lot of work to be done because we really need to identify what clinical condition we are going to treat in these patient population. Is it going to be treatment of pulmonary exacerbation? You're not going to use this product for preventing exacerbations.

And a treatment of pulmonary exacerbation in this population really has similar issues as one encounters in treating HABP/VABP, whether it be concomitant therapy or identifying the organism. And then the other challenge, also, will be to extrapolate

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efficacy from this patient population because they do have unique characteristics to the wider population.

So that takes us to our last option, which again Helen and John had mentioned in their presentations which is using the animal rule. So I'll go through some basics about the animal rule. I'll walk you through an example of how an animal model was developed for treatment of plague. I cannot go through all the details, but I think just to give you a flavor for what we are talking about when we mean animal models to be able to use the animal rule.

So we have -- it's in the code of Federal Regulations we have for drug and we have for biologics. It's when we approve new drugs when human efficacy studies are not ethical or feasible.

And it really applies to new products, you know, which are being used to treat or prevent serious or life-threatening conditions where definitive of human efficacy studies cannot be conducted because it would be unethical, so a slightly different situation at hand here because, I think, as had been mentioned, it's less about the study being unethical but more

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about the study not being feasible, given where we are today.

So they want us to use an animal study to establish effectiveness at a full criteria that have to be met. And as I mentioned, there is animal rule guidance that goes through these -- this in very detail, and it's also outlined in the regulations.

So we have to have a reasonably well-understood pathophysiologic mechanism for the disease. The effect has to be demonstrated in more than one animal species, and the animal species is expected to react with a response which is predictive of humans. The endpoint that we use in the animal study should be clearly related to the desired benefit in humans, and it's generally the enhancement of survival or preventing major morbidity.

And we have to have adequate information, the kinetics and pharmacodynamics of the drug in the animals and humans so that we are able to select an effective dose in humans. So all these criteria have to be met for us to rely on the efficacy data from animal studies to extrapolate -- or to be able to

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support approval of the product.

And there are three additional requirements. We heard about post-marketing studies, or field studies, in John Tomayko's presentation. So there is a requirement for post-marketing studies to provide evaluation of the safety and benefit if circumstances arise in which a study would be feasible and ethical, like in a bio-threat situation.

There might be a need to restrict -- impose restrictions to ensure safe use of the product. And lastly, labeling must include information to patients that explains that, for ethical or feasibility reasons, the product was approved based on studies -- efficacy studies conducted on animals.

So if we were to use the animal rule for our product X-1, we will obtain efficacy data from adequately characterized animal models. And this could be supplemented with clinical data from patients with a variety of infections caused by pseudomonas aeruginosa. This could be one or more descriptive study.

The plus to this approach is that, you know,

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if you're really not able to conduct an informative efficacy trial, then this might provide us an option to assess efficacy. However, again, as Ed had mentioned in his presentation, we really don't have any adequately characterized animal models, at least not that we're aware of, for these particular indications being considered. So a lot of work will need to be done to develop well-characterized animal models.

And unlike with bio-threat agents, it is ethical to conduct these trials. I think the issue here is really feasibility.

And unlike drugs approved for bio-threat indication, if X-1 were to be approved, then it would be used in a broader population and potentially on an empiric basis. You're really not going to save it for when an outbreak occurs as in a bio-threat scenario.

And then also raises questions about what would the field trial look like because a field trial is required when it's feasible and ethical. So if you're able to conduct such a trial right after approval, then it really invalidates the need to

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approve the product under the animal rule.
And the post-approval study would really face the same -- likely face the same challenges that you encountered pre-approval. And I think for us a bigger issue from a policy standpoint is what kind of a precedent we might set for other clinical conditions of low prevalence, so a lot of issues to work through but certainly an option worth discussing.
Here's some examples of products. I just have the list of drugs. I don't have the list of biologics here that have been approved using the animal rule. For infectious diseases, we have three products approved for plague and three approved for inhalational anthrax. There are also other products available for non-infectious disease conditions, you know, products that might help for radiologic nuclear incident, cyanide poisoning or nerve gas poisoning.
So next, I'll walk you through the plague example, you know, just sort of to, you know, let you know that this is -- it's really not that straightforward. But it's doable, I suppose, if we all decide this is the way we are going.

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So the African green monkey model of primary pneumonic plague was developed to provide a platform for testing various therapeutic intervention. Mortality outcome was assessed in AGMs with symptomatic disease, and this was done in more than one lab. The progression of the disease was described, and the potential triggers for therapeutic intervention were also evaluated.
And we had some human data available. I mean, they were not perfect, so one could compare the disease in the AGMs with that in humans. So here, naïve -- experimentally naïve AGMs healthy male and female was studied. The Colorado 92 strain of Yersinia pestis was used, and this was the exposure target. The AGMs were monitored clinically, and laboratory tests were also monitored. And then the AGMs that succumbed to disease, pathology both gross and microscopic were assessed.
So when these studies were done, the exposures did range a fair bit. AGMs clinically had fever, loss of appetite, respiratory distress, lethargy and increased respiratory secretions. From a

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laboratory test standpoint, they had leukocytosis, abnormalities in the liver function test, coagulation abnormalities.
The duration -- the onset of bacteremia was quite variable from 30 hours to 94 hours, and they had radiologic infiltrates as well. On hystopath, there was evidence of fibrinosuppurative hemorrhagic pneumonia, so not really different from what one expects in animals.
So here's -- in the next two or three tables I tried to compare how the disease looked like in the AGM compared to what we know about human pneumonic plague. So the challenge agent in the AGM model was Y. pestis CO92. In humans it's Y. pestis. The CO92 strain was isolated from a human with pneumonic plague.
The pathogenic determinants of the organism are the same monkey are to humans. The root of exposures in AGM was aerosol, had only exposure. In humans, it tends to be aerosol exposure as well, generally, when there's close contact with the -- another individual with pneumonic plague are in the

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unfortunate setting of a bioweaponized aerosol.
The exposures are quantified in the AGM. It ranged -- but as long as you got more than 20 LD50, the animals all succumbed. The infectious inoculum in humans varies. It depends on the contact and the degree of exposure.
From a pathophysiology standpoint, there were a lot of similarities between the disease you saw in AGMs and humans. The time to onset of disease of condition ranged from one to three days, slightly longer duration in humans. Time to death, again, it's not very different.
Signs and symptoms were fairly similar. There's fever, lethargy, tachypnea tachycardia. There was evidence of neutrophilic leukocytosis, coagulation abnormalities. Radiologic evaluation showed infiltrates. In humans, it's very similar -- consolidation cavities bronchopneumonia and the pathologies hemorrhagic pneumonia in both.
Both AGMs and humans are highly susceptible to the disease and uniformly fatal if untreated. The trigger to intervention in humans was based on them

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having a certain degree of body temperature elevation for a certain period of time. In humans, it certainly varies. It depends on whether or not there's an index of suspicion for plague being a possible etiology.

So based on all these, I think the four key characteristics that we took into consideration designing the animal efficacy study was that the endpoint would be mortality. So the animal's dead or alive. The timing of intervention is after the AGMs had been febrile for a certain period of time and they had met the threshold for the temperature elevation. The test drug that was being evaluated for efficacy was to -- was administered intravenously, and the dosing regimens that the AGMs received were humanized dosing regimens.

So I just picked one example for levofloxacin, but there's information on the other example -- on the other drugs as well in the public domain. And also, a lot of discussion around how these AGM models were developed if you're interested was discussed at an advisory committee in 2012. So all this information that I have presented and more is

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available on the website if you look for an advisory committee in 2012.

So if you'll -- if you take plague -- take the levofloxacin, an example, a single placebo control trial in AGMs was conducted. Now, at the time that this indication was being sought in the study, these study -- the study was being done. Levofloxacin was already approved for other indications, which included pneumonia, both community-acquired and nosocomial pneumonia.

So we though a study in one species was adequate. There was no requirement to evaluate it in two different animal species. The AGMs were exposed to a mean dose of 65 LD50 of the CO92 strain. And they were randomized. They got either 10 days of intravenous levofloxacin or placebo after they reached the pre-specified trigger. And as you can see, mortality in the levofloxacin was significantly lower compared to that in the placebo, and you have a significant P value.

So I know I walked you through a lot in the short period of time. But you know, just my sort of

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summary thoughts here are that what we know so far about Drug X-1, it certainly appears to address an unmet medical need. It has a potential, so I think we have to find a way forward to develop this drug. We do acknowledge that under the current paradigm, studying a drug such as X-1 that's only active against a single species that occurs infrequently at any one body site or even occurs infrequently across different body sites can be very challenging.

I've gone through some potential development options. Again, these are options that we've come up with, but maybe there are others that we haven't talked through. All the options I've discussed have limitations, so none of them are perfect. And I don't think any one of them is going to solve the problem right away.

And even if we -- one were to lean towards option four, which is to consider the animal rule, a lot more work needs to be done to develop a specific animal model, or models, for infection in which we can assess the efficacy of either Drug X-1 or other similar -- similarly situated products for the

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clinical conditions being considered for development.

Thank you.

(Applause)

DR. COX: Thanks, Sumathi.

Now we will have Marco Cavaleri from the European Medicines Agency, where he's the head of Anti-Infectives and Vaccines, will give a perspective from the EMA on the challenges of developing a drug that's targeting a single species.

Marco?

DR. CAVALERI: Thank you, Ed.

I think a lot has already been said. So here, I will try to focus pretty much on some aspects that are coming up based on our reflection on a case like this one, which indeed is not an easy one.

So first of all, again, as stated yesterday, I would stress that the preclinical and clinical pharmacology package has to be thorough and exhaustive as much as possible, including all the (inaudible) aspects and drug-drug interaction; metabolism and excretion; distribution in relevant body sites like ELF; as said yesterday, the PK in ICU patient and with

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augmented renal clearance should be started; the PK in renal and hepatic impairment, too, and also with the need of dose adjustment.

And of course, we would expect to see an adequate and robust PK/PD profiling, which is essential and is expected to complement as much as possible all the limitation that may derive from the clinical efficacy data set. Exposure response analysis are expected to be conducted in the efficacy trials, even if here we have to recognize that is more datasets we are talking about. And also, the concomitant therapy will confirm a lot of this kind of analysis.

So some general reflection. We heard a bit around the conduction of clinical trials what could be the role of rapid diagnostic test in order to enrich enrollment. And frankly, we've been struggling to think how you can really avoid at least thinking about using some experimental rapid diagnostic test in order to conduct trials with such kind of drug.

And of course, one of the goal will be to try to reduce the amount of patient that are enrolled

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empirically and which if on one side would add (ph) to the safety database and the other will not be useful for the sake of addressing efficacy evaluation. We would allow 24 hours of previous antipseudomonal therapy.

And even if we are encouraging the use of rapid diagnostic test, EMA will follow pragmatic approach if these are using the context of clinical trials. And therefore, for the recommendation in the context of the SMPC will have to necessary not be binding with respect to the use of the rapid diagnostic test, and we will try to figure out what is the best way forward in this in setting (ph).

In consideration of the epidemiology for this pathogen, at least in Europe, as you may know, in certain countries the MDR pseudomonas aeruginosa prevalence is very high. So at least try to enroll some of these cases, considering that these indications in the context of a limited use option. But of course, here, we will not be overly demanding.

And is said by others, it's very important for conducting trials with this kind of drug to go

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into a careful site selection and try to go to sites that are able to conduct trials in this -- with this kind of drug in the (ph) pseudomonas.

Now, I took the liberty of taking out one of the table that was introducing the document that you have seen and going back to the point of rapid diagnostic test. And I noted that the specificity of the test that was put in there was below 58 percent and quite variable.

So what I did was try to see if with the specificity of 95 percent, which we may assume is not so unrealistic, at least based on what we know in some of the rapid diagnostic tests that are under development for -- from negative pathogen and pseudomonas, then what would be the PPV. And here, you can see that if the prevalence of the illness is 15 percent and taking the sensitivity of 80 percent as was initially proposed in the paper, then the PPV will go up to 74 percent, which means that you will have to enroll 135 patients in order to get 100 patient with the illness or with a target pathogen.

So clearly, there is some benefit in

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considering the use of rapid diagnostic test in terms of clinical efficiency. At the same time, I do fully recognize that, as also has been said before, that this will not change the time you will take to run the trials. It will not change the fact that you will have to go broad with a large amount of size all over the world and that the number that you have to screen will be exactly the same, so very high.

And also, we also do acknowledge that, as I said, from an operational perspective, having a rapid diagnostic test embedded in the clinical trials could be problematic and not so straightforward. Nevertheless, it could be a good opportunity to try to make the clinical development more efficient.

So coming to what could be the options, and here I would go along pretty much what I showed you yesterday around what will be the examples that were shown in our guidance document. So along those lines, one option could be to conduct a randomized study in HAP/VAP, which is the type of infection that is most prevalent with pseudomonas aeruginosa. And we can concede that that is a very good test for any drug.

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Here, we will be open to consider enlarging the non-inferiority margin and also maybe to consider whether the alpha level could be relaxed somehow. And of course, all these elements will have to be discussed on a case-by-case basis and based on a specific proposal. But we are pretty open to talk about that.

The primary endpoint will be clinical outcome as test of cure. And of course, this can be handled with different statistical analysis plan if the FDA requires all-course mortality. And it would be good to look into option for testing of nested superiority in subgroups or based on secondary clinical irrelevant endpoints.

We do acknowledge that monotherapy's not possible, at least initially. And here, I think the proposal in the paper sound like a good approach and a valid starting point. But again, it would have to be discussed to what extent the use ertapenem would be possible in various parts of the world and whether the dose suggested would be accepted by most investigators.

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The control therapy may be a pretty fine single combination. And again, we're proposing the paper sounds (ph) as a good way forward. But again, in terms of feasibility, there might be a need to consider best available therapy.

And of course, here we don't want to end up in a situation, as Mike was showing yesterday that there are 69 different best available therapy that can be considered. So it would be very important that there is a limitation to the number of best available therapy to be considered and according to a define -- a predefined hierarchy (ph).

And this could include option for cases of MDR isolate. For that specifically, an option could be to have an additional uncontrolled study that just is recruiting the MDR cases.

Another option would be the all-comer studies, which would include the HAP/VAP, intra-abdominal, UTI and bacteremia. Again, infection specific in clinical outcome at test of cure is primary endpoint. We do not expect this study to be power for formal inferential testing.

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Superiority is not demanding. But of course, it will be very important to try to explore option for nested superiority in subgroups and secondary relevant clinical endpoints as for the case before. And an even randomization can be considered for it to four-to-one (ph). What is important here is always to have even a small control group that would help us in order to understand that, for sensitivity purposes, to understand what we are seeing in the trial.

Monotherapy is -- would not be possible at least initially, maybe with exception of UTI. But as I think already said by Sumathi, this is not very common, and so it can be very challenging to get a lot of cases with pseudomonas and UTI.

Control therapy may be as well pretty fine or be best available therapy, and the same arguments as raised before will apply on the need of hierarchy if best available therapy is used.

The last option will be an uncontrolled study, including the major indications as highlighted before with infection specific clinical outcome at

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test of cure as primary endpoint. And here, it would be essential to have adequate and convincing external and historical control.

The same argument on the monotherapy will apply, of course. But of course, in light of the hurdles in the interpretation of the data which are expected to come up, adequate justifications will be provided that this is the only way forward or the only feasible approach. And here a convincing PK/PD package will be even more critical than in the other scenarios.

So at the end of the day, the indication in line with what I told you yesterday will be for the treatment of infection due to pseudomonas aeruginosa in patients with limited treatment options. We referenced to other part of SMPC. And in particular, I would stress that in the Section 4.4, so the warning section, the limitation of the data will be explicitly stated, mentioning the relevance of population for which there are notable uncertainties as, for example, not sufficiently included or represented in the clinical studies, or for which PK data are not

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available or not fully supported of activity at that specific body site.

And I think I'll stop here. Thank you.

(Applause)

DR. REX: So, thanks to all four of our panelists. We're now going to take a break. Outside there is another handout. That handout is, in a sense, the reveal but it's also the basis for the debate. And I hope you've all come with some ideas.

We've held back showing concrete solutions so you had all the time to sort of let your brains spin around and come up with the brilliant idea that none of us have thought of. That's what we're looking for.

The -- we'll come back at 10:45 and talk to you soon.

(Off the record.)

DR. REX: -- towards getting started.

So welcome back to Drug X-1.

Maybe push that door shut. We'll deal with it in a second. So, yeah, if you would, thanks, it would be great.

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So before we go on into the clinical case and how it got developed, are there any questions by anybody on the panel or in the audience about the setup, you know, for the sort of the background on X-1? You know, there -- one of the great things about a hypothetical drug is any data that I need I can invent in my microseconds. So if there's something you'd really like to know, we can tell you the answer to it.

I realize things like, you know, what's the protein binding. Well, it didn't end there because -- okay. It's 62. You know, you just did -- the math is adjusted somewhere buried down in there.

So David (ph)?

DAVID: Just something that Sumathi mentioned, is there Phase 1 data in seriously ill ICU patients in terms of PK?

DR. REX: That's not listed in the book. That -- we haven't done it so you can add that to something you could go and dose some people with nosocomial pneumonia. What we did in the case was we said that we're going to assume the perimeter estimates -- are inflated from the healthy volunteers.

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And it -- and because it was chosen as a purely renal drug, you know, there's so much kind of known about what drugs like that do. But that's probably a good idea, is to develop some information like that. So, you know, yes you could do that.

Other questions about the setup? John?

DR. TOMAYKO: Yeah. I have a question for Marco. In your examples of the uncontrolled study and the across-body site study, what's the type of approval that that would get in the EMA?

DR. CAVALERI: Yeah. Well, that will have to be discussed in light of the data and, you know, in light of the uncertainties that will emerge on the benefit tree.

So one option might be exceptional circumstances. Another option might be a full approval if the data fully convincing and if external control, historical control can be pretty convincing in terms of demonstrating what is the effect of the drug. So I think we are keeping the options open and not ruling out what kind of approval will be most suitable.

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DR. CAVALERI: Okay. Thanks.

And then I have one comment. Sumathi made this statement that if I proposed doing a field study right after I get an approval on the animal rule, then that kind of invalidates my feasibility argument. I just wanted to add some clarity to that.

I'm looking for a little flexibility. I know that we don't have the pseudomonas animal model as of yet and there's probably some issues that have to be worked through. But what I think we might be able to do in a field study is answer questions that emerge during our clinical program, and their important clinical questions.

As an example, what if we did have in our small clinical data a few of these patients with head trauma who had poor outcomes and we'd like to understand why. Maybe it's a PK issue, and maybe we should go to the centers where those patients are more likely to be studied and try to develop a better understanding and understand how perhaps to dose better. And all of this information only improves the benefit risk once you have the approval. So that's

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what I meant about a field study.
DR. NAMBIAR: Yeah. So I think the typical sense of the word, because you're looking at bio-threat and you talk about field study, it's really when you sort of have an event, a bio-threat event. So that's a little different than here.
In here, I think the issue -- the reason one would -- when was thinking about using the animal rule is because it's really a feasibility issue, to be able to do an adequate well-controlled trial as we would like it. So even if one were to use the animal rule, we are certainly looking for some clinical data in humans, which should be available at the time that you're actually trying to approve the product based on animal rule.
So yes. And if that is a across body sites and involves patients with various degrees of comorbidities, that site will all help us. But the basis for approval in that situation would be the animal rule. So that's the difference.
DR. REX: It looks like Helen has a question and then Ed.

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DR. BOUCHER: So maybe I'll just follow up Sumathi.
So in that scenario, what would the label look like?
DR. NAMBIAR: Okay. So I'm not quite sure if we are at the label. But typically, for products that are approved under the animal rule, we describe the animal efficacy study that was the basis of approval in the clinical study section of the label. We don't have any human data other than safety, right?
The one exception is in looking at these non-infectious disease-related labels, is for the cyanocobalamin. There was actually was some data in humans who sort of were exposed in -- I think they went into burning building or something, and it was actual cyanide exposure. So there is some human data that was available, and that is included in product labeling.
But exactly what we would include, I mean, we really have to discuss. You know, the regulations do state you only include adequate well-controlled studies. But you know, we'd have to discuss that when

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we get to that point.
DR. COX: Maybe just following on this, too, one of the things I was wondering is, you know, if you think about it, if you're developing a drug, it may not be feasible to do, you know, a five-year trial that enroll an X number of patients.
But you know, if the drug were approved, you know, could you then embark upon a longer clinical trial program that might get you to something that would actually be a controlled study that would help you to understand how the drug works that, you know -- so in essence, I'm trying to figure out are there some things that might be feasible post-approval that you really just couldn't do preapproval?
DR. TOMAYKO: Well, I'll just take a chance and try to highlight what comes to mind. You know, envision that you have a drug that's approved with very limited data such as animal data and some clinical data and you just convinced your investors to invest a substantial amount of money in doing that work. And yes, you'd love to be able to do anything, but you might not be selling much of that drug at that

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point. And you might not be able to raise the money to do anything huge. That's just the reality of the situation.
I mean, if somebody were to come by and buy the drug and have greater resources and be willing to take that type of a thing on, great. But there's no easy solution to this problem, in my view.
DR. COX: Yeah. And I realize, too, that, you know, the incidence of disease may still be very low. So it's -- that doesn't change. I'm just -- something longer term, I'm just trying to figure out can you make -- you know, get something that would gather some clinical data that might help make sense of it.
DR. BORIO: I mean, just to clarify Ed and Sumathi, that the field study is something that is very, very flexible and open and, you know, how you can collect the data. So it could include registries, reliance on electronic health records. It could include, you know, just a variety -- much more flexibility than what we'd expect as an adequate and well-controlled study for an investigational product.

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DR. REX: Helen again.
DR. BOUCHER: So to that end, some things that have been discussed as part of the carb effort have included, you know, improved monitoring of antibiotic use in general through the CDC and HSN and other mechanisms really directed at stewardship. But it may not be crazy to think that those types of mechanisms might work here where, you know, a new drug for very a specific special population came out and could be monitored in that way with some kind of feedback whereby, you know, it's more real world. And so the quality of the data, you know, it may not be exactly what you're looking for, but it would -- could be a way to monitor and understand more about the potential utility and/or risks of these new agents.
DR. COX: And just thinking about things too, I mean, you know, there will be, you know, a fair -- you know, an animal rule-based approval does have, you know, a certain degree of uncertainty. And you know, those that have worked with animal models and, you know, how they're developed -- and they're sort of developed to actually show an affect. I mean, that's

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sort of why you, you know, develop the animal model in the way that you do. So getting that sort of second component of predicting human efficacy, I mean, there is a degree of uncertainty.
So the animal rule does have with it, you know, restrictions to ensure safe use. And it would seem that, you know, some of the conditions that are described might be very reasonable to consider in a circumstance like this because the drug would be -- you know, patients are out there. They're having infections, you know, from day to day. And you know, the appropriate therapeutic role for such a product, you know, this may be an appropriate area to think about some of those restrictions and how the product would be used appropriately in order to balance, you know, what's the uncertainty the -- you know, so that the product is used safely out there in the real world, so.
DR. REX: Any other questions for clarification sort of on the context in the setup?
Okay. So let's move forward then.
So I've always like this quote by George

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Box, and I think it's self-explanatory for today.
If you look at your handout, what we've done here is several of us have kind of collaborated on this. We've built up a series of approaches, and we're going to talk about, first, three scenarios that are an attempt to eke out a path to a non-inferiority-based approval. Just see what -- you know, what does it take. Kind of do a little wiggling around.
And then Scenarios D and E are -- put you -- sit down into a further corner where you just conclude that either you can't do it, or it's crazy for one reason or another. And then Scenario F is going to be that I'm looking for one of you guys to have a brilliant insight in the course of the day. Audience participation. What did we overlook? What else could we have done?
In terms of timing, I'm going to use -- it's just now 11 o'clock. We're going to go till about 12:15. I think that's probably going to be enough to walk through some of the Scenario A, basically. And then we will come back and walk through the remainder -- remaining stuff and have a moment for -- and along

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the way it's very, very informal. So you can take off your tie.
That's the other thing to know, okay? Yeah, I do tie it. If you can't tie it, you shouldn't wear it. Stop there.
(Laughter)
DR. REX: But I am -- with that said, it would going to be scary to go further. All right. So --
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: Yeah. No pressure here. It's just -- all right.
So here are the constraints. So as we were developing this case and the approaches, the goal was to make this very real, okay? So you're not permitted any imaginary thing, so -- and also excluded sort of the BFMI solutions which is an acronym for me, brute force massive ignorance, okay? So enroll 10,000. No, we're not going to do that.
We don't assume any kind of a perfect diagnostic. I don't have an instant susceptibility for all the pathogens in the sputum. I don't have

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instant knowledge that only pseudomonas aeruginosa is present. I don't have that.

