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2   MEETING

3   OF

4   Public Workshop - Facilitating Antibacterial Drug

5   Development for Patients with Unmet Need and

6   Developing Antibacterial Drugs That Target a Single

7   Species

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

9   Tuesday, July 19, 2016

10   8:30 a.m.

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13   Food and Drug Administration

14   White Oak Campus

15   10903 New Hampshire Avenue, Great Room

16   Silver Spring, MD 20993

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1   P R O C E E D I N G S

2   DR. COX: All right. Good morning

3   everybody, and welcome to Day 2 of our Public Workshop

4   series here. It's quiet and it looks like mostly

5   everybody sat down. It's 8:30, so I think it's time

6   to go. So we're very glad to see folks back here for

7   Day 2.

8   Today is a slightly different topic, perhaps

9   a little bit more challenging than what we even

10   discussed yesterday, and I expect we'll have a fairly

11   free-flowing discussion because this is such a

12   challenging area. I will be very interested to see

13   what folks' ideas are on this topic.

14   We'll be talking about developing

15   antibacterial drugs that target a single species. And

16   as I mentioned yesterday this is a workshop, so it

17   really is just an opportunity for discussion. It's

18   not one to gain consensus. It's not an advisory

19   committee, but that also should allow folks to feel

20   comfortable to, you know, discuss the issue here and

21   try to work through some of the scientific challenges

22   we face.

1   There's conflict of interest disclosures. I

2   believe they're on the agenda or at the table out

3   front. So if folks are interested in seeing those,

4   they are available.

5   And we also in the afternoon will provide an

6   open time for public comment. We wanted to reserve

7   some time for anyone who wants to make any either

8   prepared remarks or statements at that point in time.

9   I think we do that in the afternoon, if I remember

10 correctly. I'll bring the agenda up here in just a

11 minute.

12   Throughout the course of the day, too, we

13 have the microphones. And just like yesterday, if

14 folks want to get up, make comments, ask questions

15 please feel free to do so and when recognized by the -

16 - either myself or Dr. Rex. We'll be moderating

17 today's sessions.

18   And I thought what we'd do today would be to

19 start out with panel introductions so you know who's

20 up here, and I think we'll start on the far side with

21 Aaron and then work towards John.

22   MR. DANE: Hi. Aaron Dane, Statistical

1 Consultant.

2   DR. BOUCHER: Helen Boucher, Infectious

3 disease, Tufts.

4   DR. TOMAYKO: John Tomayko. I'm an

5 infectious disease physician, work for Spero

6 Therapeutics as their chief medical officer.

7   DR. BORIO: Lu Borio, FDA Acting Chief

8 Scientist.

9   DR. CAVALERI: Marco Cavaleri, European

10 Medicine Agency.

11   DR. NAMBIAR: Sumathi Nambiar, Director of

12 Division of Anti-Infective Products, CDER, FDA.

13   DR. REX: John Rex, Internal Medicine and

14 Infectious Diseases, AstraZeneca.

15   DR. COX: All right. Great. Thanks to our

16 panelists. I was just mentioning, you know, to folks.

17 I mean, there's -- this day took a fair bit of

18 preparation in preparing the case, and hopefully you

19 all had a chance to study it last night. And it was a

20 lot of work to get to something that seemed to be, you

21 know, really as spot on as we could possibly make it

22 in sort of a simulated case.

1   So for today, we'll have first an

2   introduction of the case. Peter Kim will walk through

3   some of the slides. And then we'll hear from a series

4   of different folks representing academia, industry,

5   FDA and EMA provide some perspective on the case that

6   we're presenting. And the case will be a particularly

7   development issue for a drug that targets a single

8   species.

9   We'll also have time for questions, and then

10 John Rex will go into more detail. And we'll sort

11 walk through and sort of unfold the case over time and

12 welcome folks' input during that.

13   And you know, this is an area where there is

14 interest. There is -- you know, there are compounds

15 out there that folks are trying to develop, and I

16 think if it's a compound that's targeting staph aureus

17 and the goal is to see how it works in treating

18 patients with staph aureus skin infections that's

19 probably feasible, but if you move to a gram-negative

20 rod that infrequently causes any variety of serious

21 infections, whether it be HABP/VABP, complicated

22 intra-abdominal, complicated UTI, it becomes much more

1   challenging much quickly -- much more quickly.

2   And that's really the case that we'll be

3   focusing on today. So just for clarity purposes,

4   we're talking about a drug that is only active against

5   a single species. So this is not a choice that you're

6   only going to develop it for a single species. This

7   is because the drug really is only active against that

8   single species, and you're looking to develop a drug

9   in a serious infection.

10   Rapid diagnostics -- and we talked about

11   this some yesterday -- could be very important here,

12   not only for identifying patients for a clinical

13   trial, but also for how the drug might be used out

14   there in the real world should a drug, you know, get

15   out there and be available to clinicians treating

16   patients.

17   As I mentioned, there are compounds and, you

18   know, at various different public meetings over the

19   last so many months, whether it be ASM, the Barn

20   meeting, another bio, I mean, people have talked about

21   these compounds that are really only active against a

22   single species, and they're interested in developing

1   such drugs.

2   You know, one of the ideas here, too, is

3   that if you have a drug that is only active against a

4   single species, maybe it will have less of an effect

5   on your GI normal flora. And, you know, the normal

6   flora that we have are very important to us and

7   prevent, you know, colonization with other less

8   favorable organisms, such as either those that have

9   resistance, fungal colonization of the gut and then C.

10   diff colitis.

11   So the hope is that if you can target more

12   narrowly maybe you can avoid some of these problems.

13   And you know, how a drug would be used in clinical

14   practice is, you know, still, I think, a challenging

15   question, but we hope it's a question that we can get

16   to.

17   And what I mean by that is that oftentimes

18   therapy for antibacterial diseases is empiric and

19   you're targeting a range of pathogens that are likely.

20   And you know, with a narrower spectrum agent, you

21   know, how that will figure into the paradigm I think

22   is still something that needs to be worked out. Rapid

 1   diagnostic certainly can help there, but I think we

 2   look forward to trying to solve that challenge if we

 3   get there. I hope we do.

 4   I won't say too much about this slide but

 5   talked about this some yesterday. And that is, you

 6   know, disease characteristics for serious bacterial

 7   diseases make them particularly challenging to study.

 8   We talked yesterday about, you know, diagnostic

 9   uncertainty, the urgency, you know, the start -- the

10   need to start therapy, that you really don't know who

11   these patients are. They can show up at any hospital

12   at any point in time, which can make it really

13   difficult to actually conduct a study.

14   And here, we're sort of taking it even one

15   step further. Now we're looking at a particular

16   species that makes this, you know, even more difficult

17   to identify a patient for whom the test agent is

18   likely to be -- you know, where you can evaluate the

19   test agent. If you're only looking at pseudomonas

20   aeruginosa, you've sort of cut down your set of

21   patients in whom you can study the drug even further.

22   So this brings us to the question of what do

1   you when the species of interest is infrequent. So

2   you know, it becomes, in essence, sort of a numbers

3   game on the human clinical trials side. You'll -- if

4   you have fewer patients, you just simply can't enroll

5   them. You can't find them. You'll probably end up

6   with less precise estimates of efficacy and greater

7   uncertainty around, you know, what you know about the

8   drug. That's -- you simply have less data. And so

9   you may not really be in a situation to practically be

10   able to achieve the usual statistical conventions that

11   you would expect for a clinical trial.

12   And this is particularly challenging where

13   the outcomes for serious acute bacterial diseases are

14   variable. And you know, we know some of the factors,

15   but I don't think we know them all. And we seek, you

16   know, cure rates, or success rates that can vary, you

17   know, by plus or minus 20 percent or more depending

18   upon a lot of different patient factors, some of which

19   we know, some of which we don't know.

20   And we're not -- you know, following this

21   we're not really in a situation where we have lights

22   on, lights off. I mean if you could take something

1   where, you know, there was a 90 percent bad outcome

2   and you could drop it down to 10 and you were always

3   at 90 and, you know, you clearly would never get to 10

4   without some intervention, it would be much clearer.

5   Here, I think we're in the range of -- you

6   know, it's usually sort of around 60, and maybe we can

7   drop it 40 or 30. But sometimes it may move from 60

8   to 40 just depending upon the patients that you happen

9   to enroll at a particular center or over time, so lot

10 of variability here that makes this particularly

11 challenging.

12   So some of the options that we'll be

13 discussing here today will be looking at clinical data

14 when, you know, we have smaller numbers of patients.

15 And there will be inherently greater degrees of

16 uncertainty. And the uncertainty comes not just from

17 the small numbers, but also from the challenges of

18 studying an antibacterial drug. You know, concomitant

19 therapy will probably be, you know, what patients need

20 to get, and they'll probably get some pre-study

21 antibiotics, too. So you know, this will be, you

22 know, messy data, messy information. So the question

1   is how do we make the best of it.

2   And then if clinical trials are not

3   feasible, one of the things we'll also be talking

4   about today is the animal rule to evaluate efficacy.

5   You know, in this setting you still need safety data

6   from humans, and there are also within the animal rule

7   provisions for restrictions on the conditions of the

8   availability of the drug.

9   And Sumathi in her talk will go through more

10 of the specifics of the animal rule, so we're looking

11 forward to some more details on that when she gives

12 her presentation. And we also welcome other ideas

13 folks may have about how to solve this particularly

14 challenging problem.

15   Just a comment or two about animal models

16 for evaluating efficacy under the animal rule -- and

17 as I mentioned, Sumathi will go through more details

18 and the specific criteria. But just to sort of

19 differentiate these from models where you're looking

20 at activity of an antibacterial drug, you know,

21 really, what we're trying to get at here is an animal

22 model that allows us to predict efficacy in humans.

1   So it's more than just showing activity. And, you

2   know, for some diseases, one of the first questions

3   is, is there a good animal model of infection.

4   And Sumathi will walk through some of the

5   develop efforts that have been undertaken in areas

6   where we have used the animal efficacy rule, and

7   she'll be talking about animal model development for

8   the disease of plague and some of the work that was

9   done for that. And you'll see it's a fair bit of work

10 to really try and understand these models.

11   And there's a lot of difficult questions,

12 and the questions may not be apparent until you start

13 to get into this and trying to really figure out what

14 you need in order to be able to predict human

15 efficacy. You know, which species? Which species

16 behaves similar to the humans? Some animals tend to

17 be intrinsically more resistant to certain types of

18 infections than others. What's the inoculum? You

19 know, is it -- and you sort of engineer the model,

20 too, so that it works within the model. And then the

21 question is, is does that extrapolate to humans.

22   When do you intervene with the test drug?

1   And you know, there's been enough experience to be

2   able to say that, you know, if you intervene at, say,

3   48 hours and the drug can, you know, reduce mortality

4   in the animal model of infection, is that the point in

5   time that translates to clinical benefit in patients?

6   And -- or do you need to be able to get out to, say,

7   four days or five days or six days in order to be able

8   to translate that finding in the animal model?

9   Because it's not just activity into human clinical

10   benefits.

11   So these are really challenging questions

12   that we struggle with. And you know, occasionally we

13   do have some human data, and that tells us something

14   about the animal model. And sometimes we learn that

15   we didn't know quite as much about the animal model as

16   we had thought we did.

17   And the other thing we run into is that

18   animals may metabolize or clear the drug differently,

19   and there need to be certain interventions to be able

20   to get something that's close to the human exposure.

21   We have and animal rule efficacy guidance document

22   that's out on our web that discusses a lot of these

1   issues, too, that is quite helpful.

2   So today, we'll be talking about the pros

3   and the cons of different approaches, and we'll be

4   talking about human clinical data and also animal

5   data. And this isn't sort of a binary decision. I

6   mean, there is the opportunity to have both of these

7   two types of information. You know, matter of fact,

8   the animal rule talks about utilizing available

9   clinical data. So there is -- I don't want to present

10   sort of a binary decision here. I mean, there is the

11   opportunity to draw off information from both.

12   And I think, you know, the reason that we're

13   here today -- I mean, we know that folks are

14   interested in developing these compounds, you know, if

15   they can be shown to be safe and effective, utilized

16   clinically in a meaningful way. I mean, the hope is

17   that the narrower spectrum agents will do less havoc

18   on the normal flora that we all need and that keeps us

19   out of trouble. So we think it's important to have a

20   pathway for the development of these compounds so that

21   the potential for these drugs for treating patients

22   can be evaluated.

1   And with that, I'll stop. And our next

2   speaker is Peter Kim, if I'm reading -- yeah, Peter

3   Kim will be talking to us. And he'll actually walk us

4   through the case at sort of a high level so you'll

5   know what we're dealing with.

6   Peter is a medical officer in the Division

7   of Anti-Infective Products. So he'll walk us through

8   part one of the tough case. And we'll continue to

9   build over the course of the session. So you'll see

10   as we unveil more information it'll get trickier and

11   trickier.

12   So Peter welcome to the podium, and walk us

13   through it.

14   DR. KIM: Thank you, Ed.

15   Good morning. I'll be discussing a

16   hypothetical case of an antibacterial targeting a

17   single bacterial species. The name of this drug is X-

18   1.

19   Overview. Drug X-1 is an injectable anti-

20   antibacterial with activity limited to pseudomonas

21   aeruginosa. It has no activity against gram-positives

22   or other gram-negatives, including enterobacteriaceae.

1   X-1 has a new mechanism of action. It acts on a novel

2   ribosomal target unique to pseudomonas aeruginosa.

3   Non-clinical safety. Hepatic and

4   hematologic toxicity have been identified in mice and

5   dogs. Hepatic toxicity signal is a dose-dependent

6   increase in liver enzymes associated with macrophage

7   infiltration at the mid and high doses as well as

8   reversible focal hepatocellular necrosis at the high

9   does.

10   Concerning safety margins, the liver enzyme

11   elevations were observed at four times the target

12   therapeutic dose, and the focal hepatocellular

13   necrosis occurred at eight times the targeted

14   therapeutic dose. Regarding hematologic toxicity,

15   there is some evidence of neutropenia and it occurred

16   at eight times the targeted therapeutic dose.

17   Non-clinical microbiology and PK/PD. Drug

18   X-1 is mainly active against pseudomonas aeruginosa.

19   The MICs have a bimodal distribution of 0.06 to one

20   milligram per liter for wild type and greater than 4

21   milligrams per liter for non-wild type. Ninety-nine

22   percent of isolates had an MIC of less than equal to 1

1   milligram per liter in a recent global survey.

2   The MIC distribution for wild type is

3   centered on an MIC of .25 milligrams per liter with 5

4   percent of isolates at the low and high ends of the

5   spectrum. Therefore, both the MIC 90 and MIC 99 equal

6   1 milligram per liter.

7   The frequency of spontaneous resistance is

8   low. Serial passage studies have shown no change in

9   the MIC up to 11 passages. Drug X-1 has variable

10 activity against other pseudomonas species and no

11 activity against other gram-negatives, as we had

12 discussed, or gram-positives.

13   In animal infection models Drug X-1 wasn't

14 effective in treating pseudomonas aeruginosa

15 infections based on reduction of colony-forming units

16 per gram in the thigh, pneumonia and peritonitis

17 models and based on survival in the sepsis model.

18   The PK/PD index associated with bacterial

19 killing is the percent time that free drug

20 concentrations are above the MIC over a dose interval,

21 and this index was observed in the hollow-fiber model

22 as well as in murine thigh and pneumonia infection

1   models.

2   Clinical studies. The sponsor has completed

3   some Phase 1 studies and one Phase 2 study. In Phase

4   1, the sponsors completed a healthy volunteer study, a

5   long ELF study and renal and hepatic impairment

6   studies. The sponsor is also planning a thorough QT

7   and drug-drug interaction studies.