We also presume that superiority via study of just MDR pseudomonas is not possible, much too rare. It would require well-timed outbreak, and I don’t ever want this -- I actually don't want it to be possible. All right? That'd be bad.

Assumed at least in Scenario A that there was enough money to do about 1,000 patients and they kind of -- you know, so that sort of in the 60 to $100 million range and that you can make an argument maybe with some government support that you can sort of somehow put that much money together. There's not enough money for 3,000 patients. And also, you know, it's not just money.

If you set off to do a BFMI program and you decide I'm going to need the next 5,000 patients, what does that mean for other drugs? You know, if there's a clinical trial network, it means you've consumed it for the next 10 years. I mean, no. You can't do that.

We -- there's an implicit assumption ,just

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because it's not going to get discussed further, that is that add-on therapy is not a viable strategy. And it's hard to envision how standard of care plus X-1 would show superiority to standard of care plus placebo.

I think that the clear blue water above that when standard of care is active -- you know, when standard of care is active, it's -- you know, it's active. And as John Tomayko said, how much more cured can you be than cured.

So in short, we -- the number required miracles is kept at one -- at less than one in all the solutions. I'm not going to reject a lot (ph), but I simply will not plan on it.

So this table is in your handout. A, B and C are all scenarios in which, as you'll see in a minute, we're going to actually study -- end up studying across three diseases, but principally across nosocomial pneumonia and complicated intra-ab. They all end up enrolling a little over 900 subjects. The number with the pathogen falls as you go from B to C, in particular.

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And the difference between A and B -- A is going to end up being a situation where the two study arms end up being -- just the clinical results show pretty close to similarities. So the difference between them -- the delta between them is about zero, but the confidence intervals are quite wide.

And there will be some confounding issues to deal with. But overall, Scenario A is the easiest scenario. In Scenario B, we're going to look at a boundary case version of Scenario A. The difference -- the delta will be made as wide as possible within the constraints of already very wide margins. And we're going to talk about that.

And then Scenario C, you'll find -- Scenario C is a situation where we can't enrich and we don't have very much pseudomonas. And so Scenario C winds up with confidence intervals as bad as Scenario B. That's part of the thing to watch for there, is they sort of lock-step each other.

And then in D and E the pathogen is very rare and it might no longer be pseudomonas. You know, we quit kind of fussing so much about that at this

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point. But the end is very small, even though you enroll a lot of subjects. And even if you were to triple the size of the program, you're still barely climbing up in terms of numbers to the size for the pathogen of Scenario C. So that's sort of the logic here, is to test at each step down the way.

What does it feel like in -- one, we were joking just before it started. You know, we'd like the sun and the moon and the stars, right? But when you can't have that, how big of a flashlight would you be willing to accept, you know? So that's kind of what we're after here, is how much of a flashlight will you settle for instead of the sun, the moon and the stars.

So we're all now the sponsor. So let's just do some thinking out loud. So safety database, what do we have now? Well we've got about 40 in Phase 1 who've received the full dose over 14 days. It might be a little higher. And then the 10 in the Phase 2 non-CF-bronchiectasis study. So that's 50 at full dose and duration in theory.

What we know is the preclinical signals are

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easily monitored. So what this suggests is we need -- we need to get close to 300 for our safety database. There's not an absolute requirement for 300, but you heard yesterday the notion of the rule of three. You take your safety numbers, your end, divide it by three, and you're down to the level of which you're seeing all the -- all of the events within a 95 percent confidence interval. So basically, at 300 subjects you've seen all the -- you're likely to have seen all of the one -- the 1 percent events. And because it's pretty clean, monitor won't -- you know, provided nothing leaps out at us, it's, you know, somewhere between 250 and 300 cases on full dose and duration ought to be enough.

It's pretty clear that the culture-positive rates, if they drift much below 15 percent, we're in deep trouble. And here are some simple numbers. At 80 percent response, 85 percent power, 1-to-1 randomization, you can see that you're really even with a pretty good size margin of 20 percent, your numbers are, you know, may not be even -- may not be feasible.

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So now for Scenario A, we envision -- we -- I want -- fishing for a monoclonal. And very helpfully, if you look on page 8 -- which is page 2 of the handout afterwards, but it's page 8 as labeled -- Point number 3, you'll see a citation to a paper by a guy named Pastels (ph). And they've actually invented a monoclonal against piocyan (ph) in a rather metabolite of piocyan.

And if you know pseudomonas, this is a metabolite that this organism makes that others don't. And so if you've got a monoclonal against a metabolite, you can make one of those little immunochromatographic lateral flow things where you either get one line or two lines, depending on whether or not the metabolite of interest is present. It would be simple -- no batteries. It would be rugged, but I'm not pretending it's very good, okay?

I'm just -- it's -- so we kind of invent this, and it's going to help us get a slightly higher rate of pseudomonas aeruginosa. If I had a better time or a better test and could get up to Marco's imaginary, you know, better sensitivity, that'd be great.

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Let me emphasize that I'm not using this test as definitive. Patients, to get in the micro ITT population, which will be the population of interest, you're still going to have to have positive culture.

The whole point is that this helps me more -- the people that enroll, if they're positive on this test, they're more likely to grow the organism. But I'm still not assuming that they become tremendously likely to grow the organism. It's just a little boost because you got to get to 25 percent in order to get under 1,000. I'm just going to warn you. When I did the math, I couldn't find a better way.

Concomitant antibiotics are a problem. And that's an understatement. It is important to study nosocomial pneumonia. The guidelines often lead you to using two drugs. And Sumathi pointed at this, but let me show you the wording. This is the most recently published set of guidelines from IDSA. And I've clipped out three pieces of text.

There's a place where they talk about what do you do for empiric therapy. "We suggest

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prescribing one antibiotic in patients without risk factors for antimicrobial resistance who are being treated at ICUs where less than 10 percent of gram-negative isolates are resistant to the agent being considered for monotherapy." I want to work there, okay? Where is this place? Okay.

And then they say if -- now that you know it's pseudomonas, if you've got HAP/VAP and you're not in septic shock and you're not at high risk for death -- we'll come back to that in a second -- and for whom the subject test results are known, we say monotherapy is okay with one drug. And then they say however, if you're in septic shock or you're at high risk for death, then we suggest a combination.

So let's see. Which patients aren't at high risk for death given that the mortality of this disease in untreated subjects is 60 or 70 percent and even with good therapy, it's 10 to 20 percent? So which one of you wants to say I'm not at high risk for death? I -- you know, again, I want to practice there.

So what I conclude from this is that in a

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study that I run as the sponsor where I have to get people to sign up -- and I understand that's a little different than what you might be able to do in an academic investigation, but when -- but what I'm going to do a study worldwide and convince a lot of different sponsors to work on things, a lot of different sites to work on stuff. I've got to come up with something that meets, I'm not going to call it, the lowest common denominator, but it meets a common denominator.

And so the assumption here is that, inherently, the guidelines are really going to basically say that most of the time for nosocomial pneumonia in most patients, you got to give two drugs at least empirically. Just take that as given. If for some reason, you could get 10 or 20 percent where you didn't have to give combination therapy, that's upside. But for today's problem, I'm just sort of assuming that the world says, really, you ought to do this.

You know, in two years from now, people might really be saying it even more often. Other

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information may've come out. You know, Paul Ambrose is saying -- you know, talked about the fact that variability in exposure suggests that it's favorable for everybody to get two drugs just because, you know, variability's there. But it's also important to get some data using X-1 as monotherapy. So we got to do both of these things in this program somehow.

Helen has pointed out that it's valuable to see data in more than one setting, and that seemed to me to make a lot of sense. And so the sponsor said, all right, I'm going to do two trials, but I'm going to cover three indications in my two trials.

The first trial will be a prospective, blinded, as you'll see in a moment, randomized controlled trial with separate sub-arms for nosocomial pneumonia and complication intra-ab. And it's just barely possible to kind of sort of eke out a non-inferiority sign. And then there will be a study called the Open Label LTO Study, open label and limited treatment option patients. These are for everybody else where you know it's pseudomonas and you'd like to take a shot at it with X-1. That's sort

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of the concept here of these two trials.

So just a little sidebar on entrapenem, which is going to become very important. It's a carbapenem that is stable to the ESPLs. It is inactive for all intents and purposes versus pseudomonas aeruginosa. It is indicated in complicated intra-ab, skin, CAP and UTI, and I have had a consultation with my PK-ologist. We've reviewed the literature.

There actually are ELF penetration data in VABP patients with entrapenem that are published data. It's in your -- it's cited in there somewhere that -- and including free drug measurements in the ELF and in the plasma simultaneously. And you look at that, and that's the paper by -- on Page 9 by Boselli (ph). And actually, you're hitting the -- well above the time above requirements for entrapenem in the ELF.

And then Artero (ph) and Bassetti (ph) just before that, basically give you a little dab of clinical data. So I'm not going to say this is great. There are probably some more modeling that could be done to get comfortable with it, you know, and also

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discovered along the way that entrapenem's actually been studied at two grams a day as opposed to one, so there's safety data from that. So you might even say that we come back and look at 1 gram to (ph) 12, or something with entrapenem. You know, it's sort of more work for the site.

But as it stands right now, it looks to me like entrapenem for non-pseudomonas, gram-negative nosocomial pneumonia, including VABP, is as well validated as many other things. So I'm going to sort of take that as an acceptable tool. So this is, you know, number of miracles remains less than one.

So here's the design for the randomized control trial, separate sub-arms, but it's a common protocol just for ease of implementation. And the two arms are X-1 plus erta versus meropenem. In the complicated intra-ab arm, you may add Amikacin. And when you do so, it's blinded. So you've -– you write an order for Amikacin, and it only gets given to the meropenem arm. It does not given -– get given to the X-1 arm. So it's Amikacin versus placebo.

For nosocomial pneumonia, made the decision

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to say you must give Amikacin. Just take the issue off the table. Everybody gets active drug. And you have to stop it as soon as you know your susceptibility, all right? And if by Day 4 you can't stop it or if it's -– or if the isolate is meropenem-resistant, you're out. You maybe go to the OL LTO study or something else, but no more on this, okay? Because otherwise, I can't keep you on a blinded therapy, all right?

We'll discuss in a bit the notion of a different kind of a comparator. You know, I went -– I sort of went towards the bias of let's have a –- let's at least standardize the comparator to the extent we can because maybe we can.

You can blind this. X-1 and meropenem are both Q8. Meropenem is supposed to be given over 30 minutes. All you do is make its PK/PD better if you give it over an hour, so there's no reason not to give it, you know. So meropenem and X-1 can both be a Q8 drug given over one hour.

And then the ertapenem or placebo -- everybody gets one dose of that a day because

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ertapenem is a Q24 drug, so you know, really easy to set this up. And I didn't work out the dose adjustments for renal dysfunction. But, you know, we've invented X-1 as renally cleared, and I bet it would just sort of flow down with probably similar dose adjustments to the meropenem arm and come up with something.

For both arms, if you want something for gram pauses, feel free. Put in some 1As. Look -- put in some vancomycin. It probably would specify something, but, you know, pick one.

The inclusion -- standard rules for complicated intra-abdominal nosocomial pneumonia -- I've already said that the other thing is we'd have this little lateral flow kit, and you need to -- or if you've recently grew pseudomonas, you can come in. You know, if you've got a belief that -- the baseline culture is going to have to be positive. You've got to have a reason to enroll them -- and no more than 24 hours of prior effective therapy.

So the stats will be -- the primary analysis will be in the microITT population. That is the

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subset that is positive for a baseline culture for pseudomonas. Being polymicrobial is not an exclusion. You can have pseudomonas and E. coli and Klebsiella. You've just got to have pseudomonas in there. The endpoint for clinical lab and for nosocomial are the ones that are the standard FDA-recommended ones.

So it's clinical response for intra-ab and nosocomial pneumonia. It's 28-day all-cause mortality. And of course, you'd also put clinical response and nosocomial pneumonia, so you've got data for the EMA and the FDA. It's easily done. It's -- you know -- we've recently done this, and there's just not a problem at all to collect both kinds of data.

Now we come to an interesting one. What margin am I going to argue for? If you look in your handout, you'll see that the FDA-proposed M-2 for nosocomial pneumonia is 10 percent, and the -- for intra-ab, I think it is -- I know I wrote it down. Where is it? It's 10 percent. Right? Yes, it's 10 percent. But if I look at those numbers a little more -- and the FDA said the M-1 for nosocomial pneumonia is 20 percent, and the M-1 for intra-ab is 14 percent.

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In theory, M-1 is the largest possible margin you could ever use. So if the nomenclature is not familiar to you, M-1 is the largest reliable treatment effect than anyone has agreed on.

But if you look under the hood a little bit, the FDA's M-1 is actually calculated by doing some rounding down. So if you go into the actual data used to compute it and you use -- you apply and you look -- they have two point estimates, treated and untreated -- and you look at the 95 percent confidence balance around those point estimates, the so-called 95-95 rule, and you take the difference between those, you get 29 percent. So there's been a little rounding down that's been done to get to the FDA's M-1.

I'm going to argue that, look, you know, unmet need, plausible agent, the Phase 2 data we're going -- that we've -- think -- talked about or will talk about again in a second -- 29 percent, round it to 30 percent, okay? I'm going to argue for 30 percent. And maybe I'll go find some more data and I'll maybe -- and maybe I'll do with nosocomial pneumonia what I do with intra-ab, which is -- intra-

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ab, the M-1 is incredibly conservative. I'm not going to go through how it's calculated. It's written down in the document. But it's very, very, very conservative because it actually involved preventing infection rather than treating infection as its basis.

So here I played Go Fish for some data in the modern era where someone had suffered from an outbreak of KPCs and documented the lack of response. And I find a paper by Di Carlo, which there's the -- I don't have the graph on the slide. I don't think I do. No, I don't. But it's in your handouts on Page 4. And Di Carlo found 30 patients who developed infections after open-abdominal surgery. They were in Italy, and they had this outbreak of KPC-producing Klebsiella.

And so they had 30 people who didn't get effective therapy, basically. And -- or, rather, not quite. So they started off and they were using tigecycline and colistin at sort of what they called ordinary doses, and they were doing terribly with it. And so then they bumped the dose of both of them up, and it -- and they do a whole lot better with it. And

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if you look in your handout -- should've put that on the slide -- it's this little figure that's on the lower right-hand corner of Page 4.

And so this is a Kaplan-Meier. This isn't a clinical response. It's a KM of survival, okay? And the upper line is the higher dose of tigecycline and colistin, and the lower line is the lower dose. And it's about 15 subjects in each arm.

And so I'm going to say, look, you know, intra-ab is a real disease, and maybe I'll find some other data. And I think your margin is too small, and so I'm going to somehow come up with a 25 percent. And if I can't get to 25 percent, we'll talk about the consequences of that a little bit later on.

But you know, it's that kind of data because you've actually -- can go look for some modern data to tell you whether or not you've got a problem. That's as close as I get to using a miracle.

So success would be defined as the 95 percent confidence interval of the differences within margin in both sub-arms. And the logic for approval now becomes the following pieces of data all together

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-- very strong pre-clinical dose rationale. The target exposure has been proven in the clinic -- and by the way, we're going to do population PK in the Phase 3 program, and I'm going to presume that it comes out, more or less, in the zone.

We've got a Phase 1 study that shows that it gets into the ELF. We've got a Phase 2 study in people who are -- with non-CF-bronchiectasis chronically colonized with pseudomonas.

By the way, there's literature on this. I didn't invent that. I actually looked at some cases, some little stories. And the idea of reducing most of the group by about one log and about half of them by two logs, that's entirely in the zone for an active drug in the lung. So, you know, I found a series of little papers like that.

It wasn't that it cured any of those folks. You know, it didn't make them sterile. But the point was that this study shows the drug gets into the lung, and if pseudomonas is there, the drug can act on the pseudomonas in the lung. So that was the whole reason for that.

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And then this RCT has two disease where we show an effect. And each one of them is flawed, right? Nosocomial pneumonia is going to be confounded by concomitant Amikacin. Complicated intra-ab is partially confounded by surgery, but at least we get some monotherapy data, right? So it's -- so the point is not that any one of these pieces of data is the answer, but each one of them kind of bangs around at a different edge of the problem.

And then you assume that the unmet need label will be in there, and it will only cover patients with limited treatment options. I've not talked about the open label companion study, but it would give you some data in other settings. And I've assumed that it is just an open-label study that you get some data in. You could choose to randomize. And I don't think I have that on the slide, but my sense was there were not that many cases to begin with. And so I'd rather have more exposure on X-1.

I'm trying to do it -- yeah, don't do that, right.

So here's the actual study that, of course,

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is imaginary that we invented. We powered 85 percent and assume an 80 percent response rate in both arms, and that's a simplification just -- you know, we've got a pick a number. We're going to randomize it two-to-one in both sub-arms. And I sat and played with the math a little bit, and I came up with this balance of cases. Assuming the margins of 30 percent for nosocomial pneumonia and 25 percent for intra-ab, I wanted to have something that -- where there was a little bit of tolerance for heterogeneity, though, as you'll see in a second, not a lot.

So I put about one-third on nosocomial pneumonia and two-thirds on intra-ab. And you can see what that turns into for the X-1 cases and the control arm cases. And from there, you see the math as to how many you're going to get. And in the hand into the setup, as I've talked about this hypothetical device, I'm assuming about -- I'm getting a 25 percent recovery rate for -- in nosocomial pneumonia, and 16 and a half percent for complicated intra-ab, which is two-thirds better than you get by chance, okay? So it's just arbitrary.

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In Scenario C, the device is going to fail and we're going to fall down to what happens only by chance.

So the actual study in Scenario A hits these parameters. And how long did it take me to run this study? Well, I did a little math here, and this is what I came up with was that this might do it -- 36 months, 250 sites, screening nearly 2,000 subjects.

Okay. Yes, Kenneth Hillin (ph), I'm having to pick him up off the floor.

So how did I get to this? Well, 36 times 250 is about 9,000 screening months' worth of work. I looked at some comparables, like one that's -- I've got some data from programs that we've run, and I took a haircut on the enrollment rates that I was seeing in recent studies. I'm sorted down two-thirds from that. And I said what do I need. Okay?

So I've not done super detailed feasibility work. And those of you who have done feasibility work know that it's, you know -- it's like George Box's comments. All numbers are wrong. These are really wrong. You know, the accrual rates -- predicted

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accrual rates drive you crazy.

I'll -- you know, anyway, big study, I think. And I think this is a minimum. And something that's going to come out in a second is that I think that the numbers I predicted to enroll have to be inflated up some or for some other issues that are going to come up along in a minute. But let's pretend that we do the study and our PK-ologist consultant did a great job with selecting our dose and our pop-PK (ph) is bang, on target.

And in the nosocomial pneumonia arm, the people follow the directions, and pretty much everybody gets a dose on Day 1. And -- but if falls off pretty steadily. So they're -- you know, about half the subjects only got two days. You know, it's, you know, better than a sharp stick in the eye, as my mother would say. And in the complicated intra-ab study -- I didn't put it on the slide -- you know, 10 percent get Amikacin for a couple of days. Pick a number. But it's not -- it's -- the majority don't get it on intra-ab because you don't need it. And with nosocomial pneumonia, the majority do get it, but

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I think it's not unreasonable to say that you'd know within a day or two whether you could drop it down. And so I'm just saying that by the end of day -- you know, two days, most people get two days' worth. After that, it tapers off pretty rapidly.

So here are some numbers for a made-up program. By the way, any questions about this so far? Anybody want to ponder anything before I go forward?

Yes, question.

UNIDENTIFIED MALE SPEAKER: John, can you run that by me again? You said you got 16 percent (inaudible - off mic) study?

DR. REX: Right, but we're using my device.

UNIDENTIFIED MALE SPEAKER: Using the device.

DR. REX: Right. So the raw rate is 10 -- the by-chance rate is 10 percent. And so this device -- I'm saying it boosts you up two-thirds. It gets you up to 16 and a half percent. So for intra-ab, it takes you from 10 to 16 and a half. For nosocomial pneumonia, it takes you from 15 to 25.

UNIDENTIFIED MALE SPEAKER: But I'm

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confused. How does the device increase the incidence?
DR. REX: It doesn't. It just means I only enroll the ones who have pseudomonas -- of the people I enroll, they're more likely to have pseudomonas. Right. And you can argue about where is the cost. Actually, the cost isn't just in the enrolled patients. It's in the maintenance. You know, 250 sites means I've got to visit 250 sites once or twice a year and replenish their IDP, and, oh my gosh, okay? It gets really expensive just to have 250 sites open for three years.
That might -- I don't have a good -- if anybody has a good feel for the ratio of true per-patient to site running costs underneath -- you know, I've got a whole range of estimates from my group. I'm happy to have any ratios there you come up with, but that's the notion, okay? And, once again, why those particular numbers? Because it fits inside 1,000 patients.
You know, I have played exhaustively with this, and you can come up with other variations. I didn't go to one-to-one because I needed the safety

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database on X-1, so I wanted more cases there. Didn't, you know -- one-to-one increases the -- it's -- your best statistical power is always at one-to-one. Any deviation from one-to-one costs you. But here I chose to accept that cost because I wanted the safety database, okay?
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: No, but they don't all get it for full dose and duration. So only the 48 and only the 69 are going to stay on X-1 -- are -- because if you don't have pseudomonas, you come off the study. You know what? I didn't say that. That's a good point. You could leave them on the study if you wanted to and you learn about ertapenem. That's a good point.
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: Why not? Well, it's a good point.
You could -- I'd implicitly assumed that, you know, if you didn't -- in terms of safety, you actually could have way more than enough safety here. It's a good point. Thank you. Thank you for the clarification.
This case was busily invented over the last

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four weeks, so there are holes in it.
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: Sorry, say it one more time please.
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: No, because empirically, you don't know at moment zero on Day 0. So at Moment 0, Day 0, you randomize and you start Amikacin on everybody, so everybody is going to have had that in this design.
Other questions? Question?
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: It's based on the cultures coming back. You know, by the end of the second day, you often have -- because what you all -- what you care about is the susceptibility of the pseudomonas.
So if it grows on Day 1, then you'll have susceptibility by Day 2, and that happens with Pseudomonas, but it might also take to Day 2 and then Day 3 to get it. Pseudomonas is not a particularly slow-growing organism. It's not, you know -- it doesn't hide. And anything better than this or worse than, you know -- okay, so it's three days on average,

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you know.
I -- but I sort of was thinking about what does it often feel like to me, and I often have some hint of it by the end of the second day. The morning of the third day, I can get rid of the Amikacin. You know, and maybe that's two and a half days, you know, that sort of thing. Good question.
Yes, sir?
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: Sorry, say that one more time. I'm trying to repeat the questions, but it's tricky.
UNIDENTIFIED MALE SPEAKER: All right. So the drop-off rate applies for the total MP population and not necessarily to the one who have pseudomonas, right, and get the test drug. So for those, let us say, to assess what the confounding effect of Amikacin on test track would be, those rates would be higher because those who have pseudomonas let's say probably 4 or 5 days -- 80 percent right?
DR. REX: What we're -- what I have assumed is that you're willing to drop down to monotherapy, so it goes a little bit against the IDSA guidelines.