8   Population PK model. Simulations of a

9   population PK model based on Phase 1 data showed that

10   a 100 milligram IV infusion over one hour every eight

11   hours would provide greater than or equal to 40

12   percent time above the MIC for an MIC of 1 milligram

13   per liter in more than 90 percent of patients using

14   parameter estimates from healthy volunteers and using

15   a 40 percent inflated variance. Drug X-1 is excreted

16   renally, and greater than or equal to 90 percent

17   target attainment is possible for varying degrees of

18   renal impairment based on dose adjustment.

19   Additional data. The terminal elimination

20   half-life of Drug X-1 in healthy subjects was

21   approximately two hours. No significant drug-drug

22   interactions are predicted. The ELF to plasma

1 concentration ratios of Drug X-1 were approximately 40

2 percent and 25 percent in humans and mice,

3 respectively.

4   Phase 2 proof of concept study. It

5 consisted of a 14-day, uncontrolled study conducted in

6 patients with non-cystic fibrosis bronchiectasis.

7 Drug X-1 was given as monotherapy in 10 patients. At

8 the proposed dose, the predicted PK parameters were

9 observed. Microbiologic activity was assessed in

10 terms of log reduction of pseudomonas aeruginosa in

11 sputum. Greater than 1 log reduction was seen in 9

12 out of 10 patients, and greater than 2 log reductions

13 were seen in 4 out of 10. No adverse events of

14 concern were observed.

15   And now for perspectives on the development

16 program from academia, industry, FDA and EMA.

17   Thank you.

18   DR. COX: Great. Thanks Peter

19   (Applause)

20   DR. COX: And now we'll walk through a

21 series of perspectives. And first, we'll hear from

22 Helen Boucher. And I think many folks know Helen.

1   Helen is current an infectious disease

2   physician at the Tufts New England Medical Center but

3   also has industry experience in that she was in both

4   Pfizer and Cubist over the course of her career. So

5   we greatly appreciate her perspective. And she'll be

6   providing the perspective, really, from the standpoint

7   of a practicing physician/academic physician on this

8   situation of developing a drug that's active against a

9   single species and providing us some information about

10   what she's seeing out there as a clinician these days.

11   So Helen, thank you.

12   DR. BOUCHER: So much, Ed and Dr. Nambiar

13   and Dr. Rex for inviting me. It's a real honor to be

14   here to talk some more about this really important

15   problem.

16   So my disclosures are shown here. And I'm

17   also involved with IDSA, as I showed on the first

18   slide, and have been working on this problem for a

19   number of years with many in this room.

20   So as we sort of start to look at this case

21   of X-1, I thought we could harken back a little bit to

22   some stuff that we talked about yesterday where we

1 sort of said that in a perfect world all of us would

2 want, and certainly we in academia would want, the

3 most well-justified, statistically rigorous

4 development program and studies for these new drugs

5 that would help our patients in practice and, you

6 know, answer questions to the best scientific ability

7 possible.

8   But I think we often learn that we have to

9 work in a world that isn't perfect. And when perfect

10 data is not possible, as Dr. Cox alluded to in his

11 earlier talk, these types of studies may leave us with

12 good preclinical PK and PD as well as animal studies;

13 an ability to understand what the needed exposure is

14 and how to dose these drugs; some amount of clinical

15 efficacy data, which I'm sure we'll spend a lot of

16 time talking about today; importantly, a reasonable

17 safety database -- and we talked a little bit about

18 this yesterday, but I think in this context today

19 we'll probably come back to this -- what is that; what

20 is reasonable; and all of this which will come

21 together to give us enough information to use these

22 patients -- these drugs in our patients who have

1   really limited options for treatment.

2   So I thought, for what it's worth, I might

3   start with a couple of cases, and these are cases that

4   we recently encountered.

5   So the first one is a 71-year-old lady that

6   who had laryngeal cancer a couple of years ago, and

7   she had surgery and chemo and radiation back in 2012.

8   And she was cured. She has COPD now. She's home on

9   oxygen and was recently in the hospital with

10   tracheobronchitis and came to us transferred from

11   rehab where she was living with a new fever, flank

12   pain and respiratory failure. So her history is

13   complicated.

14   Back in December of last year, she had sort

15   of a cough and sputum production and acute on top of

16   chronic respiratory failure. She wasn't otherwise

17   apparently ill with fever or other constitutional

18   symptoms. She was evaluated using rapid diagnostic

19   for viruses, and we didn't find any other source of

20   infection. But blood in sputum grew a gram-negative

21   that was ultimately identified as a multidrug

22   resistant Klebsiella that had a metallo-carbapenemase.

1   She actually did well that time. She was

2   treated for two weeks with IV tigesycline, IV and

3   inhaled colistin in combinations, so pretty aggressive

4   therapy and quite toxic therapy. She ultimately was

5   switched over to IV minocycline for a period and got

6   out of the hospital.

7   So she came again, not entirely

8   unexpectedly, in late January and again now recently.

9   And most recently, she came in with respiratory

10 failure and now has a urinary tract infection. So she

11 was seen in the emergency room and discharged on a

12 five-day course of levofloxacin and very consistent

13 with the guidelines. And her sputum and urine both

14 grew this carbapenemase-producing Klebsiella.

15   Back at the rehab she was doing worse. She

16 was requiring increased oxygen, comes back to the ER,

17 is really failing, very tired, having these urinary

18 symptoms, flank pain, fever now, needs more oxygen.

19 And the urine grows the Klebsiella again with a

20 carbapenem resistant, and it's identified as a

21 multidrug resistant organism.

22   And this is what that multidrug resistance

 1   looks like. We got Rs to all of these antibiotics,

 2   including the two new kids on the block, the

 3   ceftolozane/tazobactam and ceftazidime/avibactam. So

 4   were left with very few options for this very sick

 5   lady.

 6   So after discussion with her and her family

 7   about the limited options and the fact that there

 8   would be predictable renal, neural and other

 9   toxicities if we embarked on another

10   colistin/combination approach, she and her family

11   decided to pursue hospice care. So this lady who was

12   cured of her cancer was now left dying of this

13   infection, so certainly not something that we hope to

14   encounter in our practice very much.

15   So another case I thought that was

16   instructive is a case that's actually almost a year

17   old now that came across on the Emerging Infection

18   Network, which is a really great tool that IDSA

19   sponsors whereby everyday people can post difficult

20   cases and look for advice across the country.

21   And so this was a case of a 19-year-old

22   kidney transplant recipient who had developed

1 refractory blood stream infection due to

2 stenotrophomonas maltophilia that was multidrug

3 resistant associated, as it usually is, with a

4 catheter. The catheter had been removed, but this

5 patient, because of their transplant and other

6 reasons, was on steroids more than the usual amount

7 for a transplant patient and had this organism that

8 was resistant to just about everything they tested

9 except maybe colistin. And that's what they were

10 using.

11   So the question to us was does anyone do any

12 special in vitro testing of combinations, is there any

13 value of testing any other drugs with a fancier MIC

14 test and does anyone know anything about using

15 chloramphenicol, a very old drug that very few of use

16 and most of us don't even have in our hospitals, for

17 treating this kind of a complicated scenario. So this

18 is a 19-year-old patient who's gotten a kidney

19 transplant where we're kind of digging that deep to

20 think about.

21   So the last patient I'll share with you is

22 kind of a different category of what we might consider

 1   someone with unmet medical need. This is a 47-year-

 2   old lady, schoolteacher, who came with pain on

 3   urination and some lower abdominal pain. And she was

 4   started again by her -- by the doctor at the clinic on

 5   oral ciprofloxacin -- again, totally consistent with

 6   the guidelines.

 7   Unfortunately, though, two days later, she

 8   came back more ill with chills, nausea, back pain, and

 9   she now has a high fever and flank pain on exam. She

10   still has evidence of infection in her urine and has

11   an elevated white blood cell count. So she now has a

12   kidney infection, and she's advanced to IV ceftriaxone

13   appropriately, got one dose of that and then sent home

14   because she looked otherwise healthy enough.

15   So unfortunately, two days later again, now

16   four days after she first came in, she was much

17   sicker. Now she had a high fever, and she had a low

18   blood pressure. She wasn't able to eat or drink, and

19   she was vomiting.

20   So now she's in the Emergency Room really

21   looking quite ill with, again, sort of evidence of a

22   urinary tract infection, a kidney infection, and she

1 grows now in urine culture greater than 100,000

2 Klebsiella pneumoniae that is producing an ESBL that's

3 resistant to the drugs to which she was treated --

4 ciprofloxacin, ceftriaxone and trimethoprim sulfa. So

5 she's admitted to the hospital and treated with

6 intravenous carbapenem therapy, which is the drug of

7 choice of ESBLs.

8   So I think all these cases, while anecdotal

9 and sort of just individual cases, do sort of suggest

10 that these resistant pathogen infections are serious,

11 and they can happen and are happening. In the world

12 of clinical infectious disease, we often have less

13 data than we want. We do appreciate that the data on

14 infections at standard body sites like a urinary tract

15 infection are often the foundation on which we build.

16 But in our everyday life in clinical medicine, we have

17 to extrapolate a lot, and our patients don't always

18 present with sort of textbook, indication-based

19 infection. So we use data from a variety of sources

20 and a variety of observations to make these decisions.

21   So that kind of brings us back to where are

22 we and how do we develop Drug X-1. And there's a

1   little bit of a catch 22, I would submit, because we

2   hope to develop this drug before we actually have

3   enough drug-resistant pseudomonas infections to do the

4   big Phase 3 program that Ed alluded to earlier.

5   So you know, we never want to see so many

6   cases of resistant pseudomonas that we can do that,

7   but then that brings us to this tension between the

8   desire for the high quality volume of data and the

9   challenges in generating those data. So the question

10   is how do we interpret murky data. And in these

11   studies that are going to have small numbers of

12   patients with MDR pathogens, how can we best manage

13   that so that we can make any judgments and

14   understanding that there's going to be limited

15   inferential testing?

16   So again, as we talked about earlier, what's

17   the best path? Well, the best thing is to have all

18   adequate, well-controlled trials. And there are a

19   number of different types of adequate and well-

20   controlled trials that I think we'll discuss today.

21   But there will be a continuum of what those datasets

22   will look like. So the dataset from the standard

1 randomized controlled trial with statistical testing

2 all the way down to smaller datasets that might

3 include externally controlled or even uncontrolled

4 data if we come all the way down to the animal rule

5 that Dr. Cox alluded to earlier.

6   You know, well-controlled, randomized

7 controlled trials will tell us a lot when done on a

8 single indication and give us meaningful effectiveness

9 data and also safety data. I think it's important to

10 remember that, too. We get a lot of safety data from

11 these trials.

12   Externally controlled and even historically

13 controlled data, I would submit, especially when we

14 study patients with the most severe infections --

15 those bloodstream infections, other pneumonias with

16 high predictable mortality -- in those cases, we may

17 be able to learn valuable data from externally

18 controlled studies.

19   Whichever path we go, I think it's important

20 that they all have good preclinical PK/PD and adequate

21 safety data. And I think in however -- again,

22 whichever direction people choose to go, doing these

1   studies at sites with really good clinical trials,

2   expertise -- and coming back to that discussion we had

3   yesterday about the clinical trials network, being

4   able to really know that these data were generated in

5   the most rigorous sites by the most rigorous

6   investigators -- will be very helpful. And then

7   diagnostics to help us include patients who really

8   have the disease would be extremely helpful.

9   And I think we as clinicians have to be

10 prepared to use the drugs developed on whichever type

11 of adequate and well-controlled trials are selected.

12 We have to be prepared to use them.

13   So let's think about a couple of potential

14 examples. So one example would be to use a Tier B

15 approach, harkening back to Dr. Rex's sort of schema

16 that he presented yesterday. So this is a randomized,

17 active controlled study and standard indication, so

18 complicated inter-abdominal infection, UTI, pneumonia

19 for example.

20   Those studies allow us to have inferential

21 testing. The patients all have a standard kind of

22 proven infection. We would generate PK data at a key

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1   site of infection, and that population can be very

2   well characterized. We'll also get safety data again

3   in this kind of standard population. Those are all, I

4   think, great strengths.

5   The challenges, some of which we just talked

6   about yesterday, are enrollment. These are a large

7   number of patients, huge amount of resources that our

8   industry colleagues showed us yesterday in terms of

9   time and money in trying to enroll these patients. We

10   have challenges about whether we treat empirically or

11   we use targeted therapy. So do we wait until we know

12   it's pseudomonas? Or do we enroll people at the onset

13   of their disease? We'll be left, it appears, with

14   small numbers of patients with that pathogen of

15   interest even in a big trial.

16   There are concerns and challenges about

17   comparator choice in terms of what's the most

18   effective comparator, what's the most accepted

19   comparator in various parts of the world. And the

20   non-inferiority margins might be wide, wider than we

21   would hope.

22   So if we contrast this to a more Tier C type

1   approach where we look at infection in multiple body

2   sites, there are more considerations here. Is this a

3   randomized study versus best available therapy? Is it

4   versus external controls? Both of those would allow

5   some type of superiority testing. Would there ever be

6   a scenario where you do non-randomized studies? We

7   heard a lot of arguments yesterday, I think, that were

8   pretty compelling for the pitfalls of non-randomized

9   studies, but I leave it here as something to consider.

10   Here, we could potentially include patients

11 who are the most seriously ill with the highest in

12 predictable mortality. If this route is pursued, it's

13 really important that strict definitions of infection,

14 severity of illness scores, things like that, are used

15 so that it's very clear that every patient has the

16 infection that we care about as well as their outcome

17 is just as rigorously defined. Things like

18 adjudication committees and things may be very useful

19 in this setting.

20   And I think these studies do have some

21 strengths. So the patients have proven infection.

22 Their treatment course can be well characterized.

1   There is the ability to get PK data at these kind of

2   most interesting sites of infection like the blood,

3   the lung, even the bone and the brain. There's the

4   possibility to gain safety data. They might be less

5   resource-intensive, and I will probably spend some

6   time talking about that.

7   Certainly, there are challenges in this Tier

8   C approach. So there's less ability to do statistical

9   testing and less -- especially if no randomization is

10   undertaken. And we heard yesterday about some of the

11   challenges with external controls. There are

12   challenges in adhering to strict diagnostic criteria,

13   especially in these infections. And I alluded earlier

14   to maybe an adjudication committee would help, but

15   there's controversy about that, too. And then if one

16   pursues this approach, there's likely going to be a

17   need for other safety as well as other kinds of data.

18   So in thinking about a whole program, that's an

19   important aspect.

20   So in both of those approaches, the Tier B

21   and the Tier C type approaches, I think we're left

22   with some challenges that are shared by them,

1 actually. So at the end of day, in either of these

2 approaches, we're left with relatively small numbers

3 of patients with the pathogen of interest treated with

4 X-1. So we're still looking at a smaller dataset.

5 There's a resource intensity in either one in terms of

6 human resources, time and money.

7   There is probably less statistical power and

8 support than for the skin program that Dr. Cox alluded

9 to earlier. And then very importantly, other factors

10 impact outcome in these patients. So these are

11 patients who are critically ill and inter-abdominal

12 infection. They're having surgery. There are other

13 things. And so I think that those are all kind of in

14 the challenge or risk bucket that we have to consider,

15 whether you chose a Tier B or a Tier C type approach.

16   And I think it's also important to say, as

17 those examples I presented show, there's also a risk

18 of not proceeding with either because, if we maintain

19 the status quo, we could be left with no options.

20   So again, where would be like to be? We

21 like the perfect. But I think it's reasonable to

22 think that we could work with a program that ended up

1   with well-controlled, preclinical PK/PD in animal

2   studies, a clear understanding of the needed exposure

3   and how to dose, harkening back to Dr. Ambrose's talk

4   yesterday. Even a small amount of clinical efficacy

5   data and a reasonable safety database would all be

6   reasonable, I think.