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You're willing to go down to monotherapy once you know that the pseudomonas is susceptible to the test agents. So that's an implicit assumption here, is that by Day 2 or 3, you've got your culture, you've got your susceptibility results. And you can say, okay, it's meropenem susceptible. And for X-1, it's -- you know, they're almost always susceptible, so that says -- you know I'm going to take that as -- but you may also be able to do the local test. And so you can drop down to monotherapy.

The idea here is you're dropping down to monotherapy for the pseudomonas part. You may still be continuing the ertapenem; you may still be continuing the linezolid. You know, you can do other stuff. Does that make sense?

You know, I'm trying to say the Amikacin doesn't -- if it goes on for a week in a quarter of the patients, okay, it does. But everybody is going to have had at least a couple of days.

Yes, ma'am?

UNIDENTIFIED FEMALE SPEAKER: How do you account for the risk for CRE in the comparator arm?

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DR. REX: You -- if we believed you had CRE, you shouldn't come into this study, right? That would be one part of it. And the -- if you identify it, that's what I meant about meropenem resistance, you know, if we spot it. You need to be in a center where you would be comfortable using meropenem plus or minus Amikacin as your empiric therapy about nosocomial pneumonia. And so if you're at a center where that's not true, then I can't put this study here.

AUDIENCE MEMBER: (inaudible - off mic).

DR. REX: Yeah, I'm with you. I want to work there, too.

But so -- but you know, we've recently done a study like this where we did ceftazidime/avibactam versus meropenem. And we were able to -- we actually -- it was kind of hard. We didn't find CRE. You know, even -- we were actively excluding it, but we actually -- and we had another study where were actively looking for it, and it was kind of harder to get than you might imagine in prospective randomized trials.

Remember, the ICUs are trying very hard to

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control their outbreaks of CRE, so I think you can do this and you can avoid the problem of CRE coming in and being a big issue. So I think you can do that where the pseudomonas is often -- well, that's not the same as here. But the -- you -- so I think you could probably have the meropenem be active against the pseudomonas at least 80, 85 percent of the time.

Other questions? Okay.

So these are the data that were invented, okay? And it's important to pay attention to both the percent ratios and the absolute magnitude of things like the denominator here. So the nosocomial pneumonia arm, they're 48 and 24 in our microITT analysis. And if you want to pitch them both at about 80 percent response -- in fact, 38 out of 48 would be a little closer. I deliberately jittered that away a tiny bit to get the -- to make the delta not so boring. But you know, there's a result that, you know -- it's 20 percent up and down around a delta of zero, more or less.

And there you have an intra-ab dataset. And I left those numbers a little closer. You know, 80

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versus 80, for all intents and purposes. And then there's an open label LTO study, and this is -- I pitch this one to be -- to reflect our experience, as well, with having done a study like this as part of the CAZ-AVI program.

You get a lot of UTI. And, you know, people can find those. There's lots of urine to culture, you know. They are identifiable. And it's harder to get intra-abs and nosocomial pneumonias with highly resistant pathogens. It's just harder to pick them up in a way that makes sense.

And so just completely fictitious numbers here, just made up that this is what you managed to accrue. And I want to emphasize that these patients are going to be different qualitative than those in -- qualitatively from those in the RCT. They're going to have more comorbidities. You won't be really happy with banging them together. In your handout, I add them up if you happen to want to see an integrated summary of efficacy, but I don't really recommend doing that.

And I'm guessing that here's a place where

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you'll actually get some difficult pseudomonas because that -- why would you be in this? Because you've got a bad one, and so assuming that, you know, about 80 percent -- it won't always be the reason, but let's just assume that we get a fair -- so this is a nice feature of this open label. You can say, well, it's an open-label study, how -- lots of complaints. But on the other hand, you know, here's at least, you know, 50 or 60 cases that you can look at and see what do you think happened.

Safety. The N on full dose of duration, barring the comment from a moment ago where we could actually get a bigger N, if you just kept it down to those who grew pseudomonas, is about 240 -- 230, 240. You know, you get between 200 and 300 and you're getting really close to having enough for a reasonable safety database at this level of resolution. And unless a major new signal emerges, it's not bad. You know, you can come back to this question. How big of a flashlight do you want? So it's not bad.

MR. DANE: John --

DR. REX: Yes?

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MR. DANE: Just --

DR. REX: So now we're going to do questions.

MR. DANE: So -- and on the open label extension data -- I mean, in this example, that looks fairly supportive. The response rates are pretty high. Given the population we're dealing with, it's non-comparative small numbers. It might be worth discussing what would we do if those response rates were 30 percent or 40 percent, which may not be that outlandish. It's a small number, and it's a more severe patient population. So that might be, you know, another test case of -- well, how would we use that type of information then?

DR. REX: I have no good answer to that. I deliberately pitched those response rates to be lower than in the RCT, just saying that I thought they were going to be more difficult cases. And you know, that's -- so let's open this up. And that's a good question. So open up for questions, comments, and critiques.

So, Helen?

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MS. BOUCHER: So Aaron, I agree. I think that's a great point, and I think many of us would expect perhaps lower successes in especially the HABP/VABP group and that open label extension. And so that comes back to that notion that we were talking about a little bit earlier, the idea that really looking at each one of those 10 individuals and seeing what was going on is going to be necessary. And we've seen similar examples in the antifungal space. And we saw it a little bit, as Ed alluded to yesterday, in the daptomycin experience of having to look in the cells of each diagnosis, each group, and try to understand what you can learn from what amounts to a collection of cases.

But there may be things you could learn. And I don't think there's any shortcuts, and so you come back to the fact that -- was a diagnosis really well-established? Was the outcome really well-established? Do we have drug levels in any of those patients? You know, do we have any other data that might help us feel better or less okay with that message? But in many cases, you might end up with

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almost 50-50, or even a little less, in these really sick people.

The other point I think here is that in the HABP/VABP population, or if you were lucky enough to have a group of people with bloodstream infection, that's a group where their outcome with pseudomonas infection is pretty clearly very bad in terms of mortality, and you could look at that data. Again, with all the caveats about the fact that these people die from other reasons, you know, all those things -- and perhaps become either more comfortable or less comfortable with those data.

DR. TOMAYKO: John, could I build on what Helen said? In HABP/VABP, I actually think that in this situation it could really illustrate one of the controversies or problems that people see with an all-cause mortality endpoint. And what I mean by that is there's two ways to fail in a -- in that analysis of -- like when you're comparing a non-inferiority type analysis with an all-cause mortality endpoint. You have to realize that untreated pseudomonas pneumonia has a pretty high morality, probably higher than maybe

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some other pathogens. And that's crude mortality.

And the reason we like the endpoint is because there's a lot of improvement you could demonstrate with a good antibiotic. And if you don't demonstrate enough, then you could look inferior, so there are potential to detect an inferior therapy, if you don't work as well as your comparator. But let's say you work as well. What are you left with? You're left with some of that crude mortality that you started with but you couldn't see because so much of it was buried in the pneumonia.

So you've got this crude mortality and you have 24 patients on marrow and 48 on ertapenem, and you have to assume that you randomized that and that what's left over you're going to be able to really say that -- you know, this is a problem that I think people have with all-cause mortality because, at the end of the day, you have other things that are also responsible for those remaining deaths. And that might not be handled well here. I don't know if I said that clearly, if anybody has a better way of articulating it, but --

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DR. REX: Will the left-handed poodle owners be randomized? Right. Will the smokers be equally randomized? Will poodle ownership be equally randomized? You just have no clue.

So Helen again.

And there's somebody with a question on the mic. Yes?

MR. LOUDIT: Yes, so this is Jeff Loudit (ph). So Helen and John are much smarter than I, so I was going to make the same comments. But so quick question, John. That is all-cause mortality that you're showing there with HABP/VABP or is that --

DR. REX: Yes, the endpoint for HABP/VABP is all-cause mortality.

MR. LOUDIT: That's survival that you're showing there.

DR. REX: Excuse me, it's -- it is all-cause survival.

MR. LOUDIT: Okay. So all-cause survival that we're showing there. All right. So I would agree, though, with John and Helen's comment that I think certainly in the open label trial, your numbers

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are going to be significantly lower than that. And --

DR. REX: So feel free to knock them down.

MR. LOUDIT: -- the point is how do you deal with that and put it into perspective? And I think Helen's points are exactly right.

DR. REX: Yeah. And so, you know, keep in mind -- you know, if -- cut them in half if you'd like. They're deliberately pitched to be different and not as good. And that's sort of the concept here.

DR. CAVALERI: I'm going to just come back before we go.

So to John Tomayko's comment, I mean, it sounds like, too, I mean, you know, you're arguing that in a small group of patient you might not have really balanced things out with randomization and the impact that that might have on all-cause mortality. It could affect other endpoints too, yeah. So I just don't -- I mean, I don't know that that's exclusively a problem of all-cause mortality.

And these are -- this is a patient population where there's a lot of other things going on, and, you know, some patients will succumb to other

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conditions that they have. We just can't tell who's who and what the cause is for each of those two things.

So, yeah, I just didn't want to -- I mean, so it's not exclusively mortality, but this is a problem that we run into with smaller numbers -- and, yeah, okay.

DR. REX: David?

DAVID: Yeah, so the issue that I'm struggling with is that we spend an awful lot of money studying an awful lot of patients for an extremely fragile result.

DR. REX: I -- And that point is extremely well -- and we actually put up a slide that'll let you talk about this because if you look at -- there's a section, A45, that lists really big risks. And what you're pointing out is number 2 -- that N is tiny and there -- the risk of bouncing off that a little bit is notable.

DAVID: Yeah, so I just don't think anybody is going to do this. I think bravo for going through this. I think that this was a really rigorous look at

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the realities in a way of trying to design a trial like this, but nobody is going to do this.

DR. REX: Well, so save that comment when we get to Scenario B because I think you'll maybe want to repeat the comment.

MR. HOOFTMAN: Thank you.

My name is Leon Hooftman (ph). I'm the chief medical officer, sometimes chief medical scapegoat, of a company that has something like this.

So first of all, I would like to commend the panel and FDA and yourself, John, for doing all this work.

You know, when you're in clinical trials, as you know, sometimes you're planning for success and always optimistic. Our -- we have done surveys in the Mediterranean area regarding incidence of pseudomonas positivity, and figures are a little bit more optimistic than the sobering statistic that you have presented us with this morning, which is good because often enough you -- you know, you've got the answer because of the hope not because of the fact that somebody says, no, this is not possible.

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And sorry to come back to the issue of feasibility, but that is the word, you know, with a capital that is high on this agenda. And I agree with the previous person who said this is still probably not feasible. If we would use our positivity data -- and it's a survey, and I know you're going to shoot holes through it and it's mainly Mediterranean, you know, our hope would be to enrich the population in countries where this is more prevalent. But we shouldn't fool ourselves because, as you would say yourself, you know, the moment that you start the study, the incidence rates go down.

DR. REX: I didn't say that. Louis Lasagna said that. It's a wonderful quote -- Lasagna's Law.

So let me just point out these noteworthy risks and then we'll go to the next question -- or just so I've read through the slide. Erta at one gram -- I think I've talked about what I know about that. You know, it doesn't look dumb, but it needs some work. We've just now been talking about the small N. Those margins -- and I would like to have a reflection from our colleagues -- the statistical and regulatory

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on that.

I want to observe that the enrolled N probably needs to be 30 percent bigger, I think, and that there's going to be some unavailable. There's going to be some lost due to meropenem resistance. So if you want to maintain this blinded design, you know -- there are many sins in clinical trials. You could live without the blinded if you wanted to. That would be a best available therapy. But here, if you wanted to do it blinded, which I always like, then you've got to deal with that -- again, the small N with the pseudomonas. And we've not discussed pediatrics at all, so I'm just going to assume that you do something about generating PK data.

I want to show this just because it's in the handout. Sometimes it is suggested that we use a larger alpha. Instead of an alpha of 0.05, we use an alpha of 0.1. It's a way of, you know, describing the idea of less certainty. So the mathematical equivalent of that is to use a 90 percent confidence interval. And so here I've recomputed it with 90 percent confidence intervals.

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And so the nice thing about it -- and the numbers were, of course, chosen to do this, right? I -- this -- everything about this is set up to give you the chance to meditate on this.

So now the lower bound of the 95 -- 90 percent confidence interval is minus 19, so it's inside of FDA's actual M-1 by 1 percent, okay? And ditto the negative 13.6. Okay. So it's inside negative 14 by 0.4 percent. Do you feel any better?

MR. DANE: So, John, the other thing --

DR. REX: These are the questions I want to be sure we cover, so.

MR. DANE: Yeah, the other thing I would add on that last point, though, is that, although for a specific case when you observe the data, the confidence intervals shift by a few percent, and you could argue about whether that's important or not. Where it can be important is where you're designing the trial and having to figure out how big it's going to be and the feasibility. It can have an impact there as well. So that's where it can help as much as what the result looks like when you get to the end of

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the study.
DR. REX: Right --
MR. HOOFTMAN: So it makes it --
DR. REX: You're right. So this is powering versus actual data. So here a lot of the power questions are now gone at this point. We've invented some data. You know, we have what we have.
MR. DANE: Yeah.
DR. REX: Right. So I want to be sure we cover these questions, pros and cons from all perspectives. So we've got to talk about how to deal with two body sites. You know, what do you do there? Come back to concomitant therapy. Is there anything other than erta we could use? There's implicit approach to polymicrobial versus monomicrobial, just to double check. Any other thoughts on MDR pseudomonas and best available therapies? So we've kind of covered some of these, but if you're looking for a question to poke on, be sure we poke on one of these.
So there was somebody holding their hand up a minute ago. Yeah, Tom?

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DR. LOUIS: Tom Louis. Just to comment on the previous discussion on the 95 interval, the 90 interval, it becomes endless. And here's a perfect case where, let's say, with uninformative priors on the underlying parameters -- or if you have some knowledge on baseline, just put it in. Compute the posterior probability that the difference in -- the true difference in the parameters is in the range that it needs to be in. I don't know what that number will be in this case, but it's far better than, oh, what about the 90, what about the 95. Just have a direct answer to that underlying question and --
DR. REX: So you're getting at the -- a true posterior probability, or in terms that I understand, the likelihood?
DR. LOUIS: Well, it would be based -- is if it were uninformative and being, if you like, frequentist, it would be based on the likelihood and would ask the question directly. It would say we don't see the parameters, but we -- there is a true difference. Let's build a model that computes the posterior probability, given the data, that the truth

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is in whatever range is required, if you like. And on the design side, you can then ask what kind of a sample size would be needed if the true differences in a certain situation so that there's a high likelihood that that posterior probability will be sufficiently large. In other words, you can do -- you can reverse-engineer to do the design question, too.
MR. DANE: Yeah, I mean, I would say on that, that's true. You still need -- a company going into a study and investing still needs to have an idea of what's going to be sufficient for approval, though. So, yeah, I agree with everything you say, but in some ways, whether it's an alpha level, whether it's a likelihood, that question still remains, is what's the acceptable regulatory risk in doing some of this in terms of incorrectly approving something.
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: Yeah. Well, and I think what you're saying is that we might need to spend some time as a community getting to where we understand -- what you're talking about, I can get a feel for it from a distance, but we'd actually have to be able to

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understand it broadly enough that even if a pair who is being shown the data is -- you're able to say in a way that actually sort of conveys the feel for the strength of the information. And so that's something to work on. It's a new form of -- you know, because we haven't often -- we have never actually publicly in these conversations done anything other than standard frequentist statistics that we all learned in -- as freshmen in college, you know, that sort of thing. So it's a well-said point.
MR. DANE: John, my other point on -- just related to that was that, you know, whether we talk about alpha levels or likelihoods, that the other point is that sometimes they can be useful rather than going to bigger and bigger non-inferiority margins that people become uncomfortable with because we say, well, we can have a margin of 40 percent, for example, because it's feasible. But who's going to be happy saying, well, we could be 40 percent worse, whereas something with a tighter margin -- but you're just saying, well, we've got a big more risk of what we're doing here might be a good balance and a better

balance than going that way.

DR. REX: And so to say it back to you, in effect, that's what I did here. I made the confidence bound fit inside the margin by picking a different alpha. Actually, I did -- I set this up so that this would be true. But the point is that it's mathematically -- it's -- the underlying data are the same. It's the question of how do you talk about them and whether -- do you want to construe it as margin risk, or is it likelihood of making a certain kind of mistake risk. And -- but mathematically, it's the same. Am I saying it correctly? I mean you -- yeah, okay.

AUDIENCE MEMBER: (inaudible - off mic).

DR. REX: Well, see, I wanted this case to try to get at these debates. You're right.

Okay, so Kenneth?

MR. HILLIN: John, thanks.

It's an extremely thoughtful and thought-provoking illustration, I think, that you're given here. And I guess there's lots that we could discuss and I'm sure that we will discuss. But as you take a

step back and you look at this, I wonder if at some point during today's discussion we might take a vote in the room and ask people to put up their hands if they would be willing to run such a trial because I suspect, although I could be wrong, that they'll be very hands in the room that will go up. And so I just wanted to commend you for sharing this.

DR. REX: Okay, well, thank you. We've had a good time putting it together. Lynn?

DR. MARKS: Quick question. If you have a big issue (ph) non-inferiority margin and at the bottom of the inverted pyramid you have 20 MDRs in one arm and, I'll say, 25 and 17 and a half in the other arm and there's a descriptive but what some people would call medically interesting difference, would that be able to provide --

DR. REX: I think that's upside, you know. I think, you know, that's helpful.

DR. COX: And John, you were asking about this a little bit ago, and Sumathi and I talked some about this. And that is, you know, the margins and sort of setting them, the ones that are in the

guidance document. And I think, you know, you're asking a question of how far can you stress M-1. I mean, if you really, you know, look at this very carefully and, you know, the 29 percent, versus the 20 percent, versus the, you know, 10 or 12, 5, whatever it is --

DR. REX: Use the microphone.

DR. COX: Yeah, whatever it is in the situation that you're using it, you move from M-1 to M-2. I mean, it is a good question, and it's probably worth looking back at those numbers a little bit more and seeing, you know, how big things are. And then, you know, just to see, you know, where it is. Those numbers are pretty messy, though, from what I understand. And if I remember correctly, for complicated intra-abdominal, that was like -- I mean, it was not only sort of looking at the numbers, but there was also gymnastics involved in trying to work through that one because we didn't quite have the data that we needed. But we were able to get to something that told us about treatment effect, so --

DR. REX: Well, I want to say the approach

that was -- so that you've heard it, the approach taken for intra-ab went as follows. There are no data on placebo therapy of complicated intra-abdominal infection. No one could find any. So something was found that's kind of like that, which is in the '60s and '70s there was a serious question about whether or not you needed antibiotic prophylaxis if you were about to have bowel surgery, so what we would call a clean contaminated procedure.

I'm going to open you up. I'm going to transect your gut. So I'm going to spill bacteria. I'm going to sew you back up. Do you need prophylaxis to prevent -- so you didn't have an infection before. Do you develop one post-op?

And so there were placebo-controlled studies of that done. What's the rate of preventing development of infections? So it didn't have an infection, didn't develop, versus didn't have and did develop with or without therapy.

And so that -- and if you flip that -- so that's the closest anybody could come. And you flip that upside down and you can construe that to be the

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rate of treating infections.

So Mike Dudley is looking at me -- what does that mean? So in -- hypothetically, I've just cut through your wall of your bowel, and I've just created an infection. Let's pretend that I create a little baby infection right at that moment.

So if I then put you on an antibiotic, I'm treating this itty bitty tiny infection. Or I don't put you on an antibiotic. I'm not treating it. And post-response will control some of them. Antibiotics will control some of the others.

So that's how it was computed. And it actually showed that there is a benefit of perioperative antibiotics if I'm going to transect your gut wall. I very clearly show that, which, you know, is something we want to do.

And you find that there is a difference between -- and you can actually -- the math -- so go read the guide. Now that you've heard the story, go read the guidance document again. You know, I thought it was a -- not a bad approach, and it, you know -- show me something better. You guys -- like, all

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models are flawed. You know, if you don't like this approach, you can't just criticize. You have to solve. So you know, my hat's off for somebody for having found a path.

Question?

UNIDENTIFIED MALE SPEAKER: Well, I think it's great work, and all the discussion focused on regulatory aspects and on statistical aspects and on evidence. I just want to shed a little bit of light on those patients who actually do not have pseudomonas infection in that study.

So first of all, in the arm -- in the experimental arm that -- actually two experimental drugs because the drugs are approved, so probably you needed the DSMB on that arm. And what happens if that ertapenem actually is inferior in the non-PS, which is 75 percent of the patients --

DR. REX: That's a risk.

UNIDENTIFIED MALE SPEAKER: What happens to the study? You're going to stop the study not because the PS isn't working, the pseudomonas. You'll probably stop the study because your adjunctive

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treatment or your ertapenem isn't working. And how you can send for that in a situation of HBAP/VBAP to a patient where alternative treatments, which actually are approved, are available. So for me, that is one issue.

The second issue is that even you have a fantastic new drug called X-1. Actually, that doesn't come for free. There will be safety issues. And some you raised and whatever they are. So you're going to treat 75 percent of the patients in that trial empirically with a useless drug. And they're exposed to safety issues.

And you know, I'm 10 years plus chief medical officer of two companies. And I -- in an internal ethical committee, we would have a huge debate whether we would expose these patients to that risk and what type of warning we would give to them and how recruitable would be the study then at the end if you display that information to the participants. And so for me, it's not only a financial feasibility or an evidence issue, it is just an ethical feasibility to get all those patients on board and

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telling them what their likelihood of benefit versus their likelihood of risk is in that arm.

DR. REX: Yeah. Good point, and it actually makes Jeff Loudit's (ph) comment that you ought to keep them on the study more pointed. So if you know it's not pseudomonas, you ought to just keep on running it because now you're at least getting data on how well erta works. And so I had not thought about that aspect of it, but it's a very well -- one of the risks here is that erta is not an approved drug as the combination. But you know, look --come up with a better solution. You know, I didn't like Tigecycline, so, you know, I came down on the side of ertapenem.

Jeff and then Ian.

MR. LOUDIT: So Dave asked -- Dave said no one would run this study, so I'm going to put my neck out here. I would run this study, Dave, with three caveats.

DR. REX: Okay.

MR. LOUDIT: One, it's somebody else's money. That would be --

(Laughter)

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MR. LOUDIT: So two -- the second caveat is that the FDA agreed to those non-inferiority modules.

The third caveat, though, is the really important one to me, which is the rapid diagnostic test. So there are actually companies that are now developing almost by-the-bedside tests which can tell you within a very short period of time whether you have pseudomonas, acinetobacter, et cetera. And that significantly cuts down your costs of screening and enrollment.

So I would be willing to do this study, and we're planning to do a similar study like this, Dave, in the near future with -- I guess it -- I don't have the second caveat agreed to yet.

DR. REX: Well -- yeah, that's good. And the thing about the diagnostic, for our purposes, was we were assuming that it wasn't something that required a lot of maintenance. It didn't require a big site -- sort of a user manual at the site. It needed to be something -- because if money is no object, then you can do lots of things. But here, it's for something that you're going to be using

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infrequently. You know, I wanted something without batteries.

So Ian? And then --

DR. FRIEDLAND: I also wanted --

DR. REX: -- Paul's wiggling his fingers, so he's next.

DR. FRIEDLAND: Thank you for going through this exercise because it is very useful to take a practical example and actually look at the numbers.

There is a potential way to think about this a bit differently that could try and counter some of the points that are being made, and the one is to consider this a regimen. The regimen you're evaluating is ertapenem plus this drug. And you're not going to try and sort out what the one drug does and what the other drug does -- what the other one does. You know, one drug for one bug gets very complicated.

We also don't know -- there could be a really positive interaction between the two drugs. It could be this could synergize with ertapenem and make ertapenem active against carbapenem-resistant strains.

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And likewise, ertapenem could make this drug more effective against pseudomonas. So I think if we think about this just as a regimen, we're evaluating the two drugs together.

And at the end of the day, what you can say -- this is the safety and efficacy of this regimen, and that's the way the drug gets approved. It's in combination with ertapenem just as if we had put the two drugs together in a vial and said this is the product we're developing.

DR. COX: Do you want me to comment on that? So, I mean, just one thing to think about, though, too, is I think, you know, this is the opportunity to test the efficacy of X-1. So you know, within that population of patients that are getting the drug, you'll want to be able to discern what was the effect of X-1. And oftentimes, I mean, one of the ways to think about this is suppose that your population of patients you enrolled, you know -- very few pseudomonas aeruginosa. You know, I think it becomes more difficult. So somewhere in there, you'll want to be able to figure out, you know, what X-1 is doing.

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DR. REX: But there is the intra-ab. You could take Ian's comment and say, well, in the intra-ab component, I get the monotherapy insight. And -- but for nosocomial pneumonia, it's labeled as if it was a thing. I mean, I --

DR. CAVALERI: Yeah.

DR. REX: And I -- part of the assumption that was in the written version of the case was that the sponsor knows that something like that could come in the label, but why would I object to that being in the label, you know?

DR. CAVALERI: Right. Yeah, and we have done that -- I mean, if -- some of the drugs that are used in combination with other drugs. But, you know, I'm just sort of saying that the test needs to be sort of a valid way to assess the effect of the drug and that the drug is used with other drugs is not necessarily a problem per se. But if it obscures the ability to assess the effect of the drug, then it gets a little more complicated, so.

DR. REX: Okay. So let's look at these questions and be sure that we've -- sorry, Paul

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Ambrose is waving his hand.
Go for it, Paul. We really have plenty of time to discuss, and I don't want any idea to lie fallow.
DR. AMBROSE: All right, I don't have an idea, I -- just a comment. Is there any concern that ertapenem is being picked here because -- well, it's being picked because we think its PK/PD will predict as active, right? It's got --
DR. REX: Talk straight into the microphone.
DR. AMBROSE: It's got no randomized clinical trial in nosocomial pneumonia. It's just being picked because the PK/PD for it -- forecasts it'll work. Is there any concern that we're comparing a new drug to something we don't really understand would work? For me, I mean, I really believe in the PK/PD as you -- I put a lot of weight in it, but it's an interesting precedent that you're setting up.
DR. REX: I think that is a concern. And you know -- make another suggestion. You know, maybe as a community, we need to do an ertapenem --
DR. FRIEDLAND: There actually is a clinical

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trial with ertapenem done in HABP and non-ventilated -- and early-onset VABP. It was just never submitted for reasons other than efficacy.
DR. REX: You're kidding.
DR. FRIEDLAND: But it actually was a trial. It was actually the very first trial I ever conducted in industry was a VABP -- a HABP/VABP trial with ertapenem. It is published. It was just never submitted for approval.
DR. REX: Yeah.
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: So I was getting comments from two directions. So you're -- actually, I think -- find those data, you know. And, sir, did you say -- how did it do? I missed that part.
DR. FRIEDLAND: It was -- you know, it was done back in 2000 --
DR. REX: Back in the year aught, all right.
DR. FRIEDLAND: So way -- non-inferiority margins were acceptable, but it was like a 350-patient study versus pip/tazo, and it fell within the non-inferiority margin of 15 percent to 20 percent of --

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DR. REX: Do you remember offhand if the mortalities were comparable in the two arms?
DR. FRIEDLAND: No, I can't remember all the data. The main reason it wasn't submitted was because maybe it did too well, and at the time commercially they wanted to distinguish it from other carbapenems. They didn't want it to look as good as meropenem and ertapenem against, like, really sick patients. So it was a very strange reason why it was never actually promoted or --
DR. REX: Well, it's -- so maybe there's a bit more data than we realize. And like I say, you know, the little bit I scrounged up, actually, it looks -- it looked as if it ought to work, you know. Sorry.
MR. ARAKOFF: Dmitri Arakoff (ph), divisional and executive (ph) products of DE (ph). Since we have time for discussion, I'd like to address this question of immunotherapy versus dual therapy. Looking at the guidance, it seems that they deem immunotherapies acceptable as long as your drug is active against isolated pathogens. And the reason --

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we give dual therapies to -- not to prevent resistance, but to make sure that at least one drug is active --
DR. REX: Is active.
MR. ARAKOFF: -- meaning that if you study a drug supposedly active against resistant pathogens, maybe this criteria not applicable to your product. And it's acceptable to use a new product, at least in this active arm.
DR. REX: Yeah, so -- and I think if you felt like you could do that, that would be great upside. I considered the possibility for nosocomial pneumonia of saying -- of doing it the same way I did in complicated intra-ab, which is to say Amikacin is given, but it is blinded versus placebo. So the X-1 arm gets a placebo Amikacin, and the meropenem arm gets real Amikacin. And you somehow blind even doing of levels and things like that. And I think you could do that. And if you could, that would certainly help clarify the dataset.
I just chose for purposes of this discussion to make us deal with the possibility that there will

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be a desire for two drugs. And the -- if you look at the IDSA guidelines, you know, what they've said is, oh, wrong way. They really are kind of wishy-washy on this, you know. They -- sometimes they still want two drugs, and so I don't assume to know where the logic is going to go in the future, but your point is really good.

MR. ARAKOFF: Because what would be the argument to the second drug? This is my point if it's -- right.

DR. REX: Yeah, well, and the argument might be -- you know, Paul Ambrose yesterday said, well, even with a single active drug, there's still a tail of exposures in some subjects. And so, you know, maybe it's nice for that reason. It's not about susceptibility. It's about exposure.

Mike?

But you're right. Part of this was about not picking -- not making everything always go our way in terms of the analysis. I really wanted stuff that -- to stretch the envelope.

DR. DUDLEY: Yeah, I'd like to go back to a

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point I think Ian was making before, though, is what you really are is testing a regimen here. So this regimen is -- of ertapenem plus X-1 is a broad-spectrum regimen. And even though we've got sort of some enrichment or you've got your device and so forth, we're still treating with a broad-spectrum regimen.

I'm curious about whether or not the labeling would be then specifying that it was -- you know, this drug is being used in combination with a carbapenem, and that what you really did test specifically was a carbapenem combination with this.

And I think about -- for the -- the example that comes to mind is that piperacillin/tazobactam failed miserably as monotherapy in pseudomonas pneumonia in the initial trials -- miserably. And then when it was -- their trials were repeated in combination with an aminoglycoside, it worked because no -- it prevented resistance from emerging during therapy. So the actual label, I believe, actually states that it's indicated for use with an aminoglycoside and the treatment of pseudomonas

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pneumonia.

So I just wanted to clarify would the labeling in this case -- would be used in combination with a carbapenem in the treatment of pneumonia or HABP/VABP. But -- he said yes.

DR. REX: Whatever it is --

DR. COX: Yeah, so, I mean, I think, you know, that we can do that. We've done that. I'm thinking of ceftolozane/tazobactam, where we added, you know, to the complicated intra-abdominal we said used in combination with metronidazole. So -- but that's, I mean -- so that's a very easily solvable issue.

And it seems like -- and I'm -- in this trial where we're enrolling patients with pseudomonas aeruginosa, we've picked ertapenem because it's whole, and coverage is that it doesn't cover pseudomonas aeruginosa. It seems that what we're really trying to do is -- you know, within this regimen is to be able to test the role of X-1 by isolating it, if you will. And you know, the -- so I think -- you know, that's really what I think we're trying to learn out of this.

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DR. REX: Right. It was all about --

DR. COX: So we could say use it in combination with ertapenem --

DR. REX: Coming at it from more than one direction.

DR. COX: -- but we're really trying to figure out --

AUDIENCE MEMBER: (inaudible - off mic).

DR. REX: Oh, no, we're --

DR. COX: Agree, yes.

DR. REX: -- fully expecting E. colis and Klebsiellas and other things. Absolutely.

DR. COX: And that's why the ertapenem is there. It's, you know -- there are other things. Either we're going to have patients that we don't culture. You know, it's going to take a while to get the culture back, just like the empiric Amikacin. But what I'm trying to get to is what the -- you know, the primary analysis, it would seem, would be on those patients that have pseudomonas aeruginosa, hopefully not too much concomitant Amikacin, not too much pre-study therapy, to try and isolate the effect of X-1

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and figure out -- you know, it's only active against pseudomonas aeruginosa to try and figure out how does it perform against pseudomonas aeruginosa because, you know, in subsequent trials in patients with pseudomonas aeruginosa this drug will be used. And this is the chance to figure out whether it works or not.

DR. REX: And just for flow of time, we're going to go until 12:15, another seven minutes. And then we're going to take a break, come back at 1:00. So just so you set expectations.

The lady right here in the yellow blouse had a question and the gentleman at the mic. So I thought -- you raised your hand. I thought I saw you raise your hand.

UNIDENTIFIED FEMALE SPEAKER: Sorry, I'm at the risk of belaboring a point that isn't necessarily shared here. But I can't see how you could ethically randomize a sick patient as was described to a regimen that only included a single possibly active agent against pseudomonas. Your test agent -- you have pre-clinical data. The only clinical data you have are in

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non-CF-bronchiectasis.

It's a very small study with limited, if any, efficacy information. And you're going to randomize a patient to ertapenem plus your investigational agent when we know that the major factor that predicts mortality, which already we know is high, is being initially on appropriate therapy. I just can't see how you could randomize patients to that arm.

DR. REX: Well, I think you're asking a very general question. How then can I develop any novel antibiotic --

UNIDENTIFIED FEMALE SPEAKER: Yep.

DR. REX: -- as monotherapy? And I think that that question -- you know, we can -- we'll come -- we can come back to that after lunch, if you'd like, because there's a lot of thoughtful commentary in the literature on that point. If you say that you can't -- yeah, we do this, and this is how drugs get advanced. And if you're not willing to do at least this much, then we're at a dead stop in more than one area. I mean, I don't know what else to tell you

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about it. I --

DR. TOMAYKO: John, just to add, this is what you're saying. You're rejecting the clinical equipoise argument that would be made, and I'd take it a step further, that that's -- would apply to a broad-spectrum agent as well. It's --

DR. REX: And so that's what I'm saying --

DR. TOMAYKO: Yeah, it's not limited to a single agent. And what you have to really believe in is that, you know, you could generate PK data. You could generate efficacy data in relevant pre-clinical models, and that you've looked for resistance, that you understand the likelihood that the patient will be infected with the appropriate susceptible isolates and hopefully that you're going to conduct a clinical trial. We will be watching very closely.

Now, I will come back and say that I have had the personal experience of a whole country basically saying we're not going to let you do an intra-abdominal study in our country because you've never studied a novel agent in anything and we think that population is too vulnerable and maybe you should

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go to a UTI study first. But you get a -- the majority of countries were happy to initiate both an IAI and a UTI study.

So it is an IRB or a personal kind of determination that has to be made. But you should generate the right data.

DR. COX: So just another thought -- and this has come up in discussions, too. It is sometimes when you're trying to advance a drug to treat patients with, you know, more severe infections, with, you know, higher mortality rates, you may try and do a lesser -- less severe infection initially, something with a lower mortality rate, something where there's an opportunity to sort of test the drug and then sort of advance up the scale of things that are more severe.

But, I mean, your comment is also interesting, too, in that if you think about what we're talking about here, we're talking about the highly controlled setting of a clinical trial and then advancing a compound to be used out there in the real world. So it also is a very sobering comment with

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regards to the use of the drug out there. What types of data would we have -- what types of information we have, you know, that would allow us to be comfortable in a clinical trial and what types of information we want to have to be comfortable using this drug outside of the highly controlled setting of a clinical trial when it's out there in the real world? So …

DR. REX: Yeah, but you could run the IAI component of this program for a year and have the DSMB look at it and say, yes, it looks like it's working out. Sort of you could eke -- you could ease your way into it because the mortality in IAI -- you can sort of salvage there. The mortality tends to be very low, so a really good question. You know, I pitched it as going together, but you certainly could stagger them.

At the microphone?

UNIDENTIFIED MALE SPEAKER: Yeah, so just to touch on a point that's already been raised but it's still not clear to me, you're just ignoring the ITT population it seems here. So you have subjects who are potentially being treated three or four days before you come back with culture positivity. And you

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know, you're talking about the pseudomonas active differential. How would that ITT result factor into your interpretation then at this equivalency?

And just -- some of my Merck colleagues are here, too. I didn't work for Merck at the time, but my recollection of ertapenem was there was a grave concern about using that in the ICU because of the lack of pseudomonas activity causing resistance to carbapenems. I think that's why that decision was made not to bring that forward.

DR. REX: Yeah, you know, interesting. I think that you would have -- the full ITT would be one of your secondary analyses, and it would at least need to not show anything wildly discrepant, something like that.

MR. DANE: Yeah -- go ahead. Go ahead.

DR. COX: I was going to say, I mean, you know, the reason we're looking at the MITT here is because of the limited spectrum of the drug we're testing -- if it's only active against pseudomonas aeruginosa, you know, patients who don't have pseudomonas aeruginosa that may have something else,

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you know, I mean, maybe they don't have an infection. Maybe there's something masquerading as nosocomial pneumonia here. It would be hard to test efficacy if they don't have the pathogen of when -- which the drug as active.

Your point about the ITT, though, we do always look at the ITT because if there's something going in the wrong way, a safety issue, you know, in the overall population, maybe there's something we didn't anticipate or don't understand that's important to know about in patients who are receiving this drug, even though they don't have the target pathogen. So an ITT that was, you know, for some reason going in the wrong way would suggest there was something that we didn't know about that we should know about.

UNIDENTIFIED MALE SPEAKER: The reasons we talked about, you know, that the study should be replicating how it's going to be used in the clinic and if what we'll be proposing is a substitution of X-1, you know, into the regimen potentially with ertapenem, if that's what the decision is and the way that the labeling goes, so it is, you know, a broad

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implication. Are you absolutely going to require the diagnostic before you put them onto therapy? And then it's not being used as it was in the study because it's no longer being used more on an empiric basis but on a confirmed diagnosis, so it's --

DR. REX: I guess if I price it high enough, you'll think really hard about using it.

MR. DANE: I think the other thing to add there is that in a non-inferiority study, if hardly anybody has got the pathogen you're interested in, you may well show non-inferiority and not have the activity against pseudomonas. So I think you'd want to understand it primary there and just make sure nothing else was going wrong.

DR. REX: Yeah, okay. It's 12:15. Let's go have lunch and bring our glucose levels back up. Be back at 1 o'clock, please.

(Off the record.)

DR. REX: Okay. The last few folks are kind of drifting in. So I show a little after 1:00. My guess is we're going to -- we'll use about the next two hours, approximately. The stated end time is 4

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o'clock. I just sort of -- my guess is it's going to be a couple hours of conversation. If it goes on much longer than that, we'll stop and take a break.

So let me start by -- just look real quick at this list of questions and see if there are any other comments that anybody wants to make about the themes here -- pros and cons from a clinician's perspective, an investor's perspective, a regulator's perspective. You know, we've heard, you know, the notion that some randomization is better than none. That's where clinicians and regulators, investors very anxious about how big this program is -- since it's very inefficient, you're enrolling a lot of people to get out a very few.

Though -- and there's also a risk embedded in this, if you're looking at Bullet 4, about ertapenem. You know, in effect, we're also testing ertapenem. But it -- but there may be more data on ertapenem than we've realized. And you need to dig that out and really test it.

I think one of the takeaways I get from this is that really knowing the answer to ertapenem would

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be something that we ought to spend some time on because it could be that it's a valuable tool.

Data on how to bring the two body sites together -- I've not heard specifically on that. So let's be sure we talk about that.

We've talked a lot about concomitant therapy. So if I look at this list, the one that's not as obviously been covered is the data from two body sites. Again, one of our statistical colleagues' comment on approaches to dealing with that, you know, and keeping in mind that the margins are loose. But one of the things that I took some comfort from -- I think it's back here, like, on this slide -- was that, notionally, the program -- the logic for approval has all this stuff built into it, all these different steps, and that I -- the fact that you get a positive result in two subsets, to me, intuitively was attractive.

But you want to comment on that particular question, Aaron, Tom?

CURT: Sure. Is this --

DR. REX: Curt (ph), oh, good.

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UNIDENTIFIED MALE SPEAKER: Hold it close. All right. That's great.

DR. REX: Good.

CURT: John, could you go back to the slide that had the two -- the data for the two body sites?

DR. REX: Oh, sorry. You want, like, this -- - like, one of these?

CURT: Yeah, like that one.

DR. REX: Like that one?

CURT: Perfect.

DR. REX: Okay.

CURT: So you know, there are a couple ways you can go about this. You've got, effectively, separate analyses here. The nice thing that's reassuring is that the data seems consistent between the two body sites -- and it -- not necessarily even consistent on the mortality rates, but the fact that the treatment effect seems to be identical between the two body sites.

You know, I often feel uncomfortable about pooling because if you say, a priori, I'm going to do a pooled analysis and then the data doesn't look like

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it -- it does worse in HABP -- you can end up in a bad place.

But this gets back to some of the stuff that I was talking about yesterday where if you had some kind of model that said you borrowed dynamically. So the model's set up in advance that if you get data like this, you do something. And I don't know whether it approaches pooling, but you borrow a lot of information between those groups and amplify the similarity. And if you get data that they're different, then you would have to rely on the separate analyses, and it would let that go. But it would get rid of a lot of the risk without pooling but still get you at 30, 40 percent effective sample size boost.

MR. DANE: So Curt, how would that work in this type of example where you've only got two body sites? Because I know that performs better with three or more body sites.

CURT: So we've done -- it makes a difference. So the more body sites that you have, you get a better idea of the body site variability. If you do it with two -- we've done this in the context

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of devices where you have, say, two subsets or an old and new device, and we've borrowed between them. Two has more risks than three. But you can at least quantify those in advance about what they are. And you certainly still can do it.

And we'd have to say in advance, you know, here are the datasets and here is the potential risk to Type 1 error. And it would have to be agreed on in advance. But you can do something like that.

DR. REX: Because otherwise, intuitively, if you've got, like, three out of four pointing in the right direction, that's nice. But if it's one out of two, it's like -- kind of like you've thrown away the one you didn't like and you kept the one you did like.

CURT: Well, and that's the purpose of --

DR. REX: And then that's the problem, yeah.

CURT: -- is to say in advance when you're going to do that so you can quantify the operating characteristics.

DR. REX: Okay.

MR. DANE: John, it might be the role of the -- what you do with this pool of combined data as

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well. So is this supportive to each individual body site having a conclusion of non-inferiority as you've got here? Or is that pool dataset the primary source of --

DR. REX: Yeah.

MR. DANE: -- confirmation? Yeah, so that might make a difference to how you'd view it and how risky it might for -- to Curt's point around the areas you might be making.

DR. REX: You know, I think I was just intuitively thinking that if I had, you know, two -- a couple of different observations -- in this case, two -- that were in the same direction, I'd feel good about it. If one of them was really divergent, you know, I'm not -- I -- to my mind, that might have been a dead end for the drug and maybe it's not really working so well. It also would sort of depend on which one was divergent and why and which --

MR. DANE: Yeah, and the different endpoints as well that could well be here --

DR. REX: All right. I recognize that. So that's why I didn't really talk about any formal form

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of pooling. It was more sort of if your eyeball can see it, then -- the way I wrote it down was both have to be inside their enormous margins, you know. But having both of them inside is notionally correct.

I see Ian at the mic.

DR. FRIEDLAND: I have some reservation about IAI as a test for activity against pseudomonas. It's --

DR. REX: So do I.

DR. FRIEDLAND: -- in the setting of polymicrobial infections. You're not quite sure what role the pseudomonas is playing. And I bet if you looked at drugs that are not active against pseudomonas like ertapenem, Tygecycline, and looked at their activity against the pseudomonas, you might find that you look as active as -- so I think there's just some concern there. We need to know that this actually is a good test of a --

DR. REX: I think there's a confounding issue with any microbials in general in intra-ab that's not limited to just pseudomonas. So one of the -- so part of the reason that I suggested doing the

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two body sites was so that you had two, each one of which had a different flaw. You know, I couldn't think of a better way to get -- you can always do cUTI. But the numbers there -- we saw the numbers again. There -- chasing (ph) pseudomonas there is really hard. And so I took that one off. And I said, well, just take these two with their flaws and see where you get to.

Other questions or observations on this? So anything else here that we could -- are there any -- is there any options to ertapenem realistically? What else could you do? A bunch of microbiologists in the room -- give me something that has a pseudomonas-sized hole in its coverage.

(Crosstalk)

DR. REX: That -- you know, that's actually -- we should minute that. That's a really important observation.

Was there somebody that raised their hand?

Todd (ph)?

TODD: What about ceftaroline? I mean, it does have some enterobacteriaceae activity,

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pseudomonas --
DR. REX: It does. It tips over on ESBLs. So you know, may -- this might have been a place for ceftaroline avibactam, which actually has never been developed. It's a developable drug, but it's never been developed. So okay. So but I don't think you can stand ceftaroline up on its own because the ESBLs knock it over.
Other ideas?
I mean, this for me was one of the harder things about it, was coming up with the fact that I could only find one choice that I was comfortable with. And I -- you know, so I did find the literature on it. And I'm just delighted here there's a study that's not published that might be helpful.
On the panel, anybody else have comments on A, questions you want to get at?
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: So in the -- so use a quinolone. Use moxy -- so what's the -- I don't have that in my head -- rate of activity in moxy versus pseudomonas. Anybody know?

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(Crosstalk)
DR. REX: Very high proportionate resistant. So that might -- it's a good extra thought. But is moxy, you know --
AUDIENCE MEMBER: (inaudible - off mic.).
DR. REX: Huh?
AUDIENCE MEMBER: (inaudible - off mic).
DR. REX: But what about nosocomial pneumonia? No.
(Crosstalk)
DR. REX: Yeah. So you're in the same place you are with the erta, which is you've got -- I mean, you might know some -- this -- we can look at it. All right.
UNIDENTIFIED FEMALE SPEAKER: John, my question -- or I guess maybe it's to the regulators -- is how do they see data from this type of scenario. You develop your drug. What's getting in the label?
DR. COX: It might be a little premature. I mean, we're trying to figure out, well --
UNIDENTIFIED FEMALE SPEAKER: We're supposed to go and tell this to our management.