7   And so where does that bring us for this

8   Drug X-1? I think the minimum thing that we as

9   clinicians would hope to have in order to be able to

10   use it would be data from a well-controlled study and

11   the label -- efficacy data and safety data; and then

12   pharmacology and dosing information, including PK data

13   and, I would submit again as a clinician, from as many

14   body sites as possible and hopefully from patients who

15   are really, really sick with organ dysfunction and

16   critical illness; some information about age, gender

17   and drug interaction studies to help us, again,

18   extrapolate to the patients we see.

19   And then there's sort of this notion of

20   secondary data, the data that would ideally be

21   available and easy to find that could come from that

22   less controlled or even uncontrolled data, that could

1   include groups of patients or even individual patients

2   who had really severe infections treated with this

3   that could help inform our practice not in the same

4   way as the data from the well-controlled study, but

5   that could still be useful.

6   So some ways to help do this, again, we

7   alluded a little bit yesterday to the LPAD mechanism.

8   And the PATH Act is the current act that's in the

9   Senate that establishes a limited population

10 antibacterial approval pathway that would be limited

11 to this population most at risk. So it would create

12 an option for the development of agents where only

13 limited data are possible.

14   This legislation has a lot of safeguards to

15 ensure that the drugs are proven safe and effective

16 and used appropriately. And these include clear,

17 prominent labeling, that this drug is indicated only

18 for the limited population, FDA pre-review of

19 promotional materials and then for strict monitoring

20 of the drug use when it's approved. And we at IDSA

21 and others, many others, have been active in helping

22 to advocate for this legislation. And I think there's

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 1   still good hope that we'll see that happen.

 2              So again, in sort of our efforts to use

 3   these drugs in the most effective way possible,

 4   stewardship is really, really important.  And we're

 5   very encouraged that antibiotic stewardship programs

 6   have been proposed as a condition of participation for

 7   both hospitals and long-term care facilities in the

 8   United States.  And stewardship programs would be the

 9   best vehicle to make sure that we use these drugs in

10   the most appropriate way possible and preserve them

11   for as long as possible and for as many patients as

12   possible.

13              So that sort of brings us back to where we

14   started.  You know, I think people are asking have we

15   come to the pre-antibiotic area, and we didn't even

16   get into sort of the most recent kind of scary news

17   about MCR-1 and now MCR-2 and the potential of

18   plasmin-mediated resistance to colistin and other

19   drugs.  And I think that is somewhat scary.  The cases

20   that we looked at certainly highlight the need for

21   both parenteral and oral agents to treat specific

22   pathogens.
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1   I think it's fair to assume that we're going

2   to be forced to use these drugs with limited data, and

3   the cases that -- where we have to use IV and inhaled

4   colistin and fosfomycin for ESBL infections, which a

5   lot of us have gotten very good at doing with very

6   limited data -- tigesycline for MDR infections -- have

7   all sort of highlighted this.

8   It's very important that, obviously, we keep

9   up our efforts on infection prevention and stewardship

10 and surveillance. But for X-1, I think we hope to see

11 adequate, well-controlled data emerge from either

12 small, randomized controlled trials, perhaps with

13 wider non-inferiority margins or even some really

14 small Tier C type studies, perhaps with external

15 controls.

16   As we mentioned, you know, strong case

17 definitions and the inclusion of the most severe

18 infections, I think, are really important. High

19 quality data, hopefully from clinical trial networks,

20 could advance that.

21   For clinicians, I think having information

22 about infections at multiple body sites is very

1 useful, if possible. The LPAD mechanism can ensure

2 use in this limited population with needed safeguards,

3 and stewardship hopefully will ensure that we use

4 these antibiotics in the best way possible for the

5 patients who need them most.

6   So with that, I'll thank the committee again

7 as well as Amanda Jezek from IDSA and my colleagues

8 here on the panel for the invitation. Thanks so much.

9   (Applause)

10   DR. COX: Thanks, Helen.

11   And now our next speaker is John Tomayko.

12 I'm sure many folks are familiar with John, currently

13 chief medical officer at Spero Therapeutics and also a

14 long history in the field of infectious disease

15 development and is an infectious disease physician,

16 also, too. John will be providing us his perspective

17 from the standpoint of somebody from industry.

18   So we appreciate your joining us here today,

19 John.

20   DR. TOMAYKO: Thank you, Ed.

21   Thank you, Sumathi, for inviting me to talk

22 a little bit about this important problem.

1   These are my disclosures. And this is just

2   my opinion. I don't know that I could represent all

3   of industry.

4   So the agenda is pretty basic. I'm going to

5   just reflect a little bit on some of the success we've

6   had in the past and maybe why we're successful. I'll

7   review the case, and then I'll give you my perspective

8   on how we might develop it. And the end result that

9   I'm looking for is a regulatory approval. And since

10   this is an FDA workshop, I'm looking for an approval

11   in the U.S.

12   So the past. I think if you look back you

13   can pretty proud of what we've accomplished. We've

14   had tremendous success in identifying a number of

15   classes of antibiotics. There's two points here that

16   I want to make. The first one's obvious because

17   there's an arrow there. We haven't had a novel class

18   of gram-negatives approved in the U.S., really, since

19   the nalidixic acid story began in 1962 with

20   fluoroquinolones.

21   The other one is that these drugs were

22   broad-spectrum agents. And you were able to actually

1 go out. Maybe the parameters of your trial might have

2 been different, but you could still recruit most of

3 the patients with -- that would be causing infections

4 at various body sites. So they were easier to

5 develop, perhaps, than some of the things we're

6 talking about today.

7   In the present, we actually have a number of

8 drugs that are soon to be submitted for review and,

9 hopefully, approved. On the right, we have gram-

10 positive antibiotics that also have some respiratory

11 spectrum, such as H. flu and the atypicals. So these

12 drugs could be studied in community-acquired pneumonia

13 and skin infections. They could meet the statutory

14 requirements for approval, but they're not really

15 addressing what's considered an unmet medical need at

16 the moment, so they take in the traditional approach

17 to an approval.

18   On the left, all of these drugs, for the

19 most part, set out to take advantage of what has been

20 described multiple times, the Tier B approach.

21   In a not-so-distant future, I suspect novel

22 science is going to bring us a lot of interesting

1   approaches to managing infection. I can't go through

2   all of this. I'm sure my slides will be available.

3   But I mean, Spero Therapeutics is working on

4   potentiators. These are compounds that interact with

5   the gram-negative outer membrane and create passageway

6   that allows maybe drugs that couldn't access an

7   intracellular cytoplasmic target access to a gram-

8   negative. So that might be a nice strategy, probably

9   bring some challenges, and we hope to work that out.

10   But there are others -- single pathogen

11   antimicrobials like our Drug X-1, monoclonal

12   antibodies -- we have license in development right

13   now; therapies that modify pathogen virulence -- the

14   literature is filled with ideas about how to do this;

15   novel delivery systems, including two programs where

16   we are trying to study aerosol antibiotics in VABP.

17   And then perhaps more bold would be can we modify the

18   host response and try to help patients in that manner.

19   So this leads me to just touching on what

20   was brought up yesterday, the difference between an

21   antibiotic and an antibiotic adjunctive therapy. And

22   the adjunctive therapy really does present a

1 challenge, and that's because antibiotics are really

2 amazing therapeutics. The treatment effect is so big.

3 As you could see, you could read any of the guidance

4 documents where FDA has tried to generate supportive

5 data for an M-1. And you could see that the treatment

6 effects are huge. So how much better can you be than

7 cured?

8   And what you need to do -- and fortunately

9 we could do this with antibiotics. We have great

10 translational models. You need to create a clinical

11 equipoise argument, which really answers the question

12 that -- does the test therapeutic -- could it be as

13 good or better than a standard of care. And if it

14 could, you could conduct a non-inferiority study. And

15 I think that most of us throughout yesterday

16 recognized that a non-inferiority study, like we do in

17 Tier B, is probably the most tractable way to get a

18 drug approved.

19   Test therapeutics that cannot make an

20 equipoise argument -- like most Mabs, anti-virulence

21 therapies, aerosolized antibiotics for VABP -- have to

22 be considered adjunctive. And although they could

 1   bring great advances, they might rescue patients who

 2   would otherwise fail therapy or die. The development

 3   is particularly challenging. You have to study these

 4   in a superiority study. So here it's standard of care

 5   plus a novel adjunct versus standard of care alone.

 6   And there are a number of compounds that are

 7   facing some of these development challenges. The MvfR

 8   inhibitor that Spero and Roche were working on has

 9   presented a number of challenges, and the work is

10   diminishing there. But this is an anti-virulence

11   strategy. It would require an adjunctive approach as

12   would, I believe, any monoclonal antibodies, although

13   the MedImmune anti-pseudomonas antibody is still

14   looking for a superiority study. I think they're

15   going to pursue prophylaxis.

16   The aerosol antibiotic therapies for VABP,

17   the studies are undergoing -- ongoing now. So we

18   should soon see whether or not there's any benefit

19   from an adjunctive. I know people use aerosolized

20   antibiotics all the time, and they'll probably

21   continue to use them until we either have one approved

22   with some good data or we have some conclusive data

1   that they're not beneficial. The only antibiotic here

2   that I think could really meet that equipoise argument

3   would be Polyphor, the cyclic peptide.

4   So this is just an illustration taken from

5   the comprehensive regulatory framework, kind of tiered

6   development study that John Rex, myself and a number

7   of industry colleagues published in 2013. And it just

8   seems to me that as we address unmet need or take

9   advantage of some of the new science, we're going to

10 have to become more creative with clinical development

11 and, in general, be conducting smaller studies and

12 relying on more preclinical data and PK data.

13   So Drug X-1 I don't need to tell you about

14 since you've done your homework and Dr. Kim did a nice

15 job reviewing this. So what I'll basically say is,

16 really, the major weakness of what looks to be a

17 promising therapeutic is how are we going to get it

18 approved. And I don't think that there's a rapid

19 diagnostic that's widely available, but we'll learn

20 more about that in our discussions this afternoon.

21   So let's look down at the bottom chart here,

22 the frequency of pseudomonas, percent of all enrolled.

1 And this is interesting because I think we all

2 recognize that pseudomonas is -- we consider it a

3 common, nosocomial pathogen, and it is. But when you

4 actually try to plan a clinical trial and you look in

5 the literature or talk to your colleagues, you realize

6 that very little pseudomonas is responsible for any

7 single indication.

8   Perhaps the most pseudomonas we'll see is in

9 a nosocomial pneumonia, and that's even probably

10 skewed towards VABP. And that probably ranges between

11 10 and 20 percent, and it gets even lower as you look

12 at this illustration.

13   I've always loved this slide, and I think it

14 first appeared as we were preparing that document.

15 John Rex had presented this in several form, and I

16 like the title, "The Painful Math." But it

17 illustrates what we're up against.

18   And I guess I should just digress for a

19 second and say that if you follow my logic here, you

20 might even come to the realization that I did, that a

21 Tier C program could actually be bigger than a Tier B

22 program but generate less substantial evidence. So

1   that's -- that was an enlightenment that I had as I

2   put this together.

3   And this kind of illustrates the situation.

4   You know, if you have a typical endpoint with a 20

5   percent failure rate and you use the typical

6   parameters that we would like to use, 90 percent power

7   in industry and you're stuck with a 10 percent margin,

8   you've got a pretty decent study on your hands to

9   conduct, 335 patients per arm. But now, if you have

10   to only consider the evaluable population, culture-

11   proven pseudomonas, if the rate's 22 percent, that

12   goes up to 1,500 an arm. And you can see that it just

13   gets progressively worse.

14   So you might get a good safety database out

15   of a study like this. But is it actually feasible to

16   conduct? And that's a question that I'm going to come

17   back to multiple times today because that's part of

18   the thesis of our discussion this afternoon --

19   feasibility.

20   So for Drug X-1, what are some of the issues

21   we should consider? I already said that this was a

22   very drugable molecule, and there's clearly evidence

1   for clinical equipoise versus a standard antibiotic,

2   albeit this only has a narrow spectrum. So non-

3   inferiority is possible. But where would you study

4   it? What site of infection? Or would you pool?

5   You have to recognize, though, that if

6   you're going to enroll patients empirically, you might

7   not be right. Even with a diagnostic, they're not 100

8   percent sensitive or specific, so you're going to have

9   to provide coverage for the spectrum gaps that this

10   agent has. What are your choices? You don't want to

11   combine it with something that has activity against

12   pseudomonas, which would further confound your

13   analysis. So you're left with a few things.

14   Tigesycline doesn't have good reliable pseudomonas or

15   any, nor does ertapenem. So maybe those would be good

16   things to combine it with.

17   But you also have to face the reality of the

18   VABP guidelines, which say you need to double cover

19   patients that have VABP. And typically we use an

20   aminoglycoside. So now you've compounded your

21   analysis with some confounding coverage.

22   I want to also point out that patients with

 1   pseudomonas infections, it's not -- often not their

 2   first nosocomial infection but their second. And they

 3   get progressively debilitated in the hospital. So

 4   there, they're typically sicker. They have higher

 5   comorbidities. But as they become sicker and have

 6   higher failure rates, that could lead to the need for

 7   a larger sample size to really measure a treatment

 8   effect. So maybe in the Analysis section, is

 9   inferential testing even possible? I think we need to

10   really answer that question today.

11   And about enrollability, you know, how long

12   will it take? How much will it cost? Would a rapid

13   diagnostic help us, and is the design going to be

14   something that investigators will actually be willing

15   to accept?

16   So here, I'm going to provide just some

17   standard parameters, and I'll explain a few of those.

18   I think you heard a little bit about this yesterday,

19   but roughly speaking, a UTI and IAI study costs about

20    $50,000 per patient. And a HABP/VABP is over 100.

21   And the costs are amplified as you have to go to more

22   centers. You could imagine having to visit those

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1   centers, audit those centers, monitor those centers.

2   So the costs are amplified.

3           The time is even more worrisome than the

4   cost.  And I'm -- I'll just focus on HABP/VABP.  It

5   takes, on average, about 12 centers actively screening

6   to recruit one patient per month.  So you could turn

7   that around.  And what does that tell you?  That if

8   you have a good center, you might be lucky to get one

9   or two patients a year from that center.

10          This leads to investigator fatigue.  The

11  site staff has to work hard.  And as Helen said, we

12  want to go to the best sites, sites that have a good

13  staff.  But a good staff requires -- you know, the

14  fundamentals have to be in place.  You have to be able

15  to pay for that staff.  So these studies typically

16  compensate the sites when they recruit patients, when

17  they actually enroll a patient.

18          So these sites that have good staff

19  typically do more than one study, and your study being

20  very, very challenging may actually get less attention

21  than a study, just because they have to pay the bills,

22  that is easier to enroll.
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1   Nobody's really mentioned investor fatigue.

2   And I'm actually going to emphasize this quite a bit

3   because, as I said, these are expensive studies and

4   they have to be paid for. And I've had two

5   experiences. Now I work for a small venture backed

6   company, but before this, I worked for

7   GlaxoSmithKline. Actually, at GlaxoSmithKline, maybe

8   it was a little easier to make the argument. There

9   were so many layers of management that at one point

10   somebody says do you really think we should do this.

11   And maybe somebody like Lynn Marks would say, yeah, I

12   do, and it would get funded. Maybe it's not the

13   experience that others have had.

14   But with a venture group, you actually have

15   to explain what you're doing, and I don't think

16   they're going to be sensitive to or excited about a

17   three- or four- or five-year study. And they have

18   other choices to invest.

19   Rapid diagnostics to the rescue. We all --

20   we've mentioned this a lot, and I have actually had

21   some firsthand experience trying to use a rapid

22   diagnostic, which was approved in the United States.

1   And I'll tell you that that experience isn't worth

2   getting into too much detail, but I think we have to

3   be careful about what we -- I think we'll accomplish

4   there.