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DR. COX: Oh, yeah, yeah. So I think what we're trying to do is we're trying to figure out, you know, X-1 and its activity against pseudomonas aeruginosa. So I mean -- so it would probably be something along the lines of, you know, X-1 is active in the treatment of or, you know, it can be used to treat the following infections when caused by pseudomonas aeruginosa.
Now, if we take, you know, one of these more abbreviated pathways, it's going to have greater uncertainty around it. So I would expect, too, that it would also be a reserve this use for when you don't have anything else, you know, available.
And then depending upon where we end up, because we've still got a lot more to discuss here as we work down these various different tiers, the degree of sort of, you know, reservation and whether there's any sort of formal program in place to preserve the drug, I think you'll see that, perhaps, as we start to work through some of these other scenarios where there's even greater uncertainty.
So that's off the top of my head because we

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haven't even worked through all these yet. But if we can get to the -- you know, the information that will help us understand how the drug works, we'll be in a much better position to be able to figure this all out. And it's very hard. I mean, you know, you can see we're all struggling with trying figure out how do you actually discern the -- you know, the efficacy of the drug and then gather safety information.
DR. REX: I couldn't imagine anything less than the wording around use in only patients with limited treatment options and get an expert to help you do it.
DR. COX: Yeah. Yeah, because these are -- I mean, this is really, I mean --
DR. REX: Yeah.
DR. COX: -- a very, very limited program. So it does seem like the indication would need to have, you know, reservations and maybe even a program around it.
UNIDENTIFIED FEMALE SPEAKER: And what body sites are you describing?
DR. REX: So --

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AUDIENCE MEMBER: (inaudible - off mic).
DR. COX: So the question is, is what body sites are you describing. And you know, we would want data in the body sites because, you know, at least our experience has been we've showed some of these, you know, past experiences that, you know, there are drugs that don't perform well in some body sites. And sometimes -- I mean, you know, Paul went through a very nice discussion sort of helping us to understand that a little bit more. But sometimes it seems like we find that in the clinical trial.
So you know, not having at least some experience to be able to have some degree of understanding about what's going on in a body site would be difficult. And you know, I would think, you know, as part of this, too, as you work towards that body site, you're going to get preclinical information that's relevant to that body site to the extent possible. Understand, you know, tissue levels, whether it be blister fluid or ELF, those sorts of things, to help you sort of as you build, you know, towards doing the clinical trial. And those would be

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the sort of things you do anyways.
DR. REX: Yeah, I should have put in a fake label. I was going to pitch for all three indications. That -- the -- that was, you know -- and in the sense that HABP and the UTI -- and the intra-ab got nice RCT data, UTI, you've only got the open label. And I was going to sort of loosely make the analogy to like (ph) the as (ph) voriconazole approval where you've got a nice big randomized trial in one disease and a related setting, related organism mucormycosis where you've got some open label data. And you sort -- you line it up with urine concentrations being really high and show that, you know, the urine also became sterile and do some stuff like that.
I mean, so I was going to pitch personally for all three indications. I should have said that.
DR. COX: Yeah. And usually, too, I mean, we have -- you know, had some discussions around this, too. It seems like if -- you know, if you're going to do the multi-body site approach, you don't -- you want to have some, you know, representative amount of

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information from each of the several body sites. So you might want to do -- you know, if you're going to do two, you might shoot for, like, 50/50. Or, you know, if you think one particular site be -- might be a little more difficult, maybe you do, you know, 70/30, or something like that.
But you wouldn't want to end up -- and we've seen this sometimes in the past with, you know, two patients in this site, three patients in this site, you know, 100 in this other site and then, you know, expect that you have sufficient information to be able to draw conclusions about the -- what we sort of refer to the onsie-twosies in other sites where you really just don't have enough to be able to say too much of anything.
So balancing it out across the sites of interest I think is a good way to think about this.
Kenneth? And then we'll pop back over here.
MR. HILLIN: I just wanted to make sure we did cover a topic. You specifically requested from an investor perspective. I'm not an investor. But --
DR. REX: Well, then --

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MR. HILLIN: -- I've seen you give nice talks previously to CAC (ph). And I wonder if you could comment from maybe a pharma investor perspective if you think about the cost -- and you talked about that -- and the time and then you think of the probability of technical success, both of the executing the trial -- of the trial, demonstrating what you set up to demonstrate of the regulators approving it, so both the technical and the regulatory success versus the likely commercial return, how you -- when you integrate all those things because that's what an investor thinks about. Do you think that's going to be -- what kind of scenario will that paint?
DR. REX: So very briefly, I'll answer one part of it now, defer the others.
So can I get a return on this product if I had it developed? I think the answer to that is yes. This meets all the criteria for a new kind of fire extinguisher for which there should be a value. And I'm going to -- if I can get it developed at a reasonable price, I get I can make a reasonable return on this one. I'd be willing to make the case.

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The question of would I actually run -- would actually spend the money, ask me that question after we've looked at Scenarios B and C. You know, let's get a little further along because I want to highlight a particular problem that we've pointed at, but I'm going to make it really painful.

Have the mic? Go for it.

UNIDENTIFIED MALE SPEAKER: Can I see the statistics again, please, the chart?

DR. REX: Oh, sorry.

UNIDENTIFIED MALE SPEAKER: So what --

DR. REX: I keep going the wrong way. There you go.

UNIDENTIFIED MALE SPEAKER: Yeah. So here in the HABP/VABP only, we cross the 20 percent margin by 2 percent, and that is already a wide margin. Now, what type of discussion would a sponsor face in front of, you know, NDA submitting these data and wanting a label for HABP/VABP and cIAI, given that only the pooled, or borrowed, matter, whatever, analysis meets the 20 percent margin but not the single ones with a numerical inferiority, which is just the patient,

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actually. But that is issue of small numbers.

So what type of risk do we actually take as a sponsor? Also, imagine that probably only 36 or 48 may respond. And then we're at 28, or whatever. You know, we're five over. So what type of discussion would we face for that indication then?

DR. REX: And can I suggest --

UNIDENTIFIED MALE SPEAKER: You know, what is the risk?

DR. REX: -- the -- I'm going to -- let's hang on to that question because -- but did everybody hear what he just said? If we look at the numbers again, if that 37 over 48 becomes 38 over 48, then the difference -- because at 48, every one is worth 2 percent. So now the delta goes down to, like, minus .1, and the confidence interval shrinks a teeny, tiny bit. And I will tell you that it comes in right at minus 20 -- deliberately done to make this point.

So this is pitched to be out by the tiniest bit, and I can make that go away if you'd like by using a different alpha. And that was Aaron's point, was that if you're -- if you say, well, I can't have a

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drug that might be as much as 20 percent worse, okay, well, about -- or as much as 22 percent worse, can you have one that might be as much as 19 percent worse? Would you feel better about half a point? I just want you to be aware of the choices we're making numerically, all right?

So I'm going to -- let's push on because I think we have covered these questions.

So Scenario B, this one is chosen so the meropenem results have -- are unchanged. What's happened is that on the X-1 arm in both cases I've nudged the response rate down for X-1 as low as you can go and still have the computed 95 percent confidence bound to be within 30 for HABP/VABP and 25 for intra-ab. And remember, it was 37. It actually would -- it would probably help to see. So it's 37 and 55 is what gets you neutrality. 34 and 50 puts you in a worrisome place.

So now, would you like to have this drug?

Dr. Boucher?

DR. BOUCHER: Is this --

DR. REX: Yeah, you know, I -- let's say one

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other thing. Look at the -- the HABP/VABP is all-cost survival, so -- the endpoint. So the mortalities are 29.2 percent on the left and 20.8 percent on the right. That's 150 percent higher mortality on an absolute basis, okay?

Now Dr. Boucher?

DR. BOUCHER: So this really comes back to what we talked about earlier. The issue will become what is going on. It's five patients who have moved here now. And the data are the data, right? We have numerically lower survival and success in this scenario. And so we're going to have to understand as well as we can what's going on there.

And I think it's quite possible that there's a real problem that suggests that there is a drug either efficacy or safety. I think, really importantly, what if there's a toxicity, either something we could have predicted or something we might not have predicted, playing a role or an apparent lack of efficacy -- efficaciousness, I should say, based on serum concentrations in these patients or other things we could ascertain. But it's going to

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take a look at all 48 and 24 HABP/VABP patients and 69 and 34 cIAI patients. And it will come back to how strong -- how clear are we in what was going on in all of those individuals.

So there's really no room for poor quality data. There's no room for question about what -- whether the diagnosis is what we thought it was or whether the outcome is what we think it is. But it's a risk.

DR. REX: So Dr. Tomayko, you're an ID doc at the mic. You talk --

DR. TOMAYKO: Yeah.

DR. REX: -- talk to me about these data.

DR. TOMAYKO: I guess if I was still out in the field I'd be less interested in understanding everything here than in the last example. But still, now that I have the added experience of working for a company and looking at data, you know, the first thing I would do is focus on the word you have up there, which is the punch line and the message that I had in my presentation.

The first thing I would do is I would, like,

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sit down and look at a bunch of HABP/VABP studies and bring a statistician and say how much heterogeneity is in there and are these just sample variation issues. And if they are, then, you know, we're really stuck with a big problem, you know, I mean, as I think we're all trying to illustrate. If you can't reliably do a small sample and get an answer that tells you that this is a good drug, then you have a problem. And that's --

DR. REX: So --

DR. TOMAYKO: -- what I think we're looking at here.

DR. REX: So I didn't call up a statistician to do that, but I did do the study a second time. And this time, the results came out like this. So now X-1's -- X-1 and meropenem have basically traded places. I'm going to put them side by side on the next slide. But notice that they've now basically traded places.

And so here they are side by side. At the top is the tilt to the right. X-1 looks a wee bit better. And at the bottom is the tilt to the left. X-1 looks a wee bit worse. It depends on how you

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define wee, I suppose.

Since you were just about to talk yourself into X-1 not being a very good drug when I just showed you the bottom scenario, is X-1 a superior agent in the top scenario?

Kenneth?

MR. HILLIN: This is -- and it's relatively straightforward. This is just a tyranny of small numbers --

DR. REX: Tyranny of the dichotomous mind.

MR. HILLIN: -- and the ability of randomization in the scenario to take care of the imbalances which are inherent in the kind of design you have here.

So I think it's -- when you get down to small (ph) end (ph) streams, things happen.

So and as Helen said, actually, then you're driven by the individual characteristics of every single patient when you get down to small numbers. So it would be a statistical --

DR. REX: Well --

MR. HILLIN: -- question, though, I think --

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MR. DANE: Well, I would just add it's not just imbalances. It could be perfectly balanced and you could still see this just from random variability. So --

AUDIENCE MEMBER: (inaudible - off mic.)

MR. DANE: So I mean, in some ways, you can't avoid that. You can't magic up more precision than you've got, you know. And I mean, that's the risk with these programs, as far as I can see, unless you can supplement it with something else.

MR. HILLIN: I think they -- what would be criminal would be if you had a great drug that was truly superior and you didn't observe it and the drug was never approved. That's what we want to -- also one of the things we want to -- we don't want to miss if it turns out we have a better drug and we can't figure out how to get it approved.

DR. REX: Yeah. And this is one of the places where my decision to do two-to-one was beginning to bite me because now the meropenem arm, every movement of one is almost 4 percent. And so that -- you know, it's painful, right? You know, I --

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it was -- you know, I had a reason for doing the two-to-one. But now it's biting me in the tail.

And so you know -- and you look at how little the numbers have to move for this sort of a shift to occur. And I found that to be disturbing.

So sort of the same sorts of questions, you know, because, you know, Kenneth, you asked the question how do I feel about the risk. Now Tom's going to come to the microphone and give me some insight.

DR. LOUIS: Question on the numbers changing only a little, two points -- one is, properly done, the confidence interval knows that. We all know that, that it tries to reflect exactly that. But maybe a point that does directly relate to the -- if you only were to change one number is the strong need for high-quality data and that any kind of miscodes or anything like that can also be tilting this balance, especially in a small setting.

DR. REX: And also, if you would really like to -- I don't know how to maximize bacteremias and so forth, but you'd like to have a sort of maximum

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severity of cases. And I -- you know, you could arbitrarily seek people with APACHEs course (ph) about some threshold, I suppose. That would just further shrink your pool. You know, every one of these choices just gets -- digs you a different kind of a hole.

Yes, ma'am?

UNIDENTIFIED FEMALE SPEAKER: Yeah, I'm just thinking about the previous comment by Tom --

DR. REX: Into the microphone. Sorry.

UNIDENTIFIED FEMALE SPEAKER: Sorry. Just about the previous comment by Tom, yes, you -- it -- there is definitely a huge component of quality. But especially with the point you're making, John, as you move up in the severity index, as these patients get sicker, then their comorbidities start to come into play. And not only do you see what John Tomayko was talking about with that affecting all-cause mortality as your endpoint, but you -- it also starts to play over into your other endpoints, right, because you're not going to call a patient a clinical cure from their cUTI or their cIAI if they died. You're going to have

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to ascribe those patients to failure. So now, this is all spilling over into your other endpoints as well. So it becomes a real issue.

DR. REX: Right. Sort of the same questions -- and as -- let me see if I can back up to this. So the questions for the -- to be sure we discussed on B are the same as for A, basically.

And does anybody see anything up there that they, you know -- I think the big one for me was about the investor perspective because this was the, you know -- I was thinking about that question as I built these scenarios. And you know, John Tomayko's phrase was, you know, it's okay to understand risk. How do I manage risk? And if the drug fails, you know, that's the deal. The drugs fail. But if it fails for reasons that don't have anything to do with the drug, then, you know, you're unhappy.

And here, where it's -- you know, this is really pushing the limits, particularly since our endpoints are dichotomous, not continuous. We actually are -- you know, there's not anything else, really, to look at.

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Any other wisdom or -- Marco looks like he's about to say something.

DR. CAVALERI: Yeah. Well, I think I agree with the previous comment that, at the end, with such small datasets, you would need to look at the data one by one, subgroup and try to understand what is happening. So it's not just merely into the statistical analysis of the entire dataset -- so it's -- because we acknowledge that there is this risk that the statistic might not tell us exactly the whole truth about the product.

So it's very important to look at this data really capillary (ph), looking at the patient of the subgroup, try to understand what would be the imbalance at baseline and any other factor that could have contributed to showing a difference. And that's what we would do, and that's also why sometimes in the small dataset running after, you know, inferential testing might not be helpful at the end of the day. And that's why we're open to alternative approaches.

And so it's the entirety of the evidence that matters. And we have to look at all aspects.

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DR. REX: Yeah. And if you could maybe do a Paul Ambrose-ish pharmacometric analysis and see if you felt like there was a response in there that you could identify.

MR. DANE: Yeah, John, because -- to me, scenario where you -- or Scenario B, the investor aspect is the same in the investor aspects at the start before you've even done the study. And I think it's all about the risks you've got that you're not going to be able to support what you're trying to do because you've got more uncertainty and you don't quite know where you're going to end up. And yes, that stays somehow captured in the confidence. It's for -- but you know, it's got more potential to move around.

DR. REX: Yeah, I just spent a year raising $60 million for a drug where the story was not nearly this hard to understand. And that -- I -- that year was hard work.

Okay. So Scenario C. So what's happened here is that the -- or excuse -- back up. I want you to lock something into your brain. Lower bound --

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look at the left scenario. Lower bound is minus 29 and minus 24.5, so just inside my hypothetical -- huge margins, right?

So in Scenario C, the selection device has failed, and you get just the natural rate of pseudomonas. You get 10 percent on intra-ab, and you get 15 percent in nosocomial pneumonia. And the sponsor sees this coming because, you know, you can have blinded -- a blinded rate of pseudomonas as you're -- you can know that about the trial. But there's no more money. You know, we've just got to take what we get, okay?

So now we do -- so we run it, and it comes out like this. And now this is assuming the two drugs really match very, very tightly. And I've got a minus 29 up top and a minus 20.8 on the bottom. Now, look at that for a second and notice that it is 22 successes and 34 successes.

I'm sorry. Where did it go? Excuse me. That's going to come in a minute. It's a different analysis.

So this one, the margins are the -- the

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lower bounds are kind of like in B but with the deltas being centered on zero. I mean, it is -- so this is -- you know, you didn't even get the high quality of A because you couldn't get your device to work. So this is the problem of -- you know, and we take -- instead of enrolling 1,000, you'd have to enroll 1,600 in order to get at this if the device just flat out failed.

Comments on this? Because this, for me, really amplifies the investor concern. I don't know how this device is going to work. I -- if I've had to invent this device for my trial, goodness gracious, you know, I have no idea how it's really going to work.

MR. DANE: John, I think the thing I would say is that, although it may -- when you get -- this is what the data could look like. It might not be any worse. The time you've got an issue is that if your diagnostic doesn't work and you get this many fewer patients, your power is 50 percent, not 85 percent because what this is telling you is you've got 50/50 chance of showing something like that even if the two

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drugs are actually the same.

DR. REX: Now, every movement of -- on the -- in HABP/VABP arm of one patient is 3 percent on the X-1 arm and 6 percent in the meropenem arm. It's enormous. Move one patient, and those number -- so this just gyrates like crazy if you start to play with it.

Other insights or comments?

Okay. So we've now done A, B and C in which, you know, you can kind of sort of see, if you look sideways, a non-inferiority study buried in here. And there are other variants. You could put more energy into the nosocomial pneumonia arm and just sort of focus there.

But that actually -- Amy's question before the break was are you really comfortable doing that, right? And so -- and also, you'd like to have -- you'd like to un-confound where you can. And so I liked having the intra-ab as part of this program, even though it, too, has its flaws. As Ian pointed out, you know, it's very, you know -- inter-ab is confounded by surgery. And yet there is -- there's

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some sort of an effect there.

So let's go on to Scenario D. So inhale, exhale because now it gets awful. The culture-positive rate is now about 5 percent, and there's absolutely nothing I can do about it. You know, I just -- that's it.

So the program size explodes. At a 30 percent margin and one-to-one, I might get down to 1,276 for any one indication in order to get the same kind of crummy margins that we were getting in Scenario C. So you understand, that's -- that -- it would take 1,300 patients to get at data as bad as Scenario C.

If I bring the margin down at all, the sizes go up north of 2,000 patients. And maybe I could really enrich (ph) for high-reach cases -- for high-risk cases such as renal failure and more co-morbidities. But this, I think, is where the animal rule question becomes of interest.

So Sumathi and I went back and forth on this a little bit. And this model doesn't exist. But there's no reason to believe you couldn't do it, which

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is you can take a large enough mammal -- a piglet or a rabbit -- you can put it on a ventilator and give it nosocomial pneumonia. You know, I've got to assume that I could create something that looks a little like the human disease. But you know, Tom Walsh (ph) has been doing rabbits like this for years, and they produce a very human-like pattern. I don't really have reason to believe you can't do it. And then you actually get into the notion of the clinical trial being, effectively, a field trial. And you -- maybe you can throw in some informational (ph) control data.

So here's the results. We've -- we did it. Sumathi and I got together and did a ventilated piglet model somehow.

UNIDENTIFIED MALE SPEAKER: You've been busy.

DR. REX: Yeah, I'll tell you what. We've been busy. It's been a -- we've had a busy month since she suggested that I write this case. All right.

So in the ventilated piglet model, 18 to 20 survival with X-1 and 0/10 with placebo, P equals

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.005. And then we do the Phase 3 in nosocomial pneumonia alone, so just picking one indication, picking the most -- the important one. And we assume the things that are shown there that I won't read to you.

And at the end of the day, I get, after enrolling, 726 subjects. I have 24 and 12 on X-1 in control with my target pathogen. And there are my made-up results. And if I want -- if I'm using a boundary of negative 30 as my margin -- isn't that what I said? Where -- did I write a margin down?

UNIDENTIFIED MALE SPEAKER: Thirty-five.

DR. REX: Thirty-five. Right. If I move one patient -- instead of it being 19 to 24, it's 18 to 24 -- I actually exceed the 35 percent non-inferiority margin. Sorry I didn't write it down. So -- and I'm not doing inferential statistics. I'm signing up for no math, okay -- none. Instead, I'm signing up for the P of .005.

So now the discussion. Do these things together create Tier C minus or D plus? Discuss.

DR. TOMAYKO: John, is there any chance that

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you would be able to tell us whether or not target attainment was achieved?

DR. REX: Oh, well, absolutely. The desired exposures were hit. And so it's like in Scenario A. You know, we hired a really good PK-ologist, and we nailed it in our clinical program. And maybe we -- it's picking up on the idea that we actually dosed a couple of people with HABP, with VABP with single doses before we started the program just to be sure that we were comfortable with our exposures. You know, you can do all those things. It's all right.

Absolutely, the drug -- and the drug gets into the ELF, might or might not be able to do the non-CF bronchiectasis study, depending on -- like, if we're doing acinetobacter, I don't think I've ever seen acinetobacter colonize in that. It might not be a study, like, that you can do. But I can sure enough do an ELF.

DR. TOMAYKO: But you're basically saying that all of these folks for the MIC of pseudomonas, which is I think going to be something less than one, all the achieve (ph), the target exposure that they

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needed --
DR. REX: Let's assume that.
DR. TOMAYKO: Okay.
DR. REX: Let's assume that we've got a good exposure and that Paul Ambrose puts up one of those plots like the other day and says, you know, it looks like it's in the right spot, you know. It's not a guarantee, but it looks like it's in the right spot. I think you must assume that.
David (ph)?
DAVID: I just think -- I mean, again, it's a huge amount of work, and you're amazing for having done it. But I think it shows that you can't do non-inferiority for this sort of indication. The data just become too fragile at the end of the day, and the risk is too high. So I would reject the non-inferiority design for this sort of program.
DR. REX: And so let me be clear that I'm not actually going to propose a statistical hypothesis. I'm just going to say it's a control and it's small. And I'll bring you some external controls, and I'll show you that people in the past

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with pseudomonas died a lot.
DAVID: I think -- but again, I think if you put in the context of a different design approach, then it gets a lot easier in a way -- in some ways.
DR. REX: What is that design?
DAVID: A superiority approach using external controls and other controls, again, not necessarily powered at P .05.
DR. REX: Well, let me be sure I've heard what you said because you said use the external control to show superiority. So I can do that right now because I can tell you that, in the historical data, people with untreated nosocomial pneumonia or incorrectly treated nosocomial pneumonia have a all-cause survival of about 30 to 40 percent.
DAVID: Yeah. So --
DR. REX: So I -- so it's -- so that's buried down deep in here. And I bet I could do that with contemporaneous controls.
DAVID: Right.
DR. REX: I bet I could that with some -- like, the Di Carlo data --

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DAVID: But so I think what you -- yeah, I think what you'd have to do -- I mean, I could go through kind of a design that we went through thinking about this particular sort of drug a while ago if this is the right time to do that. Or I could wait until later or not --
DR. REX: Oh, no. There's no better time than now. So go ahead.
DAVID: Okay. So what we were thinking about was a superiority design where you had your drug, X-1. And this would -- could either be combined with ertapenem or even meropenem, depending the sensitivity of your investigators to a new drug for a dangerous infection like pseudomonas. And I can tell you that you do get pushback from investigators when you go out and talk to them about this in real life.
So and you treat these patients. You try and enroll patients with pseudomonas. You do all-comers if you like. I would do all-comers. And within that population of pseudomonas -- and you have to be careful about what centers you pick because if you do the trial in centers where there are very high

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rates of carbapenem resistance, then everybody gets put on colistin. So you actually don't want to do your trial there.
You want to do your trial where you have UDR rates of carbapenem resistance, which is on the order of 15 to 20 percent kind of globally, and their physicians are still using carbapenem mostly to treat pseudomonas aeruginosa infections.
So you then look -- so you treat everybody with your drug plus ertapenem or your drug plus carbapenem. But you specifically look from among that group --
DR. REX: This is open label --
DAVID: It's open label, yeah.
DR. REX: This is open label, one arm.
DAVID: Yeah, it's one label, one arm and historically controlled. And I'm going to get to this controls because you have to do a lot of work on the controls up front to make this all work. And I actually don't know the numbers because nobody's ever done the work that I'm -- that I have in mind.
But you treat everybody up front with this

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combination. And then your historical control should be contemporaneous. It could either be done by a retrospective analysis similar to what the medicines company people did. It should be done in centers that are going to participate in your trial. And it should be done using the inclusion-exclusion criteria that you plan to use for your trial, which I would argue would have to be fairly broad.

Then what you would need -- so that would give your control. What you're looking for is the control levels of response of people initially treated with carbapenems who have carbapenem resistant pseudomonas aeruginosa. That's the control number you want to get.

And then what you have to do --

DR. REX: So to play it back, what you're going to do is seek people who would have met the inclusion-exclusions of this trial.

DAVID: Yeah.

DR. REX: You didn't actually ask them to consent. But at least on paper, they could have consented. And then you're going to look for the

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response rate in the carbapenem resistance subset --

DAVID: Yes.

DR. REX: -- of that group.

DAVID: Right. Right. So then the other issue is monotherapy or where, you know, are you going to add Amikacin. The centers that we talked -- when we talked about this would have added Amikacin. So you'd probably have to do that so you don't answer that you're still stuck with that. But again, looking at the carbapenem resistant group gives you at least a look at the activity you want to look at.

So then what you have to do is you actually have to validate your previously constructed control group during your trial. And you can do that in two ways, or both ways, one of which is you do a prospective observational study of people who don't get enrolled. Again, and/or -- and/or -- you have something like a four-to-one randomization in your trial.

DR. REX: So to play it back, what you're saying is that after you've constructed this hypothetical -- your developed data on a response rate

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of MDR pseudomonas in a group that meet inclusion-exclusions. And now you're doing the real trial. And you either observe people who didn't go into your trial, or you do a very disproportionate randomization.

DAVID: Right.

DR. REX: So --

DAVID: The idea is to try and get numbers to support the historical control that you started with, so to avoid the Ellenburg effect of having inadequate historical controls, if you like.

DR. REX: Okay.

DAVID: So that was kind of the design in a nutshell of what we looked at for a drug like this. And the problem that you run into is that when you actually get crunch -- start crunching numbers, depending on what those controls look like, you might get down to a point where you don't have an adequate inferential test at .05. So it might have to be .1 or .2 or something, and you might have to use additional data. You'd have to rely very heavily on PK/PD data both in people and in animals.

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But I believe that that sort of program all together might provide a way forward for the smaller patient populations. And it avoids a lot of the issues that you run into in the non-inferiority designs.

DR. REX: So Ian Friedland, where are you? You're summoned to the microphone.

So help us out here. This sounds -- so just sort of feel your way into this. It -- you know, in many ways, this is a little like what you did, though -- I mean, there are clear differences. But you are -- this is about seeking the super-resistant bugs. And Sumathi did the math to suggest that 1 in 122 pseudomonases would be resistant to two drugs, which would --

DAVID: No.

DR. REX: No? Sorry. One -- no, it's the rate of dual resistance --

DAVID: These organisms are only resistant to the carbapenem. They don't have to be resistant to Amikacin in the study. You accept -- you do the same thing you did in your study. So --

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DR. REX: Okay.
DAVID: -- patients are treated for --
DR. REX: But they have to have been treated -- but in order to get a control group, it has to be those treated only with the carbapenem in order to get the response rate for carbapenem-resistant pseudomonas.
DAVID: Most of the patients that you'll find when you do your little study are going to get carbapenem plus an aminoglycoside for pseudomonas --
DR. REX: So they will have actually had -- so I guess I say again if I want to get a placebo response rate, I have to find people who didn't get an active drug.
DAVID: No, what you want is a control rate that matches the controls that you'll have in your --
DR. REX: But I have to beat the control. So if the controls --
DAVID: Yeah.
DR. REX: -- have gotten an active drug, why am I going to be superior to an active drug?
DAVID: Because Amikacin alone is not very

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good is what we find.
DR. REX: I -- boy howdy. Okay. I'm now not buying the risk, but --
AUDIENCE MEMBER: (inaudible - off mic.)
DR. FRIEDLAND: I agree. The concern would be the Amikacin because, if you treated just Amikacin alone, maybe you would, but they're not going to do that. As soon as they get the ceftaroline (ph), they're going to switch to another drug. So they're going to give you an Amikacin plus an active drug. So it's basically the 24, 48 hours in which maybe they're not covered with a --
DAVID: That's --
DR. FRIEDLAND: -- effective butolactam (ph) or some other --
DAVID: Right. But that's why the controls are mainly -- it's historical or external controls. So that's -- so you're not -- so the four-to-one randomization, you would have to deal with this confounding issue. Or you do the prospective observational study where, again, you're not treating the control group.

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DR. REX: All right. So that's an idea that fits into Scenario F of an approach that wasn't considered and which I -- we're going to come to that in a minute. We're looking for other ideas.
Can I get a little more conversation on the animal rule-ish support for this? So it's not the sun, the moon and the stars. And it's a pretty small flashlight.
Dr. Boucher?
DR. BOUCHER: I mean, I think again we'll work with what we have to work with. And if this was a drug Scenario D that worked in acinetobacter or some new place where we're really up against it, I think it's possible to work with that. You know, ideally, a little more clinical data would be nice.
And so in -- I sort of hesitate to say this. But from the clinical perspective, it still would be helpful to see those patients with the worst -- you know, with the blood stream infections or, you know, some places where clinically, even if it's individual cases, there was some evidence that the drug was effective.

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DR. REX: So --
DR. FRIEDLAND: I'll comment on the animal --
DR. REX: And -- well, actually, the two of you -- Ed asked the question of me a second ago, and I'm going to phrase it because I'd like the two of you to respond to this. How will you use this drug in the clinic? How often do you think you'll use it? Why will you use it? Because that goes in to the question of risk, benefit and labeling.
Ed, do you want to amplify it all in a question for them before we let them loose on it?
DR. COX: Yeah. I know we're still struggling. And this is why I asked John. I said is it too early to ask this question.
But you know, we're struggling with trying to figure out how we evaluate the efficacy of this drug. And at the end of the day, I mean, there's going to be tremendous uncertainty around this. And you know, maybe this drug is active against baumannii, and maybe other drug is active against pseudomonas aeruginosa.

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I mean, it would be interesting if folks have insights. You know, how would this drug actually be used in the clinical arena. I mean, would it be, you know, your institution had some tremendous problem with resistance among pseudomonas aeruginosa in patients. And could you identify risk factors? Or you know, there's an outbreak of acinetobacter baumannii in your ICU and, you know, available -- based on what you know about resistance testing from the first case or the first couple of cases, you don't have good options. So you're -- you know, that -- this is going to be the instance where you, you know, reach for an alternative.

I'm just trying to figure out where does this fit or how does this -- how would it be used. Any thoughts or insights on that?

DR. TOMAYKO: I'll take a stab. I -- as I said yesterday, I'm pretty impressed with the surviving SES (ph), this experience where we really learn to pay very careful attention to infections and manage them appropriately, be it source control or be it rapid onset of appropriate therapy.

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And I believe Anon Kumar (ph) has now followed up on his database. And he's no longer just looking at one-hour intervals increasing mortality by 7 percent. I think he's got it down to 15 minutes.

So you know, I would take -- if I had a problem in my institution and I was in my ICU and my patient was in septic shock -- because that's what he studied -- and I was concerned about pseudomonas, I'd give them whatever I had to treat pseudomonas before this drug was approved. And then I'd add this on it.

And if I came back just like I do with my Amikacin in the clinical program and found out that everything else is there and I have great evidence, then I would drop the drug X-1. If I didn't, I'd be gathering data to submit to the company that was kind enough to invest in the program and say hey, your X-1 really made a difference today.

DR. COX: And I'm not being critical. I'm just trying to understand a little bit more.

So if I'm understanding correctly, you would use this as part of your empiric regimen in the ICU for sick patients that you suspected pseudomonas

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aeruginosa so it would be empiric use, given the importance of initial therapy. So it could be a fair volume of usage that this drug would see --

DR. TOMAYKO: Well --

DR. COX: -- within your institution. Is that --

DR. TOMAYKO: I think you're getting to the point. I'm not arguing that.

DR. COX: Yeah, I'm not being --

DR. TOMAYKO: Let me tell you --

DR. COX: I'm just trying to figure it out.

DR. TOMAYKO: Let me tell you that we have some safety data on the drug, and we have a lot of preclinical safety data. I mean, that equation might change dramatically if the drug was like colistin or worse. But if it was better than colistin in terms of safety and the data was supportive, then I'm thinking, well, the big problem here is that the efficacy isn't good enough, but I don't have anything else, or I have colistin. I'd have to make a decision there. That animal data might look better. I wonder if you could study colistin in that model and see what that looks

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like.

So there's a lot of information that you could craft together. I'm kind of interested to see what Helen would say. But I would not be afraid to start the drug in a person where it could make a huge difference and I could actually advance our understanding of whether or not the drug could have an impact if it could make that difference. If nothing else was treating that patient and that patient in septic shock got better, I think you'd want to hear that data.

DR. COX: Yeah. So before -- and just because this is helpful to me, let me just -- so I'm assuming, John, sort of there's two cases that are coming to mind. Within your institution, it sounds like you have, you know, patients who are infected with pseudomonas aeruginosa that, you know, have, you know, very resistant organisms. So that's sort of one situation. The other situation I'm thinking about is the situation that Paul mentioned, which is the variability and exposure.

So I mean, I'm trying to figure out if you

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only were to use it in situation where the institution had a significant rate of resistance to, you know, available therapies, you know, that would be a more restricted population. If there's concern more generally about, you know, patients where there's going to be significant variability of exposure -- so this is, in essence, a third agent being added in -- then the use of the drug could be quite significant, I would think. Fair?

DR. TOMAYKO: I don't know. It's been a while. How many patients in my ICU are in septic shock and have some of the risk factors that would predispose them to pseudomonas? How many of the units on my hospital have this? And again, you know, if I don't need it, I'm going to stop it.

But the other place I would use it is when for some reason I got it wrong but the patient's still alive and I want to rescue them. So I would definitely use it there. But you know, you're going to have the biggest impact on an infection if you start antibiotics early. And I think that it's really what we're trained to do.

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One last comment, on that animal data that John showed, I'd certainly want to know whether or not Paul saw anything in the exposures in the animals that might not make the data look pretty robust because it did look pretty robust. You know, it was a lethal model, and the drug had a profound effect in that study, so.

DR. COX: Yeah, and I don't disagree with that. I'm just trying to figure out, you know, the development program, what the, you know, clinical data are that you accrue during that program and then what usage might look like for such a drug that was really based on a database that had a fair degree of uncertainty. And I don't disagree with what you're saying.

DR. TOMAYKO: No --

DR. COX: I'm just trying to anticipate what this might look like because I think that's important for us to understand.

DR. TOMAYKO: No, this is important, too, because you just gave me a great idea for a field study.

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DR. COX: Do tell.

DR. TOMAYKO: Well, I mean, if the drug's approved and I want to do something that's meaningful, then I get a protocol out there and, you know, figure out how to get it disseminated. I think if it's an ID program, I'd have a lot of support from my IDSA colleagues. And I would make it a pragmatic-type protocol, and I would collect rigorous data, including PK data, on this population of patients in septic shock where I could manage a real-time significant effect. And then I would pull that together and do what I can with it and submit it.

DR. COX: No, that's fair. I mean, you know, and I think, you know, one of the things we talked about this some during the preparation of the cases, is that, you know, if the overall rate of infections caused by pseudomonas aeruginosa doesn't really change, you may end up with a very large "ITT" population. You may learn something important there. You could certainly get PK, and PK would be valuable.

And then you know, it's also -- and I was thinking about this a little bit. I was sort of

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asking, you know, are there studies that you could do after a drug is approved that might become somewhat more feasible. And it sounds like you're hinting at that may be something that, in fact, would be true. And I'm -- there, I'm focusing on the MITT population and recognizing that the patients were probably getting a variety of other drugs that may make it difficult to evaluate the test drug unless there are certain resistant -- certain resistance profiles that allow you to isolate that. But there may be opportunities to try and figure out how to study the drug.

So I'm just trying to think through it.

DR. DUDLEY: Yeah. Mike Dudley. The medicine's coming out.

John, you sort of flipped the card that I think I was thinking of as well. And the new commissioner actually made some comments a few weeks ago about use of registries in the post-approval smart process and really was encouraging use of that kind of information.

So I -- where I thought David was going to

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go and which I think was on the superiority side is -- is that you may -- what we may want to be thinking about, in fact, the multi-drug-resistant situation here, not for inferential testing and -- but perhaps for trying to see signals of superiority because if the drug has a big enough treatment effect, that's probably the population where you're going to be seeing that.

So I never thought I'd see myself arguing for a superiority, but I do think that if the properties that were described in the case, that of being able to go where you think the biggest treatment effect may be.

And then thirdly, I was thinking about the population. And you know, the anti-PCRV (ph) antibody work that's been done with pseudomonas, the trials that were done in 40 hospitals in France enrolled 30 patients with pseudomonas infections in nine months. And so perhaps maybe specifying a patient population that's particularly high risk, which they identified as having tracheal bronchitis, might be a population where we could go and see that treatment effect.

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But I vote for the animal rule.

DR. COX: You know, I would vote against it.

DR. REX: Sorry. So sort of Helen and then David. Sorry. We're going to go back and forth.

DR. BOUCHER: Okay. So I would just say as much as I agree with a lot of what John said, from a clinical perspective, especially in Scenario D, I think that the way the drug would be used would be in those settings like my first patient that we talked about where we know that we've got nothing else to offer, or we know that --

DR. REX: Okay. But you're talking about your first patient from your presentation --

DR. BOUCHER: From my presentation.

DR. REX: -- from this morning.

DR. BOUCHER: The lady with the MDR Klebsiella that was resistant to everything except colistin, including the two new agents, where this drug might offer something that's potentially tolerable to this woman for whom colistin really wasn't an option and that, through our stewardship program, we would gain some experience in people with

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known infections because this dataset is small. And that's something that our community looks at when we decide to bring these drugs in.

And then perhaps -- the next place I could see early use would be in -- if, God forbid, there was an ICU kind of problem where we had a particularly nasty organism that we knew about that was circulating, you know, that that would be another place where -- thank Heavens I haven't had to do that -- but we -- where you could envision tapping into something like this.

But we'd want to see more clinical data, whether that's Phase 4 -- you know, however we got it before we moved on. And I think that's largely what's happening, at least in our hands and in those around the country with the two new agents, even though they’re kind of relatives of drugs we know well with the ceftolozane/tazo and the ceftazidime/avibactam. You know, we're using them in individual cases with the best susceptibility testing we can get and getting experience with them before we think about broader use -- in stewardship programs, you know, in a very kind

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of -- in a way that probably our sponsor colleagues don't like to hear. But that is what's happening, I would say.

So I think the answer to your question on the prior example maybe is a little more difficult. But I find it hard to imagine in 2016 with the way things are working where I work that we would be able to think about using this stuff empirically at this point.

DR. COX: So that's helpful, Helen. So that sounds like situations where culture results tell you that you essentially don't have options or in the setting of ICU outbreaks with the particularly problematic organisms circulate around where you have a resistance profile that tells you you don't have other options or you have very, very, very few what -- other options.

Okay. Thank you.

DR. REX: We need to talk about the economics of that at some point.

So David?

DAVID: Yeah, I was just going to Ed's

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question about how it would be used. So I work in a 70-bed hospital. I think 70 percent of U.S. hospitals are under 200 beds. Most of those small hospitals don't have big resistance problems. In the four years that I've been working there, we had our first case of VAP just last year. And it was pseudomonas aeruginosa but a susceptible strain.

So if you extrapolate that across the United States, I don't think there's going to be a huge amount of empiric use. It'll be mainly in academic centers where resistance is going to be a problem.

So I don't -- and also, the -- in order for anyone to make money on this, which I think is someplace John was going to go, the price in the United States is going to have to be pretty high. And stewardship programs are going to clamp down pretty hard on people who use very expensive drugs empirically for no good reason, so.

DR. REX: Right (ph), go ahead, please. And introduce yourself.

MR. WARREN: So Travis Warren (ph) from the U.S. Army.

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Could you go back to the previous slide from this one? It's the one where you introduced the animal model.

DR. REX: I think it's this one.

MR. WARREN: Next one.

DR. REX: Yeah. Well, so I've got some made-up data with the animal model here.

MR. WARREN: Okay. So well -- so it was --

DR. REX: And so -- and by the way, this is --

MR. WARREN: There was the one --

DR. REX: -- kind of like the animal model --

MR. WARREN: There was a bullet point about the -- generating the validated pig model. And so I think there's a possibility you may have violated your requirement for the miracle less than one on that one. And you know, I --

DR. REX: Oops.

MR. WARREN: -- I say that tongue in cheek. But it's an important point because I think it's important to emphasize that I'm not familiar with the

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pseudomonas models that are out there. But it's been alluded to that there's not a good animal model that's out there. And I don't want especially sponsors who were considering potentially using this type of thing to think if there's not already -- if there's not a model that's already out there -- it's not a plug-and-play system where you choose the species you're interested in and the pathogen you're interested in and put them together and, voila, you've got the disease that's indicative of the human disease.

So it's -- I think that if this is -- as sponsors are thinking about potentially using this pathway, it seems possible that there would be as much regulatory interaction just around validation and trying to have -- give the FDA confidence in that animal model because they're going to be scrutinizing those data very, very carefully, I would anticipate.

DR. REX: I want to say thank you for standing up and saying that. That's something I -- it was on my list to comment on. And Dr. Nambiar will.

DR. NAMBIAR: Yeah, I thank you for your comment. And that's what's probably (ph) was the last

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point on my slide as well. Even though the animal model seems like an approach, there is a lot of work to be done between now and getting to it. And then certainly we're talking about one model. But ideally, we need more than one model. And the disease in the animal has to be reflective of human disease.

And I think your comment is right. There's a lot of interaction, a lot of back and forth before we get to a model that we are comfortable with to decide the trigger and I think, as I mentioned, what's the inoculum, what's the organism. With bio-threat agents, it is -- it was easier because we used one strain of Y. pestis. You know, with pseudomonas, I mean, we have a lot more issues.

So even though there's an appeal to the animal rule, I think it's fair to say that it's a lot of work done. And the years and time spent in getting that to fruition, you might be able to do clinical trials. I think we have to keep that in mind.

DR. REX: And Lu to -- so Ed -- Lu and then Ed.

DR. BORIO: And I know you asked the

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question, John. But I'll ask a question to Sumathi, which is, you know, if you two can comment on the appropriateness of a placebo in the control arm in this model, you see a very dramatic treatment effect. But the control is based on a placebo. Can you comment on that? When was the last time you had an animal rule in a pivotal -- the efficacy studies that relied on a placebo control?

DR. NAMBIAR: It will -- so I think the approval for levofloxacin was levofloxacin versus placebo.

DR. REX: So was the answer that you typically do it this way?

DR. NAMBIAR: Yeah.

DR. REX: Right, since this is the model you made up. So I was --

DR. NAMBIAR: Like --

DR. REX: -- hoping it was --

DR. NAMBIAR: -- in humans.

DR. REX: -- correct.

DR. NAMBIAR: This is not good, you know.

DR. REX: Well, and the -- and you know, it

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-- the example that you showed in the real-world example of the African green monkey, you kind of had data like this at the end of the day.

DR. NAMBIAR: Yeah. I think maybe off by a couple of numbers, but it was --

DR. REX: Or less. Right.

Ed?

DR. COX: Yeah. I just wanted to thank the folks that were daring enough to postulate or speculate on how the drug might be used.

And you know, the reason I'm asking is I think that, you know, everyone recognizes that there's tremendous uncertainty around this data. And so you know, if it -- you know, if we think about, you know, managing the risk of a product out there, it seems like there would need to be some sort of program or some sort of restriction on use. And just -- it helps to have some insights into how the product might be, you know, envisioned being used to help to understand, you know, how you might put some sort of program in place to, you know, restrict the use to certain settings where it was appropriate to use it, you know,

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where the safety and efficacy, essentially, were -- you know, whether it was balance of benefit risk and then also thinking about how do you gather more data to figure out what is going on with the product. Is it -- you know, is it working well in the situation out there in the real world? Or have we uncovered something that we didn't anticipate from the premarket data in that -- you know, either with regards to safety or efficacy? So --

DR. BOUCHER: So Ed, I agree 100 percent. I think that, you know, tying it in to sort of the overall strategies that we're working on in the carb efforts, you know, the stewardship kind of being more universal in the United States as well as monitoring of antibiotic use in general but especially for these type of antibiotics seems like a very appropriate and timely kind of systems-type measure to help with this. And that's something that, you know, in our carb efforts there's a lot going on in this area. And more hospitals are using the NHSN antibiotic module already. That's capturing all the antibiotics that we use.

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So that's a system that exists. Now, it may not be 100 percent acceptable for all the need. But it's a -- it's evidence that there is a U.S.-based systematic approach to all antibiotic use, but especially for these really precious agents.

DR. TOMAYKO: And I just want to say that there are settings where we've done things in the past under a protocol. So that's what you were getting at. Maybe there should be restrictions on how the drug is used in the general sense based on that data. But maybe it really is.

I was kind of thinking on the fly. But maybe it really does become kind of a registry or a field study. And you know, we make it -- take advantage of diagnostics to try to minimize any issues and whatever. But collecting that data is critical.

DR. COX: Yeah, and I agree, John. I think we're all thinking on the fly today, and that's part of what makes this interesting. But yeah, you know, I appreciate everybody's comments and willingness to hazard an opinion on this as we try and work through it -- very helpful.

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DR. REX: So I want to be sure that we've thought about what this means economically. So what does it cost to run the plant that makes an injectable antibiotic 100,000 doses a year? My number is $20 million.

UNIDENTIFIED MALE SPEAKER: Is that a combination product of two --

DR. REX: Well --

UNIDENTIFIED MALE SPEAKER: -- of different types --

DR. REX: It's --

UNIDENTIFIED MALE SPEAKER: I mean, what --

DR. REX: This is a general -- I asked my guys for a general number for having a facility. And it definitely went just like this. Yeah, if you're making a monoclonal, it's more expensive. It sort of is. This was a general number, all in. And it doesn't mean -- it doesn't assume you have had to be -- it assumes you don't have to build your own facility. You can actually work in somebody else's, you know, shed, so to speak.

But to have the staff to make -- to have the

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runs to, you know, sort of take it in and out of production, that's the warm-based kind of a minimum cost if kind of the wind is to your back.

It can be more expensive than that depending -- it still depends on how much you want to make. You know, the actual physical cost of each vial begins to be relevant after a while. You know, making 100,000 vials or something even at 5 bucks, you know, that's half a million dollars right there -- boom, done. And that's -- it doesn't count stuff that goes in and out of date. And the occasional run, you know, sterile injectable manufacturing -- oh, my God, well, at least once a year, some batch blows apart and you lose 50,000 vials. And you -- everybody just goes bananas.

So the part -- the difficulty with what we just discussed is that if the drug is being used in the United States 100 times a year and in Europe -- so Europe -- the population of Europe is three times all of your -- even whether you -- it's in or out, it's a little over three times the United States.

So let's pretend 500 courses a year. What do I have to charge for each course to have the warm

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base exist so that Helen can do her experiment? I mean, I -- ouch. I just want to observe that.

So this -- you know, this is why I spend a lot of time on the pool models. I would want to treat this as a better fire extinguisher and argue that some countries should pay a certain access fee to guarantee that the drug exists in the pharmacy so that you can have it on an as-needed fire extinguisher-like basis.

But you know, I look this, and I wonder could I convince somebody to pay for this fire extinguisher. You know, and I'm not saying that I like my answer when I say that. You know, it doesn't make me happy. But this is the problem -- this was the reason for the case.

I don't see any hands go. So let me just show the very last slide. So this is Scenario E. It's like in Scenario D. But the animal model is -- I've pointed out it's hard. I don't know that I can do one. Well, so we tried, and it -- couldn't do one. Absolutely. The pseudomonas, piglets, rabbits -- none of it really looked like human beings.