5   And I'll start with my aside. You know, I

6   do think a rapid diagnostic, if the economics get

7   worked out and if people use it, will be very valuable

8   with antibiotic stewardship and should lead to

9   improved outcome in patients that are in our

10   hospitals.

11   But we have to remember diagnostics don't

12   create patients infected with the target pathogens.

13   Therefore, we could use them for enrichment. They may

14   allow us to save costs, but it's unlikely they're

15   going to help us save the time. And I pointed out

16   that time and risk is really what I'm focused on here.

17   I think that those are the elements that don't always

18   get the obvious attention. Cost -- you know, we have

19   a fairly good sense of what that is.

20   Why do I feel that diagnostics aren't a

21   panacea? Well, they require hardware, and you have to

22   train people on how to use that hardware. You have to

1 get that hardware to the sites that you're doing your

2 clinical work, and then you have to service it. I

3 talked to a few diagnostic companies who feel that

4 their machines need servicing at least twice a year.

5   So you could imagine that if only a few

6 people can use that diagnostic, even if it's

7 relatively simple, that could impede your ability to

8 recruit patients who might present when those few

9 people aren't there. And the other thing I should

10 point out is the companies aren't working to your

11 clinical trial timelines, which means that they might

12 not be available to initiate your center, train them

13 and make sure everything is in operational condition

14 when you want that.

15   So moving forward, Drug X-1. I'll point

16 out, first of all, that no standalone Tier C programs

17 have been submitted for review, but we're going to see

18 standalone -- we're going to Tier C-like work in Tier

19 B presented. And I'm not saying that those aren't

20 important studies to conduct. But small samples may

21 not contain sufficient numbers of the target pathogens

22 to allow inferential testing even if we take advantage

1 of wide non-inferiority margins and one-sided

2 significance testing.

3   Also, small samples from a sick population

4 may have this sample variability that we talked about.

5 With many comorbidities, we could get unpredictable

6 results, increasing our risk of failure. We've

7 already talked about what you can do, and I think you

8 need to do everything you can even for a narrow

9 spectrum drug. There's -- there is no reason to skip

10 the easy stuff, but what we're talking about is the

11 study required to generate the substantial evidence of

12 effectiveness.

13   So here's where my thesis comes in, that

14 with these feasibility challenges highlighted for Drug

15 X-1, can one expect that a clinical trial will meet

16 the requirements of substantial evidence of

17 effectiveness with any predictable certainty.

18 Remember, when you go ask for the funding, you're

19 going to have to say -- everybody's used to risk. But

20 you're going to have to tell them how you're going to

21 manage it and get people to believe that, you know,

22 what you're going to do is going to be successful.

1   So where does this substantial evidence come

2   from? I think we all know this. In Tier B, we rely

3   on a non-inferiority study against the usual drug-

4   resistant pathogens and the target pathogen study,

5   which I think is very important -- and we should find

6   ways of including that information in the label --

7   becomes supportive evidence.

8   In Tier C, we don't have the UDR study, the

9   non-inferiority study. So now suddenly we have to

10 make that target pathogen study our substantial

11 evidence, and I think that that raises a lot of

12 questions.

13   So you know, fortunately, there's the Tier

14 D, or animal rule. And here, the target pathogen

15 study could remain your supportive evidence. It still

16 should be done. It'll generate the PK. It'll be very

17 important, but the statutory requirements could be met

18 by demonstrating substantial evidence of effectiveness

19 from animal studies.

20   So I'm really saying that I know that

21 pseudomonas is an important problem. It may be more

22 common than KPCs and NDMs in the U.S. and parts of

1   Europe. There is strong supportive data for a drug

2   like Drug X-1. But I really think that the challenges

3   of recruiting a single pathogen Tier C-like study

4   carries a high degree of unmanageable risk. And I

5   don't know how I could put together an argument that

6   the results of a Tier C study, no matter how carefully

7   conducted, will favor a chance of supporting approval

8   versus condemning the drug to failure.

9   So we do need an alternate approach. At

10   least that's my thesis. And this is in the -- since

11   we're going to hear a lot more about the animal rule,

12   this is just a review of what you need to consider and

13   what the animal rule's all about.

14   But here, I've highlighted the word

15   feasible. If you cannot conduct an adequate and well-

16   controlled clinical study because it's infeasible and

17   you need to generate substantial evidence, could it be

18   -- could it come from an animal study? And first of

19   all, we have to agree that it's not feasible and

20   unlikely to work to do the clinical route. And then

21   we have to determine whether or not there's a

22   validated pseudomonas infection model that could

1   provide substantial evidence. And I'm not prepared to

2   tell you that there is or there isn't.

3   I'll just point out that there is this

4   requirement for a field study. So if you're -- take

5   advantage of the animal rule, say, for plague, when

6   you submit your NDA, you have to provide a protocol

7   that talks about a field study in the event that

8   there's a plague outbreak. And you should be prepared

9   to conduct that. I would argue that if you were to

10 take an animal rule approach here, that there are

11 questions that could be answered after approval and

12 there are enough pseudomonas isolates out there that

13 you might be able to do a selective study that might

14 improve your benefit risk.

15   So in conclusion, I think that we'll see

16 promising narrow spectrum agents and that the -- but

17 the development path is unclear. As the basic science

18 advances, we'll see more translational changes.

19 Adjunctive therapies will continue to be challenging

20 to develop. I think the blending elements proposed

21 under Tier C with the animal rule may allow FDA

22 approval for select narrow spectrum therapeutics.

 1   And I guess I'd hate to see us slip

 2   backwards to the -- a point where we don't have

 3   antibiotics to support important medical advances like

 4   bone marrow transplant, solid organ transplant and

 5   other things that have been mentioned. And I don't

 6   think we should rely on or hope for only broadly

 7   active, easier-to-develop antibacterial therapies.

 8   We're going to have to solve this problem.

 9   But thank you.

10   (Applause)

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

12   And now Sumathi Nambiar, who's the Director

13   of the Division of Anti-Infective Products, will

14   provide information on potential clinical pathways,

15   some background information about the animal rule and

16   then also describe some of the experiences with

17   development of animal models that have been utilized

18   in the area of plague.

19   So Sumathi, thank you.

20   DR. NAMBIAR: Good morning. So I think some

21   of this was touched upon by Ed in his introductory

22   talk. So we do recognize that there's a potential

1   clinical utility for antibacterial drugs that are

2   active against a single species. But we also

3   recognize that such drugs are very difficult to study

4   when the single species that the drug is active

5   against occurs infrequently.

6   This has been stated earlier. Pseudomonas

7   is not really a rare cause of certain infections, but

8   it just doesn't occur frequently enough. And so

9   enrolling such patients in a clinical trial becomes

10   particularly challenging. Certain infections like

11   hospital-acquired pneumonia or ventilator-associated

12   pneumonia, you're more likely to encounter pseudomonas

13   aeruginosa. But such infections tend to be

14   polymicrobial, necessitating the need for concomitant

15   therapy. And this concomitant therapy often has

16   overlapping spectrum of activity, which means it

17   covers pseudomonas as well. So that really confounds

18   our ability to assess treatment effect. You've heard

19   a lot about rapid diagnostics, how they could help

20   some but certainly will not solve all our problems.

21   Again, Ed mentioned this this morning. So

22   in contrast to other rare human diseases, we have

1   unique challenges when we are trying to study acute

2   bacterial infections. There is an urgent need to

3   start therapy. Patients are sick. They need to lay

4   an initiating effective therapy can impact outcome.

5   There is diagnostic uncertainty at the time of

6   presentation. Therapy tends to be empiric in most

7   instances.

8   It's difficult to identify such patients a

9   priori ahead of time. So a lot of the other rare

10   diseases, you can maintain a registry. You sort of

11   know who your patients are and you can plan and

12   conduct a trial. It's very different in this

13   particular setting.

14   And lastly, patients present at local

15   healthcare facilities rather than at a special

16   facility, and I think this, too, had come up in Dr.

17   Rex's presentation yesterday.

18   Some of the characteristics of X-1. I think

19   overall, as was mentioned, by John Tomayko, this seems

20   to be a promising candidate, appears to address an

21   unmet need, has a novel mechanism of action.

22   In vitro studies do not suggest a high

1   likelihood of resistance development. Safety profile

2   seems reasonable. We have identified hematologic and

3   hepatic toxicity, but both of them appear to be

4   monitorable. And at the proposed dose, we have a

5   safety margin for both toxicities.

6   There is evidence of antibacterial activity

7   in animal models of infection, so these are the

8   routine models that we do to assess if there's

9   activity. And they really don't rise to the level of

10   being efficacy studies that we'll talk later today.

11   There's a proof of concept study in a small

12   number of patients with non-CF-bronchiectasis. There

13   was evidence of log reduction, so there is some

14   evidence that the drug actually does impact the

15   organism.

16   Dosing rationale appears adequate, and

17   dosing has also been evaluated in patients with renal

18   impairment. So this will allow for patients in the

19   trial with renal dysfunction and, again, highlights

20   the importance of trying to enroll patients with

21   comorbidities, which tends to be more common in these

22   kinds of patients.

1   So we've certainly had a lot of discussion

2   on this within our group, and we've come up with four

3   options. Again, I'm sure there are other options out

4   there, and we look forward to the input during our

5   discussion period this afternoon. So this is not

6   meant to be an all-exhaustive list.

7   And I'll go through each one of them. But

8   broadly speaking, the first option hinges on doing a

9   non-inferiority trial. The second one is in

10   superiority trial. The third one is trying to do a

11   trial in a population that's at a high risk of

12   infection due to pseudomonas. And the last option,

13   again, has been discussed in earlier presentations, is

14   establishing efficacy under the animal rule.

15   So this is a first option. And here, I have

16   A and B which is an NI trial either at a single body

17   site or an NI trial pooling across body sites. So if

18   you look at an NI trial at a single body site, it's

19   potentially feasible if you're willing to accept a

20   greater degree of uncertainty, which translates to a

21   wider non-inferiority margin.

22   In such a trial, there is no need to enroll

1 patients who only have pseudomonas aeruginosa for

2 specific phenol types. And all-comer pseudomonas

3 aeruginosa population would be acceptable.

4   You know, we'll go through some numbers, but

5 I think we all understand that it is difficult to

6 enroll an adequate number of patients with pseudomonas

7 in a standard non-inferiority trial. Availability of

8 the rapid diagnostic might help some, but really helps

9 with enrollment. It's really not going to change the

10 frequency with which the organism causes infection.

11 Again, this has been highlighted previously.

12   I touched upon this a little bit, and I

13 think it's going to come up a fair bit for discussion

14 this afternoon. I mean, two real difficult issues to

15 deal with -- one is the need for concomitant and

16 antibacterial drugs that treat other gram-negatives

17 because HABP/VABP is polymicrobial and X-1 is rarely

18 targeted only against pseudomonas.

19   So we've talked about ertapenem as a

20 potential option, and John mentioned this earlier. I

21 do want to note that it is not indicate it for

22 HABP/VABP. It has an indication for CAP. So we will

1   need to do some work to find out if it will be

2   accepted or considered clinically okay to treat a sick

3   patient with HABP/VABP with ertapenem.

4   The second big issue that we have to deal

5   with is the dual therapy for pseudomonas aeruginosa.

6   Typically, for treatment of this condition due to

7   pseudomonas, a dual therapy is used. And again, this

8   has been -- has come up earlier. Now there -- the

9   treatment guidelines that were published just a few

10 days ago do suggest that monotherapy is acceptable.

11 They identify certain situations either based on the

12 local antibiograms and your institutional antibiogram

13 or the presence or absence of risk factors.

14   And if you go through the risk factors, it's

15 really hard to come up with too many that these

16 patients will not have by the time they develop

17 HABP/VABP. But still, there is some role for

18 monotherapy in a few patients. Again, we look forward

19 to discussing that this afternoon.

20   The other issue is, even if patients are

21 started on dual therapy, there is the option of

22 deescalating once you have the susceptibilities. And

1   what we've seen from clinical trials that have been

2   conducted in HABP/VABP, there's a great reluctance on

3   the part of investigators to deescalate. So in

4   effect, what happens is most patients get dual therapy

5   for just the entire duration of treatment.

6   So I'll just walk you through some numbers.

7   We looked at what a sample size might look like for a

8   HABP/VABP trial that uses all-cause mortality as a

9   primary endpoint with the following assumptions -- a

10 20 percent mortality rate, two-sided alpha of .05, 1-

11 to-1 randomization, 80 percent power. And I'll go

12 through a table review. The NI margins can go from 10

13 to 20 percent, and the prevalence of pseudomonas can

14 go from 10 to 20 percent.

15   And John Tomayko showed you some numbers.

16 In recent registrational trials, the prevalence has

17 been in the order of 10 to 15 percent. There are some

18 publications that do suggest that it may be closer to

19 the 20 percent or the low 20s. So we've tried to put

20 in some degree of variability and look at what sample

21 sizes might look like.

22   So if one is to do a standard NI trial with

1   a 10 percent non-inferiority margin and a 10 percent

2   prevalence of pseudomonas, you can see that the sample

3   sizes are fairly large for the total number of

4   patients just to get about 500 patients who have

5   pseudomonas alone. The widest non-inferiority margin

6   would be, really, what M-1 is, based on what's in our

7   guidance with M-1 of 20 percent. And you're at about

8   1,200 patients.

9   If you're truly able to go to sites that

10   have a higher prevalence of pseudomonas and you're

11   more in the 20 percent range, it cuts your sample size

12   in half. And certainly, if you're willing -- if you

13   or we are willing to go with the wide non-inferiority

14   margin of 20 percent, which is all of M-1, then the

15   sample sizes seem to be in the feasible range.

16   The other body sites that we've considered

17   for where one can conduct a non-inferiority trial was

18   complicated UTI. It's certainly easier to study in

19   this indication because pseudomonas can be -- can

20   cause monomicrobial infection. However, the incidence

21   is still low, and we think that such a trial might not

22   be feasible.

1   And the other issue is -- again, it was

2   discussed yesterday -- is if you have efficacy only in

3   cUTI, how much comfort does that provide that it might

4   work in other body sites, especially the lung.

5   We've also thought it would burn some

6   surgical site infections because these tend to have

7   pseudomonas infections more commonly than other

8   organisms. But I think there are a lot of challenges.

9   These indications are very difficult to study.

10   They're not very common. We really need to figure out

11   what the endpoint or the trial design might look like.

12   Another option to do a non-inferiority trial

13   we thought is maybe pooling patients who have

14   HABP/VABP and/or bacteremia and use all-cause

15   mortality as the endpoint. It might help with the

16   numbers than if you did a trial in HABP/VABP alone.

17   But again, this was discussed. It's very difficult

18   when you combine a type -- different types of

19   infections and different sources of the bacteremia.

20   It might be difficult to discern if there's a deficit

21   in efficacy at one or more body site. And again, this

22   was mentioned yesterday. Decisive treatment effect

1 does vary across the different indications.

2   So moving on to the second option, which is

3 to conduct the superiority trial, so here, we will

4 assess the superiority of Drug X-1 over best available

5 therapy. In such a trial, to be able to demonstrate

6 superiority, one would need to enroll patients with

7 pseudomonas aeruginosa, which is resistant to

8 currently available therapy.

9   You could enroll patients with different

10 types of infection. In such a trial, again, the

11 shortcomings of that we've already gone through.

12 Certainly, we wouldn't challenge the findings from

13 superiority trial. It's easy. It provides direct

14 evidence of treatment effect.

15   However, determining superiority over

16 existing therapy can be difficult. We saw some --

17 went through one example yesterday from Dr. Friedland

18 where the challenges of doing such a superiority trial

19 were very clear. I think we've touched upon that, the

20 impact of pooling. And then it's also an issue of

21 sheer numbers which we will go through in the next few

22 slides.

1   So this was a recent study from JMI Labs

2   where they looked at the prevalence of these different

3   organisms. And they used the term PHP pneumonia in

4   hospitalized patients, which essentially is everything

5   other than VABP. So it's VABP and non-VABP patients.

6   So of about 8,000 isolates, 21 percent was

7   pseudomonas. Twenty-two percent of them were

8   meropenem non-susceptible. They used a definition of

9   MIC of four or greater, though the label breakpoint to

10 the best of my understanding was eight.

11   Among the meropenem non-susceptible

12 pseudomonas, the incidence Amikacin resistance was 13

13 percent. We're trying to do this, really, to see what

14 is the likelihood of encountering a multidrug

15 resistant, a band-resistant (ph) pseudomonas because

16 that's the only opportunity you have then to

17 demonstrate a superiority.

18   And if you look at the incidence of what

19 meropenem and Amikacin resistance in the overall

20 population, so the first numbers are really if you're

21 -- if you're only studying pseudomonas. Going into

22 the study, you know, everybody has pseudomonas. But

1   if it's an all-comer HABP/VABP, the numbers are

2   really, really small. So to find one patient with

3   pseudomonas where the organism is non-susceptible to

4   meropenem and resistant to Amikacin, you would need

5   122 patients.

6   And I just have to acknowledge, you know, we

7   sort of average the numbers, but you can take a look

8   at the paper. You know, there are differences whether

9   you do U.S. sites versus X U.S. sites. There are

10 differences in non-VABP and VABP. Certainly, in a

11 VABP population, the prevalence of pseudomonas will be

12 slightly higher, and the prevalence is also higher in

13 X U.S. sites. In this study they did -- Europe,

14 Mediterranean was one group; China; and then U.S.

15   So what would the sample size look like if

16 one were to try to do a superiority trial given some

17 of these numbers I've shown you? These are our

18 assumptions -- 1-to-1 randomization, 2-sided alpha

19 .05, 80 percent power. We've estimated the control

20 group mortality rate of 40 percent. And I'll go

21 through numbers. I won't go through every one of

22 them, but we've tried to provide three sets, you know,

1 if -- depending on what the mortality rate and the

2 test control are ranging from 20 to 30 percent. So

3 obviously the greater your treatment affect, the

4 smaller your sample size would be.

5   And the frequency of MDR, we range it from 5

6 to 25. Going by the previous numbers, I think five

7 would be your best-case scenario. But again, there

8 are -- you know, that's one data set. Maybe other

9 data sets will speak otherwise. But we just had --

10 needed something to work with to go through this

11 example.

12   So if truly the frequency of MDR P --

13 pseudomonas is only 5 percent and you have a 10

14 percent improvement in the mortality rate with the

15 test drug, your sample sizes are pretty impressive,

16 whereas if you have a really good drug and your

17 treatment benefit effect is at least 20 percent, even

18 so you're in the 3,000-odd range.

19   And we've heard over and over again just to

20 do one all-comer HABP/VABP trial. The rate of

21 enrollment is dismal and doing these trials is very

22 challenging. But if your frequency of MDR PA is

1   really high, you're in the 25 percent range and your

2   drug really works, then you might have a number that

3   you can live with.

4   So then moving on to the third option is

5   really targeting a patient population where the

6   prevalence of pseudomonas infections is much higher.

7   So that could include patients with either cystic

8   fibrosis or bronchiectasis. And we know that these

9   patient -- this patient -- these patient populations

10 tend to have pseudomonas more commonly than some of

11 the other patient populations.

12   But again, there's a lot of work to be done

13 because we really need to identify what clinical

14 condition we are going to treat in these patient

15 population. Is it going to be treatment of pulmonary

16 exacerbation? You're not going to use this product

17 for preventing exacerbations.

18   And a treatment of pulmonary exacerbation in

19 this population really has similar issues as one

20 encounters in treating HABP/VABP, whether it be

21 concomitant therapy or identifying the organism. And

22 then the other challenge, also, will be to extrapolate

 1   efficacy from this patient population because they do

 2   have unique characteristics to the wider population.

 3   So that takes us to our last option, which

 4   again Helen and John had mentioned in their

 5   presentations which is using the animal rule. So I'll

 6   go through some basics about the animal rule. I'll

 7   walk you through an example of how an animal model was

 8   developed for treatment of plague. I cannot go

 9   through all the details, but I think just to give you

10   a flavor for what we are talking about when we mean

11   animal models to be able to use the animal rule.

12   So we have -- it's in the code of Federal

13   Regulations we have for drug and we have for

14   biologics. It's when we approve new drugs when human

15   efficacy studies are not ethical or feasible.

16   And it really applies to new products, you

17   know, which are being used to treat or prevent serious

18   or life-threatening conditions where definitive of

19   human efficacy studies cannot be conducted because it

20   would be unethical, so a slightly different situation

21   at hand here because, I think, as had been mentioned,

22   it's less about the study being unethical but more

 1 about the study not being feasible, given where we are

 2 today.

 3   So they want us to use an animal study to

 4 establish effectiveness at a full criteria that have

 5 to be met. And as I mentioned, there is animal rule

 6 guidance that goes through these -- this in very

 7 detail, and it's also outlined in the regulations.

 8   So we have to have a reasonably well-

 9 understood pathophysiologic mechanism for the disease.

10 The effect has to be demonstrated in more than one

11 animal species, and the animal species is expected to

12 react with a response which is predictive of humans.

13 The endpoint that we use in the animal study should be

14 clearly related to the desired benefit in humans, and

15 it's generally the enhancement of survival or

16 preventing major morbidity.

17   And we have to have adequate information,

18 the kinetics and pharmacodynamics of the drug in the

19 animals and humans so that we are able to select an

20 effective dose in humans. So all these criteria have

21 to be met for us to rely on the efficacy data from

22 animal studies to extrapolate -- or to be able to

 1   support approval of the product.

 2   And there are three additional requirements.

 3   We heard about post-marketing studies, or field

 4   studies, in John Tomayko's presentation. So there is

 5   a requirement for post-marketing studies to provide

 6   evaluation of the safety and benefit if circumstances

 7   arise in which a study would be feasible and ethical,

 8   like in a bio-threat situation.

 9   There might be a need to restrict -- impose

10   restrictions to ensure safe use of the product. And

11   lastly, labeling must include information to patients

12   that explains that, for ethical or feasibility

13   reasons, the product was approved based on studies --

14   efficacy studies conducted on animals.

15   So if we were to use the animal rule for our

16   product X-1, we will obtain efficacy data from

17   adequately characterized animal models. And this

18   could be supplemented with clinical data from patients

19   with a variety of infections caused by pseudomonas

20   aeruginosa. This could be one or more descriptive

21   study.

22   The plus to this approach is that, you know,

1   if you're really not able to conduct an informative

2   efficacy trial, then this might provide us an option

3   to assess efficacy. However, again, as Ed had

4   mentioned in his presentation, we really don't have

5   any adequately characterized animal models, at least

6   not that we're aware of, for these particular

7   indications being considered. So a lot of work will

8   need to be done to develop well-characterized animal

9   models.

10   And unlike with bio-threat agents, it is

11 ethical to conduct these trials. I think the issue

12 here is really feasibility.

13   And unlike drugs approved for bio-threat

14 indication, if X-1 were to be approved, then it would

15 be used in a broader population and potentially on an

16 empiric basis. You're really not going to save it for

17 when an outbreak occurs as in a bio-threat scenario.

18   And then also raises questions about what

19 would the field trial look like because a field trial

20 is required when it's feasible and ethical. So if

21 you're able to conduct such a trial right after

22 approval, then it really invalidates the need to

1   approve the product under the animal rule.

2   And the post-approval study would really

3   face the same -- likely face the same challenges that

4   you encountered pre-approval. And I think for us a

5   bigger issue from a policy standpoint is what kind of

6   a precedent we might set for other clinical conditions

7   of low prevalence, so a lot of issues to work through

8   but certainly an option worth discussing.

9   Here's some examples of products. I just

10 have the list of drugs. I don't have the list of

11 biologics here that have been approved using the

12 animal rule. For infectious diseases, we have three

13 products approved for plague and three approved for

14 inhalational anthrax. There are also other products

15 available for non-infectious disease conditions, you

16 know, products that might help for radiologic nuclear

17 incident, cyanide poisoning or nerve gas poisoning.

18   So next, I'll walk you through the plague

19 example, you know, just sort of to, you know, let you

20 know that this is -- it's really not that

21 straightforward. But it's doable, I suppose, if we

22 all decide this is the way we are going.

 1   So the African green monkey model of primary

 2   pneumonic plague was developed to provide a platform

 3   for testing various therapeutic intervention.

 4   Mortality outcome was assessed in AGMs with

 5   symptomatic disease, and this was done in more than

 6   one lab. The progression of the disease was

 7   described, and the potential triggers for therapeutic

 8   intervention were also evaluated.

 9   And we had some human data available. I

10   mean, they were not perfect, so one could compare the

11   disease in the AGMs with that in humans. So here,

12   naïve -- experimentally naïve AGMs healthy male and

13   female was studied. The Colorado 92 strain of

14   Yersinia pestis was used, and this was the exposure

15   target. The AGMs were monitored clinically, and

16   laboratory tests were also monitored. And then the

17   AGMs that succumbed to disease, pathology both gross

18   and microscopic were assessed.

19   So when these studies were done, the

20   exposures did range a fair bit. AGMs clinically had

21   fever, loss of appetite, respiratory distress,

22   lethargy and increased respiratory secretions. From a

1   laboratory test standpoint, they had leukocytosis,

2   abnormalities in the liver function test, coagulation

3   abnormalities.

4   The duration -- the onset of bacteremia was

5   quite variable from 30 hours to 94 hours, and they had

6   radiologic infiltrates as well. On hystopath, there

7   was evidence of fibrinosuppurative hemorrhagic

8   pneumonia, so not really different from what one

9   expects in animals.

10   So here's -- in the next two or three tables

11   I tried to compare how the disease looked like in the

12   AGM compared to what we know about human pneumonic

13   plague. So the challenge agent in the AGM model was

14   Y. pestis CO92. In humans it's Y. pestis. The CO92

15   strain was isolated from a human with pneumonic

16   plague.

17   The pathogenic determinants of the organism

18   are the same monkey are to humans. The root of

19   exposures in AGM was aerosol, had only exposure. In

20   humans, it tends to be aerosol exposure as well,

21   generally, when there's close contact with the --

22   another individual with pneumonic plague are in the

1   unfortunate setting of a bioweaponized aerosol.

2   The exposures are quantified in the AGM. It

3   ranged -- but as long as you got more than 20 LD50,

4   the animals all succumbed. The infectious inoculum in

5   humans varies. It depends on the contact and the

6   degree of exposure.

7   From a pathophysiology standpoint, there

8   were a lot of similarities between the disease you saw

9   in AGMs and humans. The time to onset of disease of

10 condition ranged from one to three days, slightly

11 longer duration in humans. Time to death, again, it's

12 not very different.

13   Signs and symptoms were fairly similar.

14 There's fever, lethargy, tachypnea tachycardia. There

15 was evidence of neutrophilic leukocytosis, coagulation

16 abnormalities. Radiologic evaluation showed

17 infiltrates. In humans, it's very similar --

18 consolidation cavities bronchopneumonia and the

19 pathologies hemorrhagic pneumonia in both.

20   Both AGMs and humans are highly susceptible

21 to the disease and uniformly fatal if untreated. The

22 trigger to intervention in humans was based on them

1   having a certain degree of body temperature elevation

2   for a certain period of time. In humans, it certainly

3   varies. It depends on whether or not there's an index

4   of suspicion for plague being a possible etiology.

5   So based on all these, I think the four key

6   characteristics that we took into consideration

7   designing the animal efficacy study was that the

8   endpoint would be mortality. So the animal's dead or

9   alive. The timing of intervention is after the AGMs

10 had been febrile for a certain period of time and they

11 had met the threshold for the temperature elevation.

12 The test drug that was being evaluated for efficacy

13 was to -- was administered intravenously, and the

14 dosing regimens that the AGMs received were humanized

15 dosing regimens.

16   So I just picked one example for

17 levofloxacin, but there's information on the other

18 example -- on the other drugs as well in the public

19 domain. And also, a lot of discussion around how

20 these AGM models were developed if you're interested

21 was discussed at an advisory committee in 2012. So

22 all this information that I have presented and more is

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1   available on the website if you look for an advisory

2   committee in 2012.

3   So if you'll -- if you take plague -- take

4   the levofloxacin, an example, a single placebo control

5   trial in AGMs was conducted. Now, at the time that

6   this indication was being sought in the study, these

7   study -- the study was being done. Levofloxacin was

8   already approved for other indications, which included

9   pneumonia, both community-acquired and nosocomial

10 pneumonia.

11   So we though a study in one species was

12 adequate. There was no requirement to evaluate it in

13 two different animal species. The AGMs were exposed

14 to a mean dose of 65 LD50 of the CO92 strain. And

15 they were randomized. They got either 10 days of

16 intravenous levofloxacin or placebo after they reached

17 the pre-specified trigger. And as you can see,

18 mortality in the levofloxacin was significantly lower

19 compared to that in the placebo, and you have a

20 significant P value.

21   So I know I walked you through a lot in the

22 short period of time. But you know, just my sort of

1 summary thoughts here are that what we know so far

2 about Drug X-1, it certainly appears to address an

3 unmet medical need. It has a potential, so I think we

4 have to find a way forward to develop this drug. We

5 do acknowledge that under the current paradigm,

6 studying a drug such as X-1 that's only active against

7 a single species that occurs infrequently at any one

8 body site or even occurs infrequently across different

9 body sites can be very challenging.

10   I've gone through some potential development

11 options. Again, these are options that we've come up

12 with, but maybe there are others that we haven't

13 talked through. All the options I've discussed have

14 limitations, so none of them are perfect. And I don't

15 think any one of them is going to solve the problem

16 right away.

17   And even if we -- one were to lean towards

18 option four, which is to consider the animal rule, a

19 lot more work needs to be done to develop a specific

20 animal model, or models, for infection in which we can

21 assess the efficacy of either Drug X-1 or other

22 similar -- similarly situated products for the

  1   clinical conditions being considered for development.

  2   Thank you.

  3   (Applause)

  4   DR. COX: Thanks, Sumathi.

  5   Now we will have Marco Cavaleri from the

  6   European Medicines Agency, where he's the head of

  7   Anti-Infectives and Vaccines, will give a perspective

  8   from the EMA on the challenges of developing a drug

  9   that's targeting a single species.

 10   Marco?

 11   DR. CAVALERI: Thank you, Ed.

 12   I think a lot has already been said. So

 13   here, I will try to focus pretty much on some aspects

 14   that are coming up based on our reflection on a case

 15   like this one, which indeed is not an easy one.

 16   So first of all, again, as stated yesterday,

 17   I would stress that the preclinical and clinical

 18   pharmacology package has to be thorough and exhaustive

 19   as much as possible, including all the (inaudible)

 20   aspects and drug-drug interaction; metabolism and

 21   excretion; distribution in relevant body sites like

 22   ELF; as said yesterday, the PK in ICU patient and with

1 augmented renal clearance should be started; the PK in

2 renal and hepatic impairment, too, and also with the

3 need of dose adjustment.

4   And of course, we would expect to see an

5 adequate and robust PK/PD profiling, which is

6 essential and is expected to complement as much as

7 possible all the limitation that may derive from the

8 clinical efficacy data set. Exposure response

9 analysis are expected to be conducted in the efficacy

10 trials, even if here we have to recognize that is more

11 datasets we are talking about. And also, the

12 concomitant therapy will confirm a lot of this kind of

13 analysis.

14   So some general reflection. We heard a bit

15 around the conduction of clinical trials what could be

16 the role of rapid diagnostic test in order to enrich

17 enrollment. And frankly, we've been struggling to

18 think how you can really avoid at least thinking about

19 using some experimental rapid diagnostic test in order

20 to conduct trials with such kind of drug.