So now we're down to can't do it, can never

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do it. What do -- and yet X-1, honestly, looks like it ought to be of some value. I mean, honestly, it does.

So discuss. I told you the cases were going to get harder. Everybody take a deep breath.

MR. DANE: You know, I guess it ranks (ph) to some of the earlier discussion, John, is that when we're in this situation, it's -- yeah, it's hard whatever we do. And in one way, the idea of open label trials with external control may sound appealing, but the trouble is are they really comparable. And you'd have to do a lot of work to be sure they were unless you had a very big effect. So if you had a very big effect, you could be a bit more confident that, actually, you had the benefit. Otherwise, it's just all getting mixed up in noise.

But at the same time, yeah, it normally (ph)randomize. But if you've got a small number of heterogeneous cases, does it really help you? So it avoids the bias of treatment choice, but it doesn't necessarily give you balance in your groups.

So I'm not sure I've given any answers there

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other than more problems. But I think it was -- it's just the caution around this idea of external controls can solve all our problems. We just have to be a big careful with that and make sure that's sufficiently comparable to be able to do something with that.

DR. REX: So let's talk a little more about external controls. I mean, I -- you're right. I'm teasing you a little bit to -- the -- no, you didn't help me at all there. So I'm still stuck. Okay.

So I've got this thing. And the -- really, the best thing I can imagine is I'm going to go find folks who they've grown it. And now I'm going to -- maybe it's acinetobacter, you know, right? Now I can kind of do this with acinetobacter, that, well, you see one of those, pretty high frequency of I don't have any drug at all that works. And I could do an open label case series.

What about -- you know, David Shlaes was pointing at the idea of some sort of a contemporaneous control group. I mean, is there anything -- and I know there are strong allergies to external controls because previous datasets have been really messy.

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Marco's smiling at me fixedly. And Ed and Sumathi are in deep debate.

So opine on agents approved based solely on external controls.

DR. COX: So yeah, we were talking about something else.

(Laughter)

DR. NAMBIAR: Well, I can reveal what that is, is I was asked to find another job.

(Laughter)

DR. REX: Well, at least we all share the pain here. That's the good thing.

DR. COX: So yes, I mean, we do use external controls and historical controls. And the times we use them are in situations where, you know, the outcome is -- you know, I like to use the term -- you saw it on my slides today -- lights on, lights off, for it's -- you know, it's dependable. It happens all the time, and it doesn't really change that much. And you're not quite as susceptible, you know, within the group that you're looking at to variability with regard to outcomes.

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You know, I've talked some with my colleagues in oncology, and I asked them about, you know, the situations where they've used historical controls. And you know, they'll sometimes say to me so, like, you know, tumors just don't get smaller on their own. They just don't do that. So if you have something that makes tumors get smaller on their own, you know, that as a surrogate (ph) endpoint, helps us to understand that we think we have an active drug. And then some other studies can happen, you know, longer term that tells us more about the effect of the drug clinically.

So when you -- so there are some infectious disease conditions where, you know, the progression is invariable and, you know, unfortunately, I mean, it's, you know, the really bad diseases. And you know, we have used historical controls in those sort of circumstances where we think we've got a situation where, you know, progression will be essentially relentless if you don't have an active drug.

And I think the last time we did something like that was for isavuconazole, which is approved for

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invasive aspergillosis and also for mucormycosis. And we focused in on that -- in that application. You know, it was very helpful to have data form the invasive aspergillosis study. And then you know, we recognize these are different agents, and I mean the agent causing the infection.

But with mucormycosis, we were able to look at patients with hematologic malignancies, a group that we thought would have, essentially, relentless progression if they didn't see an effective antifungal agent. And you know, we looked at that group of patients and saw something that we thought wouldn't have happened absent an effective antifungal drug.

So there are scenarios where such an approach is, I think, informative. There are, you know, many other scenarios where, you know, the outcome and can change tremendously. You know, the variability and outcome may be as large as the treatment effect that you might expect, depending upon who gets in the trial, what their, you know, baseline conditions and comorbidities are. And when you're in that scenario, it can be very difficult to,

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essentially, you know, sort out, you know, what -- whether the drug is having an effect or not.

And you know, we've seen situations, too, where, you know, despite thinking that we understand the factors that impact upon outcomes, you know, the patients that actually end up in a clinical trial do better. And that's not just us, but that's an ICHE (ph) tend that essentially says that, you know, patients that end up in a control group within a historic -- within a clinical trial typically do better than their historical counterparts.

So I mean, that's what makes it really hard, is when there is this variability. If it's lights on, lights off, something that never happens, then historical controls, you know, can be a good and reliable way to do this. If it -- if there's a lot of variability and it's hard to understand all the factors that impact upon that variability, it can be really tough.

DR. REX: Have you ever seen anybody do what David described, which isn't -- it isn't just the last 50 cases with X, but rather, they've been filtered.

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And at least you've looked at them at the level of I think they could have been enrolled in the trial had I been in that hospital at the right time. Have you ever seen that done?

DR. COX: So I don't know that we've seen exactly what David's described. But we have seen people make a fairly valiant effort to pull together historical controls. And you know, it usually -- it -- this is not the way to do it. But usually, it's done sort of after the fact, and it's sort of, you know, where can I go and sort of pick through a collection of patient records and find some patients that I think, you know, could have been enrolled in my trial and trying to get to something similar. And it's -- that is very, very difficult.

So I think, I mean, you know -- and everybody, you know, who I think advises on what you ought to be doing if you're trying to put together an external control will be talking about, you know, trying to be in the same institutions, trying to have the same protocol, trying to do it at a similar time period to get patients that are as comfortable as

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possible so that you're reducing the likelihood that your historical control is not, you know, related -- is not comparable to your patients that you're actually getting your therapeutic.

And we've also heard a couple of times, I think, from our statistical colleagues the idea of having, if at all possible, some concurrent controls, even if the randomization is disproportionate so that you can do some techniques to try and understand who's in the trial and how they might relate to the external controls, too.

So I mean -- so external controls, I think, you know, are useful in certain situations. Understand the characteristics of a particular disease that you're studying. But you also do have to be careful of situations where they may not be, you know, as helpful as you might hope they would be.

DR. REX: Yeah. And Jack (ph) then one made -- once made the observation to me about people with cryptococcal meningitis that got into the early protocols. He said they were unusual because they lived long enough to make it to the NIH. You know,

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and so they were a selected subset.

Marco, do you have any comment?

DR. CAVALERI: Well, I think, yeah, indeed, as Ed said, in the antifungal space, we had a number of cases, isavuconazole as being the last one for us, too. And you know, at the end, we went positive as well for mucormycosis, despite we were not really overenthusiastic about how historical control were put together. So it could have been better, frankly.

Yeah, I think, indeed, there is a lack of this idea of setting up robust external or historical control that could be used for the sake of interpreting, you know, single on (ph) trials. And that is a matter where maybe there is a need to think about what could be the option. And now we can do it better in order to make them useful in a setting like this one.

MR. DANE: I do wonder is whether there's -- I'm not sure this is even feasible. But could you set something off prospectively that? And, yes, under a similar type of trial program that a sponsor would conduct, you have something that runs, you know, maybe

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a bit more like a network so that you -- you're generating data an on ongoing basis. Then it's all under the same protocol. And the prospectives, you've got those issues of comparability still. But at least you're doing it all under the same banner, if you like, rather than going back and trying to do it.

DR. COX: Right. You know, thanks, Aaron.

Yeah, you know, this is -- I mean, we've talked some about this. But the idea of a clinical trial network, I think, is sort of an ideal sandbox to try and work through some of these questions. You know, if you just slightly change, you know, the inclusion-exclusion criteria within a trial, if you change the institutions where the trial is taking place, if the comparator drug changes over time, you know, we may not sort of fully take that into consideration when we're looking at the outcomes of Trial A to Trial B to Trial C.

So it is possible that if you had a clinical trial network this would -- you know, where you've got a protocol that's stable, you're at similar or the same institutions over time, it might give you some

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important insights into what -- you know, what is happening with regards to patient outcomes and whether, you know, I mean, what is the degree of variability. We see the variability. I'm not sure we fully understand it.

And the question is, is could -- I mean, could you, using, you know, those sorts of -- if -- I don't know -- using a network, could you figure that out in a way that, you know, you could convince yourself that things were sufficiently consistent and sufficiently reliable over time that they didn't change. I think it's a good question and one where, you know, data would help us through that. And a clinical trial network could help tremendously.

DR. REX: Lynn?

DR. MARKS: We talked a good bit about what I think -- I don't know what the right term is -- but augmented control arms so that you do have a small randomization number -- let's -- I'll make it up -- 10 to 1. So it's very disproportionate. And then you run in the same time frame, same institution, et cetera, to get that baseline.

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But then you get into that small numbers part because in the -- and you have so much belief that the one that's in the real trial is the real number. So if it deviates in the wrong way from this larger body of data, sometimes, you know, your mind goes to the fact, well, those were just sort of the fake controls and this is the real control and one person in that kind of disproportionate stuff. So I'm not sure it makes you -- it makes a heck of a lot of difference.

Now, if everything goes in the right way, then life's good. And then you have these kind of trials because most of the time we've focused on the non-inferiority downside as opposed to the non-inferiority upside. But then again, since I'm up here, I'll say I have a hard time thinking of that non-inferiority drug because that's not how I was planning on using the drug in the real world to what you guys talked about. I mean, this is something that's on top of something else to make sure that your percent susceptibility or that difficult to treat or that outbreak or that scenario's there rather than

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just I've got something else I'm going to add in.

MR. DANE: So on the augmented control, I don't know if maybe Kert wants to make a comment, but I would agree that in this setting -- so when we -- we tend to look at that when you've got a few hundred patients and then you've still got a reasonable amount and a reasonable amount of precision to compare with your external dataset, whereas here, if you're only talking -- I mean, in that example, it was 12. And if you did a more extreme randomization ratio, it's less. So it seems a lot more difficult to actually do something that formal. Yeah, exactly.

UNIDENTIFIED MALE SPEAKER: John, going back to the estimate that you were saying where we are treating 100 patients in the U.S. and maybe 500 in Europe, I just cannot fit it with some statistics that I've seen. So CDC estimates that there are 51,000 total cases of so the --

DR. REX: Oh, sorry. But wait. I'm sorry.

In D and E, I've drifted -- pseudomonas is definitely more frequent than this. So like, maybe this is acinetobacter. Maybe this is

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stenotrophomonas, you know, something that's even less common. So it's no longer pseudomonas, necessarily.

UNIDENTIFIED MALE SPEAKER: Okay. Okay. So you were not --

DR. REX: Is that --

UNIDENTIFIED MALE SPEAKER: -- talking about pseudomonas.

DR. REX: No, because we know we can get -- we know we got the slightly higher numbers. And so I made this -- and I suppose you could --

UNIDENTIFIED MALE SPEAKER: No, no. I was talking about the scenario --

DR. REX: No, no. You are correct. Pseudomonas is definitely more frequent than that -- but acinetobacter, stenotrophomonas, things of interest.

UNIDENTIFIED MALE SPEAKER: Fine.

DR. REX: Thank you.

UNIDENTIFIED MALE SPEAKER: Bye.

UNIDENTIFIED MALE SPEAKER: Hi. At the risk of going really sideways here, instead --

DR. REX: Well, actually, let me say this is

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the time to go sideways because we're to Scenario F and you're the first up.

What else?

UNIDENTIFIED MALE SPEAKER: Right. So we know some standard drug works, at least to some -- at a level of efficacy that we like, right? Maybe it's meropenem against pseudomonas. It has a certain probability of hitting an effective exposure, does it not? So why not compare for our new drug, new regimen, its probability of hitting those effective exposures? And that's where comparing those exposure distributions, knowing that, for the drug we know, that exposure distribution is tied to an efficacy level that we like. And that's really what we're making our comparison on.

DR. REX: So if I play it back, you're proposing approval on the basis of adequate PK with the definition of adequate being really pretty sophisticated. It's tied into an exposure --

UNIDENTIFIED MALE SPEAKER: But we know that --

DR. REX: -- response curve.

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UNIDENTIFIED MALE SPEAKER: We know that exposure is associated with a certain level of efficacy.

DR. REX: Right. And we -- it's tied into the animal responses, and it's tied into the risk factors and familiarity (ph), you know, and the changes in PK due to underlying diseases.

And so Dr. Cox?

DR. TOMAYKO: That's the animal rule, isn't it? You know, you do the good animal data to show it's an antibiotic. And then you know what the target exposure has to be. And then you show in the target population that you achieve those exposures in a certain percentage of the population. I think that's -- that sounds great. That's what I'm advocating for.

UNIDENTIFIED MALE SPEAKER: It's the human --

DR. TOMAYKO: It's the human version of it, yeah.

DR. COX: So I think --

DR. REX: It's the large animal rule.

DR. COX: So I think, you know, John, when

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you're bringing up -- you know, one of the criteria for the animal rule is when you have the outcome in the animal model. And then what you're trying to do is to, you know, link the exposure from the animal to the exposure in the human. If you look at our animal rule guidance document, it actually recommends, you know, that you try and exceed that exposure with the human exposure that would exceed the animal exposure by some multiple, if at all possible, recognizing that sometimes we run into safety issues.

And I think, Paul -- so what you're describing is -- so you've got -- and I'm going to say you've another carbapenem and you have an idea of what your exposure target is for carbapenem. And you're trying to -- so you've now got another drug from the same class. And you're trying to, essentially, achieve a similar target for this new agent that's also from the same class, if I understood correctly. Is that fair?

UNIDENTIFIED MALE SPEAKER: They could be from the same class or a different class, theoretically.

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DR. COX: If you get to a different class, it gets a little tougher, though, doesn't it, because you don't actually have -- you don't actually know exactly where you're going.

UNIDENTIFIED MALE SPEAKER: Yeah, but you do know that, you know, your chances of curing the pneumonia go up with killing bacteria. So you're picking an exposure threshold target that's associated with a certain --

DR. COX: Okay.

UNIDENTIFIED MALE SPEAKER: -- killing of cells.

DR. COX: Okay. So you're picking the target from other drugs, yeah.

I mean, so I don't know that I would replace what it is that we're talking about here, trying to replace a clinical outcome. But I think what you're describing could be very helpful in deciding, you know, what dose to use. Fair?

UNIDENTIFIED MALE SPEAKER: I'm not saying replace.

DR. COX: Okay.

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UNIDENTIFIED MALE SPEAKER: You've got this study in which you show one at 74 percent in a couple fistfuls of patients and the other at 77. And you're worried that it's -- that there's not enough evidence there.

DR. COX: Yeah.

UNIDENTIFIED MALE SPEAKER: Well, maybe because we know so many other factors cause failures in this disease state that you've all pointed out, right -- their protein status, all the other things that we all know --

DR. COX: Right.

UNIDENTIFIED MALE SPEAKER: -- and you're worried that the new regimen looks a little bit lower than the old regimen, and it's stressing you out. I think the way to not be stressed is to look at the exposures you achieved and are you hitting things you know.

DR. COX: Yeah. So I mean, I think, you know, throughout all the discussions, you know, I think the importance of PK and getting the dose right is, you know, clearly there. I -- some of the

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examples from yesterday I thought were particularly striking and really underscored the importance of doing that.

And I think, you know, to your point of will we still be stressed if the clinical outcome data looks a little bit lower. I think our stress will continue. But I don't think that takes away anything from the importance of, you know, trying to do the best you can with the PK.

DR. REX: Mike?

MIKE: Yeah. So you -- maybe it was covered in Scenario XY, or something, and may -- as on the cutting room floor. But I'm curious. I was trying to think about dose response as a form of control and has been used for some programs. But I was trying to come up with whether or not that's more efficient than using sort of a simultaneous control but perhaps in the setting of the external controls, which I think everyone sort of is feeling is a little bit more doable.

So it -- maybe you could talk a little bit about dose response control, where there we're not

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trying to meet certain margins. Or what are the criteria where in a dose response control are you -- you're not looking for necessarily statistically significant differences between groups? Or are you?

And obviously, we would pick our doses to be informed by PK/PD so we're not unnecessarily exposing patients at risk to sub-therapeutic doses just to squeak out a control group.

DR. COX: Do you want to do this one, John?

DR. REX: Oh, I just -- I was going to suggest we -- my comment is I left dose response out deliberately because I don't tend to see how I can choose two doses, both of which are going to be efficacious, and have them be meaningful different because my general sense is I have to -- doses have to be quite different going (ph). One mg per kg versus five mgs per kg will get really separate exposures. One mg per kg versus one and a half, you know, the --

MIKE: Yeah, maybe like --

DR. REX: And -- sorry. The last thing is the one mg per kg has to be acceptable.

MIKE: Yeah. So let me clarify a little

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bit.
So I think what you're -- what you want to do is you want to be -- there's going to be variability. So what the dose response curve essentially does is it spreads your exposure response out over a greater period -- a greater number of exposures. Obviously, you could have somebody in the high-dose arm be among those patients that had actually the lowest exposures because of variability.
So I think the dose response is, more or less, just sort of spread the field. You'd obviously not be wanting to choose the lowest dose that would be getting you 90 percent of your patients having a sub-therapeutic exposure --
DR. REX: No, I just said that I --
MIKE: -- but it would be --
DR. REX: -- would not be willing to sign on to the one -- to even the one mg per kg having a low target attainment because that sets me up for public shaming. You know, I --
MIKE: Well, I --
DR. REX: -- I'm just not willing to do

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that.
MIKE: I don't think it has to be -- you know, again, I don't think it has to be, you know, low target attainment. As I've -- as we've talked about before, we always -- we pot our doses up to get 100 percent target --
DR. REX: Right.
MIKE: -- attainment. So --
DR. REX: But then you're --
MIKE: So I think you could --
DR. REX: -- Paul and -- but Paul -- what Paul said was that I'm picking them both to be efficacious. I mean, I -- it's -- you're asking for both sides of this simultaneously.
MIKE: But again, the objective of trying to get, you know, information about safety as well as efficacy in that population having dose response or exposure response as the ultimate analysis plan, that would do that compared to a simultaneous external control group. What are the thinking about dose response or exposure responses in control?
DR. TOMAYKO: Mike, can I just ask a

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different way? Because yesterday, Paul presented a number of examples. And I think some of them were related to pseudomonas -- the doripenem (ph) data, the Ceftobiprole data, maybe some Tigecycline data. And if you do a pharmacometric analysis and you see that when you achieve exposure, if you have those failures already and you could make an argument that those failures are dose-related, well, it just basically says I didn't have an antibiotic here.
So you can get a pretty good estimate of what it's like not to treat one of these patients. I mean, is that not correct, Paul? I mean, do you --
DR. AMBROSE: Yeah, I think what you're -- what you may be referring to is when you model the exposure response and you can basically use the intercept of the no exposure as kind of your equivalent placebo by extrapolating back to that. That then allows you to estimate the magnitude of the treatment effect.
UNIDENTIFIED MALE SPEAKER: And between what Paul -- I guess I'm taking it one step further. He showed it -- made the point in a number of different

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programs. And FDA probably has a number of different databases where maybe we could even fortify that learning. And that could be useful information, and it may be better than an external control.
UNIDENTIFIED MALE SPEAKER Yeah. Well, I think you use -- you may be able to use the intercept if you're doing that intercept pharmacometric method to be able to compare that to the external control data just to sort of see where you are in terms of your treatment effect.
DR. REX: Ed. Sorry. We kind have been going around.
DR. COX: Yeah. So I think our experience has been, you know, similar to the debate that you and John were having, which is, you know, most folks going into the serious infection, you know, the dose that they pick is going to be one that's going to be ideally on the flat part of the curve. So I think that's one part of it. I understand you're asking about a second part.
So the -- you know, the idea of doing a second dose, I mean, and most -- it seems like most

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people would be shooting for that flat part of the curve where the likelihood of showing it -- an effect is going to be, you know, not so great.

Now, if there's equipoise and you pick two doses and you get the degree of variability that Paul shows with your low dose, that's -- you know, there's equipoise for doing that and you happen to find a difference there for those two dose groups, then I mean, you've got something that, you know, suggests -- I mean, you've got, essentially, a superiority design where you've shown a clear effect.

Obviously, with serious diseases, you want to have a DSMB in place. I mean, you couldn't -- I don't think -- you couldn't plan to do this, is what I'm thinking. You can't plan to give patients with serious infections sub-therapeutic doses.

So is that -- that's part one of your question, I think, right?

UNIDENTIFIED MALE SPEAKER: I think that's right. I mean, I think that what Paul's data showed vividly there --

DR. COX: Yeah.

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UNIDENTIFIED MALE SPEAKER: -- in the best laid plans --

DR. COX: Right.

UNIDENTIFIED MALE SPEAKER: -- there are still going to be patients who have low exposures and/or higher (inaudible - off mic) ranges.

DR. COX: Right.

UNIDENTIFIED MALE SPEAKER: So unless you're doing a concentration control trial because you're -- that's the only way that you're ever going to prevent that.

DR. COX: Right. And you know, it's hard because, as you start to learn that, you have to push the dose because you have this concern that with this variability you're going to have some patients that are sub-therapeutic. It becomes hard not to try and push the dose to get to something that's on the flat part of the curve, you know, to, essentially, create a scenario where the likelihood of showing this difference is going to decrease to some extent.

Is that fair? Have I answered your question? Or was there another part to it? I

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couldn't tell if you were getting to sort of, you know, exposure response, what happens in the trial and trying to sort through that. Is that your other question?

UNIDENTIFIED MALE SPEAKER: Yeah, I think I --

DR. COX: Okay.

UNIDENTIFIED MALE SPEAKER: But I think it's more of --

DR. COX: And John, you're going to have to cut us off in a moment because I think some other folks might want to ask some questions.

UNIDENTIFIED MALE SPEAKER: -- more of like, you know, can we use -- I think Paul's getting at this, was the exposure response --

UNIDENTIFIED MALE SPEAKER: Yeah.

UNIDENTIFIED MALE SPEAKER: -- relationship that would come as part of a dose ranging trial. I absolutely agree that, you know, you're not going to try and sign this. We all have limitations. I mean, I haven't seen very many 10-gram doses of carbapenems, although I know a 10-gram dose of carbapenem would

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clearly get concentrations where we need it. So --

DR. COX: Right.

UNIDENTIFIED MALE SPEAKER: -- there's always limitations that you're always going to have on these things.

But I think that's the nature of the trials, are going to give you an exposure response curve. And therefore, by modeling that effect, is that evidence of a treatment effect, therefore, when reflected against external controls, that give you evidence of efficacy?

DR. COX: Right. So --

UNIDENTIFIED MALE SPEAKER: And so --

DR. COX: And you said dose ranging trial, which again makes me think you're talking about going in with different doses.

UNIDENTIFIED MALE SPEAKER: Yeah. I --

DR. COX: Okay.

UNIDENTIFIED MALE SPEAKER: I would say that we would pick doses that --

DR. COX: Yeah.

UNIDENTIFIED MALE SPEAKER: -- are above,

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based upon the Phase 1 data that are above the expected therapeutic effect. One, you know, is at therapeutic effect and then some multiple of that, knowing that we're going to have variability and exposures in those patients and in ELF if we're doing a HABP/VABP trial. And therefore, we would de-convolute that as part of the analysis plan and then be able to show then those exposure response or evidence of an --

DR. REX: So to play it back, you might deliberately use a range of doses in order to ensure that you got a reasonably broad range of actual exposures and then hope that you have enough cases to fill in some of the cells at the lower end of the exposure, which gets into how many of those you've got to have, which might -- makes to be a reasonably good-sized program, which maybe you could do something else.

So I -- good. So we're -- so --

DR. COX: Maybe just one last quick comment and then I'll stop.