21   And of course, one of the goal will be to

22 try to reduce the amount of patient that are enrolled

1 empirically and which if on one side would add (ph) to

2 the safety database and the other will not be useful

3 for the sake of addressing efficacy evaluation. We

4 would allow 24 hours of previous antipseudomonal

5 therapy.

6   And even if we are encouraging the use of

7 rapid diagnostic test, EMA will follow pragmatic

8 approach if these are using the context of clinical

9 trials. And therefore, for the recommendation in the

10 context of the SMPC will have to necessary not be

11 binding with respect to the use of the rapid

12 diagnostic test, and we will try to figure out what is

13 the best way forward in this in setting (ph).

14   In consideration of the epidemiology for

15 this pathogen, at least in Europe, as you may know, in

16 certain countries the MDR pseudomonas aeruginosa

17 prevalence is very high. So at least try to enroll

18 some of these cases, considering that these

19 indications in the context of a limited use option.

20 But of course, here, we will not be overly demanding.

21   And is said by others, it's very important

22 for conducting trials with this kind of drug to go

1   into a careful site selection and try to go to sites

2   that are able to conduct trials in this -- with this

3   kind of drug in the (ph) pseudomonas.

4   Now, I took the liberty of taking out one of

5   the table that was introducing the document that you

6   have seen and going back to the point of rapid

7   diagnostic test. And I noted that the specificity of

8   the test that was put in there was below 58 percent

9   and quite variable.

10   So what I did was try to see if with the

11 specificity of 95 percent, which we may assume is not

12 so unrealistic, at least based on what we know in some

13 of the rapid diagnostic tests that are under

14 development for -- from negative pathogen and

15 pseudomonas, then what would be the PPV. And here,

16 you can see that if the prevalence of the illness is

17 15 percent and taking the sensitivity of 80 percent as

18 was initially proposed in the paper, then the PPV will

19 go up to 74 percent, which means that you will have to

20 enroll 135 patients in order to get 100 patient with

21 the illness or with a target pathogen.

22   So clearly, there is some benefit in

 1   considering the use of rapid diagnostic test in terms

 2   of clinical efficiency. At the same time, I do fully

 3   recognize that, as also has been said before, that

 4   this will not change the time you will take to run the

 5   trials. It will not change the fact that you will

 6   have to go broad with a large amount of size all over

 7   the world and that the number that you have to screen

 8   will be exactly the same, so very high.

 9   And also, we also do acknowledge that, as I

10   said, from an operational perspective, having a rapid

11   diagnostic test embedded in the clinical trials could

12   be problematic and not so straightforward.

13   Nevertheless, it could be a good opportunity to try to

14   make the clinical development more efficient.

15   So coming to what could be the options, and

16   here I would go along pretty much what I showed you

17   yesterday around what will be the examples that were

18   shown in our guidance document. So along those lines,

19   one option could be to conduct a randomized study in

20   HAP/VAP, which is the type of infection that is most

21   prevalent with pseudomonas aeruginosa. And we can

22   concede that that is a very good test for any drug.

1   Here, we will be open to consider enlarging

2   the non-inferiority margin and also maybe to consider

3   whether the alpha level could be relaxed somehow. And

4   of course, all these elements will have to be

5   discussed on a case-by-case basis and based on a

6   specific proposal. But we are pretty open to talk

7   about that.

8   The primary endpoint will be clinical

9   outcome as test of cure. And of course, this can be

10   handled with different statistical analysis plan if

11   the FDA requires all-course mortality. And it would

12   be good to look into option for testing of nested

13   superiority in subgroups or based on secondary

14   clinical irrelevant endpoints.

15   We do acknowledge that monotherapy's not

16   possible, at least initially. And here, I think the

17   proposal in the paper sound like a good approach and a

18   valid starting point. But again, it would have to be

19   discussed to what extent the use ertapenem would be

20   possible in various parts of the world and whether the

21   dose suggested would be accepted by most

22   investigators.

 1   The control therapy may be a pretty fine

 2   single combination. And again, we're proposing the

 3   paper sounds (ph) as a good way forward. But again,

 4   in terms of feasibility, there might be a need to

 5   consider best available therapy.

 6   And of course, here we don't want to end up

 7   in a situation, as Mike was showing yesterday that

 8   there are 69 different best available therapy that can

 9   be considered. So it would be very important that

10   there is a limitation to the number of best available

11   therapy to be considered and according to a define --

12   a predefined hierarchy (ph).

13   And this could include option for cases of

14   MDR isolate. For that specifically, an option could

15   be to have an additional uncontrolled study that just

16   is recruiting the MDR cases.

17   Another option would be the all-comer

18   studies, which would include the HAP/VAP, intra-

19   abdominal, UTI and bacteremia. Again, infection

20   specific in clinical outcome at test of cure is

21   primary endpoint. We do not expect this study to be

22   power for formal inferential testing.

1   Superiority is not demanding. But of

2   course, it will be very important to try to explore

3   option for nested superiority in subgroups and

4   secondary relevant clinical endpoints as for the case

5   before. And an even randomization can be considered

6   for it to four-to-one (ph). What is important here is

7   always to have even a small control group that would

8   help us in order to understand that, for sensitivity

9   purposes, to understand what we are seeing in the

10   trial.

11   Monotherapy is -- would not be possible at

12   least initially, maybe with exception of UTI. But as

13   I think already said by Sumathi, this is not very

14   common, and so it can be very challenging to get a lot

15   of cases with pseudomonas and UTI.

16   Control therapy may be as well pretty fine

17   or be best available therapy, and the same arguments

18   as raised before will apply on the need of hierarchy

19   if best available therapy is used.

20   The last option will be an uncontrolled

21   study, including the major indications as highlighted

22   before with infection specific clinical outcome at

1   test of cure as primary endpoint. And here, it would

2   be essential to have adequate and convincing external

3   and historical control.

4   The same argument on the monotherapy will

5   apply, of course. But of course, in light of the

6   hurdles in the interpretation of the data which are

7   expected to come up, adequate justifications will be

8   provided that this is the only way forward or the only

9   feasible approach. And here a convincing PK/PD

10 package will be even more critical than in the other

11 scenarios.

12   So at the end of the day, the indication in

13 line with what I told you yesterday will be for the

14 treatment of infection due to pseudomonas aeruginosa

15 in patients with limited treatment options. We

16 referenced to other part of SMPC. And in particular,

17 I would stress that in the Section 4.4, so the warning

18 section, the limitation of the data will be explicitly

19 stated, mentioning the relevance of population for

20 which there are notable uncertainties as, for example,

21 not sufficiently included or represented in the

22 clinical studies, or for which PK data are not

 1 available or not fully supported of activity at that

 2 specific body site.

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

 4   (Applause)

 5   DR. REX: So, thanks to all four of our

 6 panelists. We're now going to take a break. Outside

 7 there is another handout. That handout is, in a

 8 sense, the reveal but it's also the basis for the

 9 debate. And I hope you've all come with some ideas.

10   We've held back showing concrete solutions

11 so you had all the time to sort of let your brains

12 spin around and come up with the brilliant idea that

13 none of us have thought of. That's what we're looking

14 for.

15   The -- we'll come back at 10:45 and talk to

16 you soon.

17   (Off the record.)

18   DR. REX: -- towards getting started.

19   So welcome back to Drug X-1.

20   Maybe push that door shut. We'll deal with

21 it in a second. So, yeah, if you would, thanks, it

22 would be great.

1   So before we go on into the clinical case

2   and how it got developed, are there any questions by

3   anybody on the panel or in the audience about the

4   setup, you know, for the sort of the background on X-

5   1? You know, there -- one of the great things about a

6   hypothetical drug is any data that I need I can invent

7   in my microseconds. So if there's something you'd

8   really like to know, we can tell you the answer to it.

9   I realize things like, you know, what's the

10   protein binding. Well, it didn't end there because --

11   okay. It's 62. You know, you just did -- the math is

12   adjusted somewhere buried down in there.

13   So David (ph)?

14   DAVID: Just something that Sumathi

15   mentioned, is there Phase 1 data in seriously ill ICU

16   patients in terms of PK?

17   DR. REX: That's not listed in the book.

18   That -- we haven't done it so you can add that to

19   something you could go and dose some people with

20   nosocomial pneumonia. What we did in the case was we

21   said that we're going to assume the perimeter

22   estimates -- are inflated from the healthy volunteers.

1 And it -- and because it was chosen as a purely renal

2 drug, you know, there's so much kind of known about

3 what drugs like that do. But that's probably a good

4 idea, is to develop some information like that. So,

5 you know, yes you could do that.

6   Other questions about the setup? John?

7   DR. TOMAYKO: Yeah. I have a question for

8 Marco. In your examples of the uncontrolled study and

9 the across-body site study, what's the type of

10 approval that that would get in the EMA?

11   DR. CAVALERI: Yeah. Well, that will have

12 to be discussed in light of the data and, you know, in

13 light of the uncertainties that will emerge on the

14 benefit tree.

15   So one option might be exceptional

16 circumstances. Another option might be a full

17 approval if the data fully convincing and if external

18 control, historical control can be pretty convincing

19 in terms of demonstrating what is the effect of the

20 drug. So I think we are keeping the options open and

21 not ruling out what kind of approval will be most

22 suitable.

1   DR. CAVALERI: Okay. Thanks.

2   And then I have one comment. Sumathi made

3   this statement that if I proposed doing a field study

4   right after I get an approval on the animal rule, then

5   that kind of invalidates my feasibility argument. I

6   just wanted to add some clarity to that.

7   I'm looking for a little flexibility. I

8   know that we don't have the pseudomonas animal model

9   as of yet and there's probably some issues that have

10   to be worked through. But what I think we might be

11   able to do in a field study is answer questions that

12   emerge during our clinical program, and their

13   important clinical questions.

14   As an example, what if we did have in our

15   small clinical data a few of these patients with head

16   trauma who had poor outcomes and we'd like to

17   understand why. Maybe it's a PK issue, and maybe we

18   should go to the centers where those patients are more

19   likely to be studied and try to develop a better

20   understanding and understand how perhaps to dose

21   better. And all of this information only improves the

22   benefit risk once you have the approval. So that's

1 what I meant about a field study.

2   DR. NAMBIAR: Yeah. So I think the typical

3 sense of the word, because you're looking at bio-

4 threat and you talk about field study, it's really

5 when you sort of have an event, a bio-threat event.

6 So that's a little different than here.

7   In here, I think the issue -- the reason one

8 would -- when was thinking about using the animal rule

9 is because it's really a feasibility issue, to be able

10 to do an adequate well-controlled trial as we would

11 like it. So even if one were to use the animal rule,

12 we are certainly looking for some clinical data in

13 humans, which should be available at the time that

14 you're actually trying to approve the product based on

15 animal rule.

16   So yes. And if that is a across body sites

17 and involves patients with various degrees of

18 comorbidities, that site will all help us. But the

19 basis for approval in that situation would be the

20 animal rule. So that's the difference.

21   DR. REX: It looks like Helen has a question

22 and then Ed.

 1   DR. BOUCHER: So maybe I'll just follow up

 2   Sumathi.

 3   So in that scenario, what would the label

 4   look like?

 5   DR. NAMBIAR: Okay. So I'm not quite sure

 6   if we are at the label. But typically, for products

 7   that are approved under the animal rule, we describe

 8   the animal efficacy study that was the basis of

 9   approval in the clinical study section of the label.

10   We don't have any human data other than safety, right?

11   The one exception is in looking at these

12   non-infectious disease-related labels, is for the

13   cyanocobalamin. There was actually was some data in

14   humans who sort of were exposed in -- I think they

15   went into burning building or something, and it was

16   actual cyanide exposure. So there is some human data

17   that was available, and that is included in product

18   labeling.

19   But exactly what we would include, I mean,

20   we really have to discuss. You know, the regulations

21   do state you only include adequate well-controlled

22   studies. But you know, we'd have to discuss that when

1   we get to that point.

2   DR. COX: Maybe just following on this, too,

3   one of the things I was wondering is, you know, if you

4   think about it, if you're developing a drug, it may

5   not be feasible to do, you know, a five-year trial

6   that enroll an X number of patients.

7   But you know, if the drug were approved, you

8   know, could you then embark upon a longer clinical

9   trial program that might get you to something that

10   would actually be a controlled study that would help

11   you to understand how the drug works that, you know --

12   so in essence, I'm trying to figure out are there some

13   things that might be feasible post-approval that you

14   really just couldn't do preapproval?

15   DR. TOMAYKO: Well, I'll just take a chance

16   and try to highlight what comes to mind. You know,

17   envision that you have a drug that's approved with

18   very limited data such as animal data and some

19   clinical data and you just convinced your investors to

20   invest a substantial amount of money in doing that

21   work. And yes, you'd love to be able to do anything,

22   but you might not be selling much of that drug at that

1   point. And you might not be able to raise the money

2   to do anything huge. That's just the reality of the

3   situation.

4   I mean, if somebody were to come by and buy

5   the drug and have greater resources and be willing to

6   take that type of a thing on, great. But there's no

7   easy solution to this problem, in my view.

8   DR. COX: Yeah. And I realize, too, that,

9   you know, the incidence of disease may still be very

10   low. So it's -- that doesn't change. I'm just --

11   something longer term, I'm just trying to figure out

12   can you make -- you know, get something that would

13   gather some clinical data that might help make sense

14   of it.

15   DR. BORIO: I mean, just to clarify Ed and

16   Sumathi, that the field study is something that is

17   very, very flexible and open and, you know, how you

18   can collect the data. So it could include registries,

19   reliance on electronic health records. It could

20   include, you know, just a variety -- much more

21   flexibility than what we'd expect as an adequate and

22   well-controlled study for an investigational product.

 1   DR. REX: Helen again.

 2   DR. BOUCHER: So to that end, some things

 3   that have been discussed as part of the carb effort

 4   have included, you know, improved monitoring of

 5   antibiotic use in general through the CDC and HSN and

 6   other mechanisms really directed at stewardship. But

 7   it may not be crazy to think that those types of

 8   mechanisms might work here where, you know, a new drug

 9   for very a specific special population came out and

10   could be monitored in that way with some kind of

11   feedback whereby, you know, it's more real world. And

12   so the quality of the data, you know, it may not be

13   exactly what you're looking for, but it would -- could

14   be a way to monitor and understand more about the

15   potential utility and/or risks of these new agents.

16   DR. COX: And just thinking about things

17   too, I mean, you know, there will be, you know, a fair

18   -- you know, an animal rule-based approval does have,

19   you know, a certain degree of uncertainty. And you

20   know, those that have worked with animal models and,

21   you know, how they're developed -- and they're sort of

22   developed to actually show an affect. I mean, that's

1 sort of why you, you know, develop the animal model in

2 the way that you do. So getting that sort of second

3 component of predicting human efficacy, I mean, there

4 is a degree of uncertainty.

5   So the animal rule does have with it, you

6 know, restrictions to ensure safe use. And it would

7 seem that, you know, some of the conditions that are

8 described might be very reasonable to consider in a

9 circumstance like this because the drug would be --

10 you know, patients are out there. They're having

11 infections, you know, from day to day. And you know,

12 the appropriate therapeutic role for such a product,

13 you know, this may be an appropriate area to think

14 about some of those restrictions and how the product

15 would be used appropriately in order to balance, you

16 know, what's the uncertainty the -- you know, so that

17 the product is used safely out there in the real

18 world, so.

19   DR. REX: Any other questions for

20 clarification sort of on the context in the setup?

21   Okay. So let's move forward then.

22   So I've always like this quote by George

1   Box, and I think it's self-explanatory for today.

2   If you look at your handout, what we've done

3   here is several of us have kind of collaborated on

4   this. We've built up a series of approaches, and

5   we're going to talk about, first, three scenarios that

6   are an attempt to eke out a path to a non-inferiority-

7   based approval. Just see what -- you know, what does

8   it take. Kind of do a little wiggling around.

9   And then Scenarios D and E are -- put you --

10   sit down into a further corner where you just conclude

11   that either you can't do it, or it's crazy for one

12   reason or another. And then Scenario F is going to be

13   that I'm looking for one of you guys to have a

14   brilliant insight in the course of the day. Audience

15   participation. What did we overlook? What else could

16   we have done?

17   In terms of timing, I'm going to use -- it's

18   just now 11 o'clock. We're going to go till about

19   12:15. I think that's probably going to be enough to

20   walk through some of the Scenario A, basically. And

21   then we will come back and walk through the remainder

22   -- remaining stuff and have a moment for -- and along

1   the way it's very, very informal. So you can take off

2   your tie.

3   That's the other thing to know, okay? Yeah,

4   I do tie it. If you can't tie it, you shouldn't wear

5   it. Stop there.

6   (Laughter)

7   DR. REX: But I am -- with that said, it

8   would going to be scary to go further. All right. So

9   --

10   AUDIENCE MEMBER: (inaudible - off mic).

11   DR. REX: Yeah. No pressure here. It's

12 just -- all right.

13   So here are the constraints. So as we were

14 developing this case and the approaches, the goal was

15 to make this very real, okay? So you're not permitted

16 any imaginary thing, so -- and also excluded sort of

17 the BFMI solutions which is an acronym for me, brute

18 force massive ignorance, okay? So enroll 10,000. No,

19 we're not going to do that.

20   We don't assume any kind of a perfect

21 diagnostic. I don't have an instant susceptibility

22 for all the pathogens in the sputum. I don't have

1   instant knowledge that only pseudomonas aeruginosa is

2   present. I don't have that.

3   We also presume that superiority via study

4   of just MDR pseudomonas is not possible, much too

5   rare. It would require well-timed outbreak, and I

6   don't ever want this -- I actually don't want it to be

7   possible. All right? That'd be bad.

8   Assumed at least in Scenario A that there

9   was enough money to do about 1,000 patients and they

10   kind of -- you know, so that sort of in the 60 to $100

11   million range and that you can make an argument maybe

12   with some government support that you can sort of

13   somehow put that much money together. There's not

14   enough money for 3,000 patients. And also, you know,

15   it's not just money.

16   If you set off to do a BFMI program and you

17   decide I'm going to need the next 5,000 patients, what

18   does that mean for other drugs? You know, if there's

19   a clinical trial network, it means you've consumed it

20   for the next 10 years. I mean, no. You can't do

21   that.

22   We -- there's an implicit assumption ,just

 1   because it's not going to get discussed further, that

 2   is that add-on therapy is not a viable strategy. And

 3   it's hard to envision how standard of care plus X-1

 4   would show superiority to standard of care plus

 5   placebo.

 6   I think that the clear blue water above that

 7   when standard of care is active -- you know, when

 8   standard of care is active, it's -- you know, it's

 9   active. And as John Tomayko said, how much more cured

10   can you be than cured.

11   So in short, we -- the number required

12   miracles is kept at one -- at less than one in all the

13   solutions. I'm not going to reject a lot (ph), but I

14   simply will not plan on it.

15   So this table is in your handout. A, B and

16   C are all scenarios in which, as you'll see in a

17   minute, we're going to actually study -- end up

18   studying across three diseases, but principally across

19   nosocomial pneumonia and complicated intra-ab. They

20   all end up enrolling a little over 900 subjects. The

21   number with the pathogen falls as you go from B to C,

22   in particular.

1   And the difference between A and B -- A is

2   going to end up being a situation where the two study

3   arms end up being -- just the clinical results show

4   pretty close to similarities. So the difference

5   between them -- the delta between them is about zero,

6   but the confidence intervals are quite wide.

7   And there will be some confounding issues to

8   deal with. But overall, Scenario A is the easiest

9   scenario. In Scenario B, we're going to look at a

10   boundary case version of Scenario A. The difference -

11   - the delta will be made as wide as possible within

12   the constraints of already very wide margins. And

13   we're going to talk about that.

14   And then Scenario C, you'll find -- Scenario

15   C is a situation where we can't enrich and we don't

16   have very much pseudomonas. And so Scenario C winds

17   up with confidence intervals as bad as Scenario B.

18   That's part of the thing to watch for there, is they

19   sort of lock-step each other.

20   And then in D and E the pathogen is very

21   rare and it might no longer be pseudomonas. You know,

22   we quit kind of fussing so much about that at this

1   point. But the end is very small, even though you

2   enroll a lot of subjects. And even if you were to

3   triple the size of the program, you're still barely

4   climbing up in terms of numbers to the size for the

5   pathogen of Scenario C. So that's sort of the logic

6   here, is to test at each step down the way.

7   What does it feel like in -- one, we were

8   joking just before it started. You know, we'd like

9   the sun and the moon and the stars, right? But when

10 you can't have that, how big of a flashlight would you

11 be willing to accept, you know? So that's kind of

12 what we're after here, is how much of a flashlight

13 will you settle for instead of the sun, the moon and

14 the stars.

15   So we're all now the sponsor. So let's just

16 do some thinking out loud. So safety database, what

17 do we have now? Well we've got about 40 in Phase 1

18 who've received the full dose over 14 days. It might

19 be a little higher. And then the 10 in the Phase 2

20 non-CF-bronchiectasis study. So that's 50 at full

21 dose and duration in theory.

22   What we know is the preclinical signals are

 1   easily monitored. So what this suggests is we need --

 2   we need to get close to 300 for our safety database.

 3   There's not an absolute requirement for 300, but you

 4   heard yesterday the notion of the rule of three. You

 5   take your safety numbers, your end, divide it by

 6   three, and you're down to the level of which you're

 7   seeing all the -- all of the events within a 95

 8   percent confidence interval. So basically, at 300

 9   subjects you've seen all the -- you're likely to have

10   seen all of the one -- the 1 percent events. And

11   because it's pretty clean, monitor won't -- you know,

12   provided nothing leaps out at us, it's, you know,

13   somewhere between 250 and 300 cases on full dose and

14   duration ought to be enough.

15   It's pretty clear that the culture-positive

16   rates, if they drift much below 15 percent, we're in

17   deep trouble. And here are some simple numbers. At

18   80 percent response, 85 percent power, 1-to-1

19   randomization, you can see that you're really even

20   with a pretty good size margin of 20 percent, your

21   numbers are, you know, may not be even -- may not be

22   feasible.

 1   So now for Scenario A, we envision -- we --

 2   I want -- fishing for a monoclonal. And very

 3   helpfully, if you look on page 8 -- which is page 2 of

 4   the handout afterwards, but it's page 8 as labeled --

 5   Point number 3, you'll see a citation to a paper by a

 6   guy named Pastels (ph). And they've actually invented

 7   a monoclonal against piocyan (ph) in a rather

 8   metabolite of piocyan.

 9   And if you know pseudomonas, this is a

10   metabolite that this organism makes that others don't.

11   And so if you've got a monoclonal against a

12   metabolite, you can make one of those little

13   immunochromatographic lateral flow things where you

14   either get one line or two lines, depending on whether

15   or not the metabolite of interest is present. It

16   would be simple -- no batteries. It would be rugged,

17   but I'm not pretending it's very good, okay?

18   I'm just -- it's -- so we kind of invent

19   this, and it's going to help us get a slightly higher

20   rate of pseudomonas aeruginosa. If I had a better

21   time or a better test and could get up to Marco's

22   imaginary, you know, better sensitivity, that'd be

1   great.

2   Let me emphasize that I'm not using this

3   test as definitive. Patients, to get in the micro ITT

4   population, which will be the population of interest,

5   you're still going to have to have positive culture.

6   The whole point is that this helps me more -

7   - the people that enroll, if they're positive on this

8   test, they're more likely to grow the organism. But

9   I'm still not assuming that they become tremendously

10   likely to grow the organism. It's just a little boost

11   because you got to get to 25 percent in order to get

12   under 1,000. I'm just going to warn you. When I did

13   the math, I couldn't find a better way.

14   Concomitant antibiotics are a problem. And

15   that's an understatement. It is important to study

16   nosocomial pneumonia. The guidelines often lead you

17   to using two drugs. And Sumathi pointed at this, but

18   let me show you the wording. This is the most

19   recently published set of guidelines from IDSA. And

20   I've clipped out three pieces of text.

21   There's a place where they talk about what

22   do you do for empiric therapy. "We suggest

1 prescribing one antibiotic in patients without risk

2 factors for antimicrobial resistance who are being

3 treated at ICUs where less than 10 percent of gram-

4 negative isolates are resistant to the agent being

5 considered for monotherapy." I want to work there,

6 okay? Where is this place? Okay.

7   And then they say if -- now that you know

8 it's pseudomonas, if you've got HAP/VAP and you're not

9 in septic shock and you're not at high risk for death

10 -- we'll come back to that in a second -- and for whom

11 the subject test results are known, we say monotherapy

12 is okay with one drug. And then they say however, if

13 you're in septic shock or you're at high risk for

14 death, then we suggest a combination.

15   So let's see. Which patients aren't at high

16 risk for death given that the mortality of this

17 disease in untreated subjects is 60 or 70 percent and

18 even with good therapy, it's 10 to 20 percent? So

19 which one of you wants to say I'm not at high risk for

20 death? I -- you know, again, I want to practice

21 there.

22   So what I conclude from this is that in a

1   study that I run as the sponsor where I have to get

2   people to sign up -- and I understand that's a little

3   different than what you might be able to do in an

4   academic investigation, but when -- but what I'm going

5   to do a study worldwide and convince a lot of

6   different sponsors to work on things, a lot of

7   different sites to work on stuff. I've got to come up

8   with something that meets, I'm not going to call it,

9   the lowest common denominator, but it meets a common

10   denominator.

11   And so the assumption here is that,

12   inherently, the guidelines are really going to

13   basically say that most of the time for nosocomial

14   pneumonia in most patients, you got to give two drugs

15   at least empirically. Just take that as given. If

16   for some reason, you could get 10 or 20 percent where

17   you didn't have to give combination therapy, that's

18   upside. But for today's problem, I'm just sort of

19   assuming that the world says, really, you ought to do

20   this.

21   You know, in two years from now, people

22   might really be saying it even more often. Other

1   information may've come out. You know, Paul Ambrose

2   is saying -- you know, talked about the fact that

3   variability in exposure suggests that it's favorable

4   for everybody to get two drugs just because, you know,

5   variability's there. But it's also important to get

6   some data using X-1 as monotherapy. So we got to do

7   both of these things in this program somehow.

8   Helen has pointed out that it's valuable to

9   see data in more than one setting, and that seemed to

10   me to make a lot of sense. And so the sponsor said,

11   all right, I'm going to do two trials, but I'm going

12   to cover three indications in my two trials.

13   The first trial will be a prospective,

14   blinded, as you'll see in a moment, randomized

15   controlled trial with separate sub-arms for nosocomial

16   pneumonia and complication intra-ab. And it's just

17   barely possible to kind of sort of eke out a non-

18   inferiority sign. And then there will be a study

19   called the Open Label LTO Study, open label and

20   limited treatment option patients. These are for

21   everybody else where you know it's pseudomonas and

22   you'd like to take a shot at it with X-1. That's sort

1 of the concept here of these two trials.

2   So just a little sidebar on entrapenem,

3 which is going to become very important. It's a

4 carbapenem that is stable to the ESPLs. It is

5 inactive for all intents and purposes versus

6 pseudomonas aeruginosa. It is indicated in

7 complicated intra-ab, skin, CAP and UTI, and I have

8 had a consultation with my PK-ologist. We've reviewed

9 the literature.

10   There actually are ELF penetration data in

11 VABP patients with entrapenem that are published data.

12 It's in your -- it's cited in there somewhere that --

13 and including free drug measurements in the ELF and in

14 the plasma simultaneously. And you look at that, and

15 that's the paper by -- on Page 9 by Boselli (ph). And

16 actually, you're hitting the -- well above the time

17 above requirements for entrapenem in the ELF.

18   And then Artero (ph) and Bassetti (ph) just

19 before that, basically give you a little dab of

20 clinical data. So I'm not going to say this is great.

21 There are probably some more modeling that could be

22 done to get comfortable with it, you know, and also

1   discovered along the way that entrapenem's actually

2   been studied at two grams a day as opposed to one, so

3   there's safety data from that. So you might even say

4   that we come back and look at 1 gram to (ph) 12, or

5   something with entrapenem. You know, it's sort of

6   more work for the site.

7   But as it stands right now, it looks to me

8   like entrapenem for non-pseudomonas, gram-negative

9   nosocomial pneumonia, including VABP, is as well

10 validated as many other things. So I'm going to sort

11 of take that as an acceptable tool. So this is, you

12 know, number of miracles remains less than one.

13   So here's the design for the randomized

14 control trial, separate sub-arms, but it's a common

15 protocol just for ease of implementation. And the two

16 arms are X-1 plus erta versus meropenem. In the

17 complicated intra-ab arm, you may add Amikacin. And

18 when you do so, it's blinded. So you've -- you write

19 an order for Amikacin, and it only gets given to the

20 meropenem arm. It does not given -- get given to the

21 X-1 arm. So it's Amikacin versus placebo.

22   For nosocomial pneumonia, made the decision

1   to say you must give Amikacin. Just take the issue

2   off the table. Everybody gets active drug. And you

3   have to stop it as soon as you know your

4   susceptibility, all right? And if by Day 4 you can't

5   stop it or if it's -- or if the isolate is meropenem-

6   resistant, you're out. You maybe go to the OL LTO

7   study or something else, but no more on this, okay?

8   Because otherwise, I can't keep you on a blinded

9   therapy, all right?

10   We'll discuss in a bit the notion of a

11 different kind of a comparator. You know, I went -- I

12 sort of went towards the bias of let's have a -- let's

13 at least standardize the comparator to the extent we

14 can because maybe we can.

15   You can blind this. X-1 and meropenem are

16 both Q8. Meropenem is supposed to be given over 30

17 minutes. All you do is make its PK/PD better if you

18 give it over an hour, so there's no reason not to give

19 it, you know. So meropenem and X-1 can both be a Q8

20 drug given over one hour.

21   And then the ertapenem or placebo --

22 everybody gets one dose of that a day because

1 ertapenem is a Q24 drug, so you know, really easy to

2 set this up. And I didn't work out the dose

3 adjustments for renal dysfunction. But, you know,

4 we've invented X-1 as renally cleared, and I bet it

5 would just sort of flow down with probably similar

6 dose adjustments to the meropenem arm and come up with

7 something.

8   For both arms, if you want something for

9 gram pauses, feel free. Put in some 1As. Look -- put

10 in some vancomycin. It probably would specify

11 something, but, you know, pick one.

12   The inclusion -- standard rules for

13 complicated intra-abdominal nosocomial pneumonia --

14 I've already said that the other thing is we'd have

15 this little lateral flow kit, and you need to -- or if

16 you've recently grew pseudomonas, you can come in.

17 You know, if you've got a belief that -- the baseline

18 culture is going to have to be positive. You've got

19 to have a reason to enroll them -- and no more than 24

20 hours of prior effective therapy.

21   So the stats will be -- the primary analysis

22 will be in the microITT population. That is the

1   subset that is positive for a baseline culture for

2   pseudomonas. Being polymicrobial is not an exclusion.

3   You can have pseudomonas and E. coli and Klebsiella.

4   You've just got to have pseudomonas in there. The

5   endpoint for clinical lab and for nosocomial are the

6   ones that are the standard FDA-recommended ones.

7   So it's clinical response for intra-ab and

8   nosocomial pneumonia. It's 28-day all-cause

9   mortality. And of course, you'd also put clinical

10 response and nosocomial pneumonia, so you've got data

11 for the EMA and the FDA. It's easily done. It's --

12 you know -- we've recently done this, and there's just

13 not a problem at all to collect both kinds of data.