It's just the issue of -- I mean, if you

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were, you know, allocating patients to different dose groups, then you've got comparisons between dose groups and you're trying to show superiority of one group to the other. If the exposures happen, you know, and you're trying to look at the exposures that actually happen to patients compared to outcome. You know, there's always the question of is the reason that the exposure is low in a particular patient also something that's associated with the poor outcome. And that's the difficult question.

DR. REX: The exposure --

DR. COX: So the de-convolution is very difficult.

DR. REX: So we're going to move on.

UNIDENTIFIED MALE SPEAKER: We've heard that argument before, and there's not a lot of evidence that have that because you're going to be able to de-convolute that. There is --

DR. COX: So you -- so --

UNIDENTIFIED MALE SPEAKER: So you're saying that are there patients that are at greater risk for a bad outcome that just have goofy pharmacokinetics.

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DR. COX: Yeah. I mean, are the patients that, you know, are hyper-metabolizers that clear the drug more quickly? Are there -- is that somehow associated with a worse outcome?

UNIDENTIFIED MALE SPEAKER: Yeah, biologically.

DR. COX: Yeah, yeah, yeah.

DR. REX: Because the exposure is --

DR. COX: Yeah, and you say there's no data for that.

UNIDENTIFIED MALE SPEAKER: Not really --

DR. COX: Okay.

UNIDENTIFIED MALE SPEAKER: But --

DR. REX: Yes, ma'am?

DR. COX: All right. So a topic for a longer discussion.

DR. REX: All right. So I've accumulated on my list for Scenario F things like think about exposure response, the Shlaes case control model. And I've also jotted down Bayesian prior.

So yes, ma'am? On to you.

UNIDENTIFIED FEMALE SPEAKER: Okay. So the

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difference between X-1 and some of the other things that we're looking at to treat multidrug-resistant organisms is that X-1 and a couple of other things that some of us are more familiar with don't have any effect on other organisms. And that's makes the challenge because if you've got something like isavuconazole, you have got clinical data and you've got something to base your efficacy on.

DR. REX: Right.

UNIDENTIFIED FEMALE SPEAKER: If you have new aminoglycosides, if you have new versions of classes which are expanding, they are completely different from what we're looking at with X-1.

Now, what I am going to suggest, which might be that we could look at the sort of thing with -- that we did with isavuconazole where we looked at Fungiscope, which is a registry of rare fungus diseases where we got the data from that we used for a lot of the case controls.

And I'm just going to ask if -- particularly from Helen -- whether actually we ought to be keeping a registry of these difficult cases like the first

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case you presented because that's exactly what we do with things like Fungiscope. We collect these cases. We track them. We look at the outcome. Obviously, with fungal infections like mucor, they're much longer conditions.

But perhaps that's what we should be doing and not trying to get our safety and clinical data separately in more conventional trials for those programs and look at using external controls from the data that, perhaps, those kind of registries could be set up so that we're not trying to push the envelope and spend an awful lot of money looking at the edges of very good drugs in other ways but actually have been expanded a little.

For those things that are -- have no other activity, I think we should be going to John looking at what they bring in addition to what is there already, which is the adjunctive elements of those projects. So I kind of think we should be looking at this rather differently, looking at what we're trying to achieve in terms of the clinical things with the established products that we can get data on other

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areas. And for those that are completely novel, look at the adjunctive programs in a completely different way because we are looking there. I think we can't get away from superiority studies against placebo and normal control because we are trying to do something different to support those patients.

So I would advocate the registry element if Helen thinks that's viable.

DR. REX: A long-term registry after the fashion of Fungiscope. Okay.

MR. DANE: So I suppose my only question comes back to the external control again. Is it comparable or not? So and it comes back to whether you just (ph) pay a big benefit over that external group, I think.

DR. BOUCHER: You know, there's been a lot of discussion over the years. So Ed and I go back to the voriconazole days and caspofungin, which was approved on 61 cases with historical control. So you know, we've come full circle in some ways.

But in discussions both in the fungal space and the antibiotic space, there's been a lot of, I

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would say, healthy debate about the benefit of registries. I mean, I think in a lot of ways, I mean, academic. You know, I love to learn about these thing -- you know, there's a lot of upside to learning about the natural history of these diseases. And I think groups in the IMI and other places are taking little pieces of this in the ARLG here in the U.S.

But the consensus that I've heard has been that a registry, per se, wouldn't meet the criteria that we need for the external control, necessarily. So that's been part of the reason for the lack of enthusiasm in funding. It's very expensive.

So the question would come down to, well, who pays for this. The NIH? You know, it gets to -- the sponsor has an interest for his or her compound for that period of time, but not in perpetuity.

DR. TOMAYKO: So Helen, you mentioned IMI. And before I left GSK, I was working with Jesus Rodriguez-Bano. And I've presented this before. And IMI was sponsoring and designing and, I presume, still executing a study that was -- it was looking at a very sophisticated way of collecting the natural history

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data of carbapenem resistance in Europe.

And my hope was, is that that could be, you know, initiated and completed before the natural history or the natural -- the management changes dramatically. I'm sure they'll figure out ways of incorporating what -- what's changed from polymyxin-based therapies to Avycaz when it becomes available and some of the other products we've heard of.

But I think combining all of these things, I mean, thinking Bayesian. You know, if you have the exposure response data that Paul's already presented, you know what, you know, a placebo effect might look like from a pharmacometric approach with some of this stuff. The data -- the understanding probably gets strong and stronger. And then maybe it helps us if the treatment effect, as Aaron said, is big enough, which we would think it might be with an antibiotic -- that was what makes adjunctive work so hard -- you know, maybe you could get comfortable with small datasets if you could start to believe what all this other data is telling you.

MR. DANE: Yeah, it might help you

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understand the area rather than be a direct comparator. That's what I could imagine. So you -- yeah, you understand your risk factors and things like that. It's that comparison, that direct comparison, that becomes more challenging.

DR. REX: Kenneth?

Sorry. Did you have a follow-up? No, you didn't. Okay.

Kenneth?

MR. HILLIN: I think one of the things that's become very clear to me is that, for these types of drugs, you won't have evidence of -- substantial evidence of safety and efficacy for these drugs for the purposes of approval. And I have lots of questions about the animal model and even how biologics and small molecules might behave differently in those models which are intrinsically human.

So if we can't get to the stage where we have substantial evidence of safety and efficacy, is there a different way to get these drugs approved and available so that we can study them further? In the oncology world and in many other places, you have, for

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example -- it would be different from this -- but accelerated approval. And I lived through the pain of Avastin being approved for breast cancer based on PFS and then having to be -- that label be withdrawn for breast cancer. So I know it doesn't always work out well.

But I wonder if there would be a way to have a two-step approval based on a minimal dataset. And that could be defined relatively well. It could, you know, include preclinical as well as clinical data so you actually have some safety data. And then there will be a commitment. And I think this in the world of anti-infectives would have to be in conjunction with the government in some ways. So perhaps that clinical trial network actually continues to help to study the drug beyond then. And then a further dataset would be brought back to the FDA for, perhaps, a full approval.

So it would be a two-stage process. And you would put in place restrictions both in terms of the label and also the use, perhaps even the types of centers. Maybe the CDC, based on the monitoring, says

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it's actually only these centers that would be eligible for this drug based on the resistance levels.

You know, I don't exactly know how that would work, but perhaps a two-stage approval process because we can't get to substantial evidence of safety and efficacy as part of the statute.

DR. REX: So both Ed and Marco should comment.

DR. COX: Yeah. So you know, the accelerated approval still is substantial evidence of efficacy, but it's based on the surrogate marker. So and I see, Kenneth, I mean, you're already recognizing that.

So you know, and usually, it's used in situations where the clinical outcome for the disease is sometime removed. So you may see something like, you know, a reduction in tumor size or, you know, a decrease in HIV viral load or hepatitis C viral load, whatever the case may be. And you know, some of these surrogates are, you know, very, very well correlated with the clinical outcome that may happen many years down the road.

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You want to amend your question, I see.

MR. HILLIN: Well, I was actually -- we did -- at Genentech, we did lots of analysis about the correlation between PFS and overall survival. And actually, I think killing the pathogen is actually a much better surrogate than reduction and shrinkage of a tumor, so.

AUDIENCE MEMBER: (inaudible - off mic).

DR. COX: Which is? We'll give Marco a chance to talk in just a minute.

AUDIENCE MEMBER: (inaudible - off mic).

DR. COX: Sorry?

MR. HILLIN: We're choosing a way what is the standard for anti-infectives in Europe, which is test of cure, which is basically looking at the microbiological response, which could be -

DR. COX: Most tests of cures are a clinical response. The patient's better.

AUDIENCE MEMBER: (inaudible - off mic).

DR. COX: It's a clinical response. Yeah, yeah. Okay.

So just to clarify that issue, so usually,

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with accelerated approval, you're looking at a surrogate. And oftentimes, the diseases that you're using those surrogates in are outcomes that have been some time removed.

So if you think about what happens in an acute bacterial disease, you may have, you know, a particular biomarker that you're looking at. But you also usually have the clinical outcome staring you right in the face before you. And you don't -- I mean, you know, there's not necessarily a one-to-one correlation with these two events. And so you end up in the somewhat awkward scenario of saying I believe the biomarker, but I don't believe the clinical outcome.

And I know it's tough because there are patients, obviously, that succumb to their underlying illness. And the issue becomes it's difficult to understand, you know, in whom that's true and in whom that's not true. So it creates a little bit of an issue.

So I'm not -- you know, so that's why we have not -- you know, in acute bacterial diseases

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where you achieve the clinical outcome within a -- you know, within a couple of weeks or, you know, you're looking at Day 28 mortality, we haven't looked so much at, you know, clearance of biomarkers or, you know, a microbiologic endpoints alone because if there is a discord and you're going to let the biomarker trump the clinical outcome, it's a little bit of a -- you know, it's a little bit of an odd scenario in some ways.

MR. HILLIN: No, thanks. And I appreciate a lot of that. I actually wasn't advocating for accelerated group. It would be a new mechanism because accelerated approval is absolutely on a surrogate, as you spoke about.

But in some ways, if you think about it, why do we approve things for accelerated approval when you could actually just wait until the outcomes mature for overall survival, wait two years, find out the outcome? It's because of the feeling in oncology of the urgency to have these new therapies be made available for patients who have few options. And we're in the scenario where we have patients, as Helen

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so, I think, described it very in a sort of heartbreaking way, the patients that she sees.

And so is there a way to have options available in a controlled way until such time as we do gather more data in the future. That was my point. Could we come up with a new way, not called accelerated approval, but specific for anti-bacterials targeting pathogens, particularly from multidrug resistance.

DR. COX: Right. So it sounds like, you know -- I mean, everybody feels the urgency. That's why we're trying to figure out ways to do this. There's no question about that. It sounds like what you're almost describing -- and David Shlaes I see back there. We talked about this not too long ago. And he brought up the idea many years ago and, you know, I -- you know, the idea of some sort of gray approval or some sort of conditional approval.

And you know, right now, I mean, the options that we have are sort of standard, full approval, accelerated approval using a surrogate marker, availability under IND, you know, usually not the

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scenario here that we're talking about, but, you know, in the setting of, you know, a national emergency -- we've got emergency use authorization. But that really doesn't seem to fit here either.

So could somebody do this? Yeah, somebody could do this, I mean, you know, change the way you look at approvals and such. And I think that's what you're getting at. You're getting at more sort of a conditional sort of situation.

And it -- given that's what you're asking about, maybe Marco wants to make some comments.

DR. CAVALERI: Yeah. Indeed, as I explained yesterday, we have tools in Europe for this early access regulatory route. And of course, the condition marginalization (ph) is the lead one, indeed, where we stayed, that the benefit of having other drug available earlier outweighs any risk associated with the uncertainties that will derive from the data that will be initially submitted. So that is pretty clear and is a pathway that could be used.

Of course, it is very important to see what can come next because the condition of marginalization

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is it's quite serious, you know, requiring that post-approval specific obligation are committed to and that dataset are provided. And if we are in a situation that then these data are not provided or delayed or even come out with negative result, that is a big problem and could put us in a very difficult situation. But of course, it's a tool that is not being used for antibacterial so far. And maybe it's the time to think about whether there are situation for which it can be used.

The alternative, of course, will be the exceptional circumstances which may be fitting into situation for which the new drug is supposed to be working just in rare populations. So why not also considering that? And on top of that, also, as said, we have the new pharmaco-regional (ph) legislation which allows us to pose even in the context of a full marginalization to the sponsor to conduct post-authorization safety or efficacy study. And I think the receftor (ph) is a good case because, you know, we received recently positive opinion from the CHMP. And there was a post-authorization efficacy study imposed,

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which essentially is the (inaudible) nosocomial pneumonia study.

So we have a lot of tools to look into having more data come in the post-authorization phase. And we should look seriously about how can we improve these mechanisms so that new drugs that have a potential of addressing on a need (ph) can reach patient needs earlier with enough certainty about what it can do, but them supplement it after authorization (ph) with other data that could bring us to a full understanding of the benefit risk.

And registries, of course, are an important area. And I think they should be disease or pathogen registries. And it would be very important to think about a mechanism worldwide, or at least in the U.S. and in Europe, about setting up this registry because this will be extremely useful information for everybody, including sponsors.

DR. REX: So we're going to try to wrap up in about the next 15 minutes. And before we leave this one, everybody should look up marketing authorizations under exceptional circumstances. And

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then put in the word V -- V as in Victor, O-S-S-E-N. It's a man's name -- Vander (ph) Vossen. It's a lovely paper about four drugs that got approved under exceptional circumstances and about how miserably they did in the marketplace. And that's the story.

So John and then Dave.

UNIDENTIFIED MALE SPEAKER: So I guess it was kind of getting at my question. But I was going to ask about the role of an expanded access program and as far as generation of data and what that could ultimately -- how that can be looked at.

And secondly, how the -- potentially the clinical trials network could be involved because know -- so Helen, when I looked at your -- when I think of your patients, I think of the patient that you sent to hospice because you had nothing else available. And if there was something that was being developed clinically, if there -- if you could utilize that in whatever outcome and how that could be utilized because I think back to, putting back my clinical hat on, when we were developing these problems when you had a patient like that, what you did was go around

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fishing to all these different pharmaceutical companies that were doing something and trying to find someone who had something to be able to give this patient the chance.

If there was an opportunity to go to a network of people who are -- all knew all the different studies that were ongoing and if you could figure out a way to get that patient tapped in, generate some data but then, most importantly, how that data could be utilized.

DR. REX: Well, I have lived that. Expanded access programs -- you can't ask for clinical data as a condition of receiving the drug. You just can't. And so you end up -- and the problem then is also drug supply and having to give away drug supply that you need to actually run your Phase III program. It's less useful than you think. And it's really better to have an open label study that you stick people in so you can gather data.

UNIDENTIFIED MALE SPEAKER: Yeah, but the problem, I guess, becomes, is that if it's an open label study in an institution, what happens is you get

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the phone call from the hospital that's not participating in your study.

DR. REX: So we put a study kit in a box, and we hired a company called Clinigen to have depots around the world so that we can actually do that in 24 to 48 hours, any country in the world.

So Dave?

DR. COX: To your second point, too, about a clinical trial network, I mean, it may -- I think it -- I would expect it would help. And I think it would push forth the threshold of what it is that is achievable. And you would be able to study things that, you know, were on the cusp previously. And it -- you know, it may also be a mechanism, too, if there's the need to do studies after a drug is approved to be able to further understand how the drug is performing.

So and I agree completely --

DR. REX: Yeah.

DR. COX: -- with John on the expanded access part. It's -- you know, it's hard to do much of anything there. But the clinical trial network is

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promising.

DR. REX: Yeah. That's actually one of my summary points, is that if you have this warm base network running, you drop a diagnostic in and you start playing go fish for the cases of pseudomonas. Then it's efficient to be looking for pseudomonas at all these sites. And the investigators have other things to do.

Dave?

DAVID: I just wanted to go back to this idea of conditional approval and the differences between Europe and the U.S. and see if there are ways we could think about this.

So along the lines of what Marco was suggesting, actually, so going back to that conversation that we had, which was 15 years ago now, I think, but I think we talk -- more recently talking about this, the idea would be that you would do a full approval based on small datasets. You would require some post-market studies. But then you would pre-specify some review, which could be an advisory committee review, or something. I mean, you can

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always ask for more data and another review.

So that would be one -- I would think one way maybe you could ask. I guess the question is would that be one way. Is that an option for you?

And then I was going to ask -- the other issue is if one went to Europe and got a conditional approval in Europe, gathered more data, then that would bolster the dataset you could then present to the FDA, I would think. So --

DR. COX: So maybe just to an overall comment, which is, you know, most of the time what we end up doing in the U.S. pretty much mirrors what happens in Europe. And you know, Marco was talking about ceftazidime and avibactam and, you know, similar circumstances, similar approaches, similar outcomes for that application here.

You know, the reason that we're talking through all this today and trying to figure out how to handle these difficult situations is a recognition that it's going to be hard to get much data here. And you know, we can look at substantial evidence in terms of, you know, the degree of unmet need, what we can

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actually, you know, accrue.

And so I think that there are ways to work, you know, with what we are -- you know, with what we have, the tools, you know, to be able to evaluate a product, recognizing the limitations of what's achievable.

And then, you know, I think, David, you're asking about -- you know, and we've talked some about how a drug might be utilized. There may be some sort of program about its availability and a recognition for the need for additional data, which can be done through post-marketing commitments, post-marketing requirements.

So there are ways to gather additional data and -- you know, after a drug is approved for its initial indication. And it's -- you know, I mean, I'm -- you guys already know this because you're the ones doing it for the most part. And that is, is that, you know, oftentimes, a drug will get an initial indication, but further study will follow to further understand the therapeutic role of the drug, whether it be in other indications.

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And with regards to opportunities to look at a drug at some later point in time, you know, have an advisory committee discussion, I mean, sure. I mean, those things could be an option. I mean, obviously, once a drug is out there and it's approved, you know, it is an approved agent. It can be used. And you know, I think Kenneth, who's now left was talking some about, you know, some of the experiences with Avastin. So we won't get into the -- those situations.

But you know, the hope is, is that, you know, if a drug gets out there, there's further study, it will help to further characterize its safety and efficacy. We hope that everything looks good. And you know, the usual scenario, at least in the antibiotics base, has been when a drug -- when the new data becomes available about an indication or an agent that, you know, has safety problems that are, you know, significant or major or significant efficacy issues are uncovered in a subsequent study, usually, that leads to either that indication going away or that drug going away because there's mutual recognition that there's a problem here and it's not

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an appropriate agent for being out there, so.

DR. REX: All right. So I've got six things that I'd like to offer as a summary of stuff I've learned today. And then I'd like to turn it over to Ed to talk about what's kind of the next step in this conversation.

So actually, first, is thanks to all of you for participating in this. We had no idea how this was going to work out. The fact that you've all been so energized and bring so many ideas, I'm really grateful for it.

So the first thing I learned is that all approaches that we've discussed are flawed, including the approach of not having an approach. And that's actually a really important thing to say, is that it -- that not having an approach is as flawed as everything else. And actually, it could hurt us over time. But you know, that's -- sometimes you have to point stuff out like that to make it clear why we have to make some other tradeoffs.

The second thing I've learned is that everything is going to be based on having fabulous

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pharmacology and PK understanding and that you're just going to have to presume that you're going to have to do a lot more work there than at other times in the past.

The third thing is that a clinical trial network doing ordinary studies could be the foundation that enables us to study less common things. So I could fully imagine running a HABP/VABP clinical trial network, having a diagnostic running for acinetobacter. And it's not efficient to search for those rare cases of acinetobacter and put them into a clinical program that could accrue with reasonable efficiency. And I think it's -- suggest to me it's possible.

The fourth thing I've learned is there's no easy way out of this. The animal rule is really -- you look at D and E, and you go, wow, that would be a tough sell. And the open labels with external or historical controls or external contemporaneous controls, you know, that, too, causes a great sucking in of breath and is not satisfactory. You know, it's -- somehow we have to get at least a little clinical

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data.

Number five is we need to validate ertapenem. Somebody needs to help me figure out how to do that.

And number six is we have got to get the pool incentives working so that people will pay for these things as fire extinguishers because paying for them on a per-use basis, that's going to be $100,000 a course in order to make it make sense. And that's not going to fly.

So those are my six quick observations from today.

So again, thanks to all of you for your participation.

Ed?

DR. COX: Thanks, John.

And thanks to everybody who joined us. And you know, we really do appreciate, you know, the continued attention to development in this area. We think it's an important area. There's patient needs out there that need to be met currently, and we expect that will continue to be the case in the future, just

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given what we know about microbes and their ability to evade our therapeutics. So many thanks.

Many thanks, too, to all the panelists who gave up their time both before the meeting and during the meeting and to the many, many people who made the meeting possible.

In particular, I want to thank Sonita (ph), too, who also helped us tremendously with our workshop and getting it together.

You know, this is a difficult problem. I mean, the easy problems we don't bring to you because we can solve those. So we bring you the difficult ones because we're having, you know, significant challenges we -- as we work through them.

I -- somebody asked me yesterday what did I think about the workshop. And I said I thought it was going to be good, but it exceeded my expectations. And I find the same here today, too. I mean, these are difficult discussions, and I appreciate everybody's willingness to express their opinions and to, you know, offer suggestions and ideas.

We're all working through this, you know, at

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this present time. So not everything has been completely figured out. But the willingness to sort of talk about things I think helped us to move the field forward.

You know, this is clearly an important area of development. You know, there are folks out there with compounds. The ability to not destroy the -- you know, the normal flora of the GI tract and the consequences that can result thereafter seems like, you know, a very important therapeutic area to try and explore and develop products.

You know, we -- this is really sort of the first real public discussion we've had about these, you know, more narrow-spectrum drugs, you know, drugs targeting a single species. And clearly, you know, our goal here is to get to a pathway so that there is a pathway for development. And we recognize, too, that the problem is, you know, not so much in areas where -- you know, the example I used in my slides, staph aureus and skin infections -- it's typically for gram-negative rods and more serious infections like HABP/VABP, complicated -- abdominal-complicated UTI.

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So you know, we're committed to continue to work on this to get to the point of, you know, having a pathway and trying to figure out exactly how this will work. And you know, some of this will need to continue to be worked out because we had some discussions about how would such a product be available. How do people see this product being used clinically?

And I think it's important that we also think about, you know, how the product would be available -- you know, restrictions for use, those sorts of things, which seem commensurate with a product that this degree of uncertainty, which is considerable but also is some way to essentially have such products have a pathway for developing.

And clearly, you know, as we work through the science, I mean, if the -- and I'm sure all of my fellow panelists are somewhat tired and probably more tired -- humbled by the science and what the biology continues to teach us day to day as we continue to work through these difficult problems.

So I want to thank everybody. And we will

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continue to work on this. If you have a product and you're targeting something, you know, like, you know, a species that occurs rarely, please do come in and talk to us. The particular cases in hand help us to sort of work through these situations.

You know, we will continue to try and, you know, have discussions within our group and look forward, perhaps to additional public meetings and/or, you know, putting out, you know, pathways on how you might approach this situation because there clearly is a need. And to the extent that we can get to, you know, approaches that have been, you know, described and articulated, I think that's the best situation for everybody. It helps everybody to sort of know where they're going.

So thank you very much for participating in the challenging discussion that we've had over the last day and the day prior.

And with that, any final words, John? Or -- all right.

We will close the meeting. And thank you. And we wish you all safe travels back to home and look

forward to seeing everybody again sometime soon.

So thank you.

(Proceedings concluded at 3:15 p.m.)

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I, Michael Farkas, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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07/27/2016 Karynn Willman

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