14   Now we come to an interesting one. What

15 margin am I going to argue for? If you look in your

16 handout, you'll see that the FDA-proposed M-2 for

17 nosocomial pneumonia is 10 percent, and the -- for

18 intra-ab, I think it is -- I know I wrote it down.

19 Where is it? It's 10 percent. Right? Yes, it's 10

20 percent. But if I look at those numbers a little more

21 -- and the FDA said the M-1 for nosocomial pneumonia

22 is 20 percent, and the M-1 for intra-ab is 14 percent.

1   In theory, M-1 is the largest possible

2   margin you could ever use. So if the nomenclature is

3   not familiar to you, M-1 is the largest reliable

4   treatment effect than anyone has agreed on.

5   But if you look under the hood a little bit,

6   the FDA's M-1 is actually calculated by doing some

7   rounding down. So if you go into the actual data used

8   to compute it and you use -- you apply and you look --

9   they have two point estimates, treated and untreated -

10   - and you look at the 95 percent confidence balance

11   around those point estimates, the so-called 95-95

12   rule, and you take the difference between those, you

13   get 29 percent. So there's been a little rounding

14   down that's been done to get to the FDA's M-1.

15   I'm going to argue that, look, you know,

16   unmet need, plausible agent, the Phase 2 data we're

17   going -- that we've -- think -- talked about or will

18   talk about again in a second -- 29 percent, round it

19   to 30 percent, okay? I'm going to argue for 30

20   percent. And maybe I'll go find some more data and

21   I'll maybe -- and maybe I'll do with nosocomial

22   pneumonia what I do with intra-ab, which is -- intra-

1   ab, the M-1 is incredibly conservative. I'm not going

2   to go through how it's calculated. It's written down

3   in the document. But it's very, very, very

4   conservative because it actually involved preventing

5   infection rather than treating infection as its basis.

6   So here I played Go Fish for some data in

7   the modern era where someone had suffered from an

8   outbreak of KPCs and documented the lack of response.

9   And I find a paper by Di Carlo, which there's the -- I

10   don't have the graph on the slide. I don't think I

11   do. No, I don't. But it's in your handouts on Page

12   4. And Di Carlo found 30 patients who developed

13   infections after open-abdominal surgery. They were in

14   Italy, and they had this outbreak of KPC-producing

15   Klebsiella.

16   And so they had 30 people who didn't get

17   effective therapy, basically. And -- or, rather, not

18   quite. So they started off and they were using

19   tigecycline and colistin at sort of what they called

20   ordinary doses, and they were doing terribly with it.

21   And so then they bumped the dose of both of them up,

22   and it -- and they do a whole lot better with it. And

1   if you look in your handout -- should've put that on

2   the slide -- it's this little figure that's on the

3   lower right-hand corner of Page 4.

4   And so this is a Kaplan-Meier. This isn't a

5   clinical response. It's a KM of survival, okay? And

6   the upper line is the higher dose of tigecycline and

7   colistin, and the lower line is the lower dose. And

8   it's about 15 subjects in each arm.

9   And so I'm going to say, look, you know,

10 intra-ab is a real disease, and maybe I'll find some

11 other data. And I think your margin is too small, and

12 so I'm going to somehow come up with a 25 percent.

13 And if I can't get to 25 percent, we'll talk about the

14 consequences of that a little bit later on.

15   But you know, it's that kind of data because

16 you've actually -- can go look for some modern data to

17 tell you whether or not you've got a problem. That's

18 as close as I get to using a miracle.

19   So success would be defined as the 95

20 percent confidence interval of the differences within

21 margin in both sub-arms. And the logic for approval

22 now becomes the following pieces of data all together

1 -- very strong pre-clinical dose rationale. The

2 target exposure has been proven in the clinic -- and

3 by the way, we're going to do population PK in the

4 Phase 3 program, and I'm going to presume that it

5 comes out, more or less, in the zone.

6   We've got a Phase 1 study that shows that it

7 gets into the ELF. We've got a Phase 2 study in

8 people who are -- with non-CF-bronchiectasis

9 chronically colonized with pseudomonas.

10   By the way, there's literature on this. I

11 didn't invent that. I actually looked at some cases,

12 some little stories. And the idea of reducing most of

13 the group by about one log and about half of them by

14 two logs, that's entirely in the zone for an active

15 drug in the lung. So, you know, I found a series of

16 little papers like that.

17   It wasn't that it cured any of those folks.

18 You know, it didn't make them sterile. But the point

19 was that this study shows the drug gets into the lung,

20 and if pseudomonas is there, the drug can act on the

21 pseudomonas in the lung. So that was the whole reason

22 for that.

1   And then this RCT has two disease where we

2   show an effect. And each one of them is flawed,

3   right? Nosocomial pneumonia is going to be confounded

4   by concomitant Amikacin. Complicated intra-ab is

5   partially confounded by surgery, but at least we get

6   some monotherapy data, right? So it's -- so the point

7   is not that any one of these pieces of data is the

8   answer, but each one of them kind of bangs around at a

9   different edge of the problem.

10   And then you assume that the unmet need

11   label will be in there, and it will only cover

12   patients with limited treatment options. I've not

13   talked about the open label companion study, but it

14   would give you some data in other settings. And I've

15   assumed that it is just an open-label study that you

16   get some data in. You could choose to randomize. And

17   I don't think I have that on the slide, but my sense

18   was there were not that many cases to begin with. And

19   so I'd rather have more exposure on X-1.

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

21   right.

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

```
 1   is imaginary that we invented.  We powered 85 percent

 2   and assume an 80 percent response rate in both arms,

 3   and that's a simplification just -- you know, we've

 4   got a pick a number.  We're going to randomize it two-

 5   to-one in both sub-arms.  And I sat and played with

 6   the math a little bit, and I came up with this balance

 7   of cases.  Assuming the margins of 30 percent for

 8   nosocomial pneumonia and 25 percent for intra-ab, I

 9   wanted to have something that -- where there was a

10   little bit of tolerance for heterogeneity, though, as

11   you'll see in a second, not a lot.

12           So I put about one-third on nosocomial

13   pneumonia and two-thirds on intra-ab.  And you can see

14   what that turns into for the X-1 cases and the control

15   arm cases.  And from there, you see the math as to how

16   many you're going to get.  And in the hand into the

17   setup, as I've talked about this hypothetical device,

18   I'm assuming about -- I'm getting a 25 percent

19   recovery rate for -- in nosocomial pneumonia, and 16

20   and a half percent for complicated intra-ab, which is

21   two-thirds better than you get by chance, okay?  So

22   it's just arbitrary.
```

1   In Scenario C, the device is going to fail

2   and we're going to fall down to what happens only by

3   chance.

4   So the actual study in Scenario A hits these

5   parameters. And how long did it take me to run this

6   study? Well, I did a little math here, and this is

7   what I came up with was that this might do it -- 36

8   months, 250 sites, screening nearly 2,000 subjects.

9   Okay. Yes, Kenneth Hillin (ph), I'm having

10   to pick him up off the floor.

11   So how did I get to this? Well, 36 times

12   250 is about 9,000 screening months' worth of work. I

13   looked at some comparables, like one that's -- I've

14   got some data from programs that we've run, and I took

15   a haircut on the enrollment rates that I was seeing in

16   recent studies. I'm sorted down two-thirds from that.

17   And I said what do I need. Okay?

18   So I've not done super detailed feasibility

19   work. And those of you who have done feasibility work

20   know that it's, you know -- it's like George Box's

21   comments. All numbers are wrong. These are really

22   wrong. You know, the accrual rates -- predicted

1   accrual rates drive you crazy.

2   I'll -- you know, anyway, big study, I

3   think. And I think this is a minimum. And something

4   that's going to come out in a second is that I think

5   that the numbers I predicted to enroll have to be

6   inflated up some or for some other issues that are

7   going to come up along in a minute. But let's pretend

8   that we do the study and our PK-ologist consultant did

9   a great job with selecting our dose and our pop-PK

10   (ph) is bang, on target.

11   And in the nosocomial pneumonia arm, the

12   people follow the directions, and pretty much

13   everybody gets a dose on Day 1. And -- but if falls

14   off pretty steadily. So they're -- you know, about

15   half the subjects only got two days. You know, it's,

16   you know, better than a sharp stick in the eye, as my

17   mother would say. And in the complicated intra-ab

18   study -- I didn't put it on the slide -- you know, 10

19   percent get Amikacin for a couple of days. Pick a

20   number. But it's not -- it's -- the majority don't

21   get it on intra-ab because you don't need it. And

22   with nosocomial pneumonia, the majority do get it, but

1   I think it's not unreasonable to say that you'd know

2   within a day or two whether you could drop it down.

3   And so I'm just saying that by the end of day -- you

4   know, two days, most people get two days' worth.

5   After that, it tapers off pretty rapidly.

6   So here are some numbers for a made-up

7   program. By the way, any questions about this so far?

8   Anybody want to ponder anything before I go forward?

9   Yes, question.

10   UNIDENTIFIED MALE SPEAKER: John, can you

11 run that by me again? You said you got 16 percent

12 (inaudible - off mic) study?

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

14   UNIDENTIFIED MALE SPEAKER: Using the

15 device.

16   DR. REX: Right. So the raw rate is 10 --

17 the by-chance rate is 10 percent. And so this device

18 -- I'm saying it boosts you up two-thirds. It gets

19 you up to 16 and a half percent. So for intra-ab, it

20 takes you from 10 to 16 and a half. For nosocomial

21 pneumonia, it takes you from 15 to 25.

22   UNIDENTIFIED MALE SPEAKER: But I'm

1 confused. How does the device increase the incidence?

2   DR. REX: It doesn't. It just means I only

3 enroll the ones who have pseudomonas -- of the people

4 I enroll, they're more likely to have pseudomonas.

5 Right. And you can argue about where is the cost.

6 Actually, the cost isn't just in the enrolled

7 patients. It's in the maintenance. You know, 250

8 sites means I've got to visit 250 sites once or twice

9 a year and replenish their IDP, and, oh my gosh, okay?

10 It gets really expensive just to have 250 sites open

11 for three years.

12   That might -- I don't have a good -- if

13 anybody has a good feel for the ratio of true per-

14 patient to site running costs underneath -- you know,

15 I've got a whole range of estimates from my group.

16 I'm happy to have any ratios there you come up with,

17 but that's the notion, okay? And, once again, why

18 those particular numbers? Because it fits inside

19 1,000 patients.

20   You know, I have played exhaustively with

21 this, and you can come up with other variations. I

22 didn't go to one-to-one because I needed the safety

1 database on X-1, so I wanted more cases there.

2 Didn't, you know -- one-to-one increases the -- it's -

3 - your best statistical power is always at one-to-one.

4 Any deviation from one-to-one costs you. But here I

5 chose to accept that cost because I wanted the safety

6 database, okay?

7   AUDIENCE MEMBER: (inaudible - off mic).

8   DR. REX: No, but they don't all get it for

9 full dose and duration. So only the 48 and only the

10 69 are going to stay on X-1 -- are -- because if you

11 don't have pseudomonas, you come off the study. You

12 know what? I didn't say that. That's a good point.

13 You could leave them on the study if you wanted to and

14 you learn about ertapenem. That's a good point.

15   AUDIENCE MEMBER: (inaudible - off mic).

16   DR. REX: Why not? Well, it's a good point.

17   You could -- I'd implicitly assumed that,

18 you know, if you didn't -- in terms of safety, you

19 actually could have way more than enough safety here.

20 It's a good point. Thank you. Thank you for the

21 clarification.

22   This case was busily invented over the last

1   four weeks, so there are holes in it.

2   AUDIENCE MEMBER: (inaudible - off mic).

3   DR. REX: Sorry, say it one more time

4   please.

5   AUDIENCE MEMBER: (inaudible - off mic).

6   DR. REX: No, because empirically, you don't

7   know at moment zero on Day 0. So at Moment 0, Day 0,

8   you randomize and you start Amikacin on everybody, so

9   everybody is going to have had that in this design.

10   Other questions? Question?

11   AUDIENCE MEMBER: (inaudible - off mic).

12   DR. REX: It's based on the cultures coming

13   back. You know, by the end of the second day, you

14   often have -- because what you all -- what you care

15   about is the susceptibility of the pseudomonas.

16   So if it grows on Day 1, then you'll have

17   susceptibility by Day 2, and that happens with

18   Pseudomonas, but it might also take to Day 2 and then

19   Day 3 to get it. Pseudomonas is not a particularly

20   slow-growing organism. It's not, you know -- it

21   doesn't hide. And anything better than this or worse

22   than, you know -- okay, so it's three days on average,

1 you know.

2   I -- but I sort of was thinking about what

3 does it often feel like to me, and I often have some

4 hint of it by the end of the second day. The morning

5 of the third day, I can get rid of the Amikacin. You

6 know, and maybe that's two and a half days, you know,

7 that sort of thing. Good question.

8   Yes, sir?

9   AUDIENCE MEMBER: (inaudible - off mic).

10   DR. REX: Sorry, say that one more time.

11 I'm trying to repeat the questions, but it's tricky.

12   UNIDENTIFIED MALE SPEAKER: All right. So

13 the drop-off rate applies for the total MP population

14 and not necessarily to the one who have pseudomonas,

15 right, and get the test drug. So for those, let us

16 say, to assess what the confounding effect of Amikacin

17 on test track would be, those rates would be higher

18 because those who have pseudomonas let's say probably

19 4 or 5 days -- 80 percent right?

20   DR. REX: What we're -- what I have assumed

21 is that you're willing to drop down to monotherapy, so

22 it goes a little bit against the IDSA guidelines.

1   You're willing to go down to monotherapy once you know

2   that the pseudomonas is susceptible to the test

3   agents. So that's an implicit assumption here, is

4   that by Day 2 or 3, you've got your culture, you've

5   got your susceptibility results. And you can say,

6   okay, it's meropenem susceptible. And for X-1, it's -

7   - you know, they're almost always susceptible, so that

8   says -- you know I'm going to take that as -- but you

9   may also be able to do the local test. And so you can

10   drop down to monotherapy.

11   The idea here is you're dropping down to

12   monotherapy for the pseudomonas part. You may still

13   be continuing the ertapenem; you may still be

14   continuing the linezolid. You know, you can do other

15   stuff. Does that make sense?

16   You know, I'm trying to say the Amikacin

17   doesn't -- if it goes on for a week in a quarter of

18   the patients, okay, it does. But everybody is going

19   to have had at least a couple of days.

20   Yes, ma'am?

21   UNIDENTIFIED FEMALE SPEAKER: How do you

22   account for the risk for CRE in the comparator arm?

1   DR. REX: You -- if we believed you had CRE,

2   you shouldn't come into this study, right? That would

3   be one part of it. And the -- if you identify it,

4   that's what I meant about meropenem resistance, you

5   know, if we spot it. You need to be in a center where

6   you would be comfortable using meropenem plus or minus

7   Amikacin as your empiric therapy about nosocomial

8   pneumonia. And so if you're at a center where that's

9   not true, then I can't put this study here.

10   AUDIENCE MEMBER: (inaudible - off mic).

11   DR. REX: Yeah, I'm with you. I want to

12   work there, too.

13   But so -- but you know, we've recently done

14   a study like this where we did ceftazidime/avibactam

15   versus meropenem. And we were able to -- we actually

16   -- it was kind of hard. We didn't find CRE. You

17   know, even -- we were actively excluding it, but we

18   actually -- and we had another study where were

19   actively looking for it, and it was kind of harder to

20   get than you might imagine in prospective randomized

21   trials.

22   Remember, the ICUs are trying very hard to

1 control their outbreaks of CRE, so I think you can do

2 this and you can avoid the problem of CRE coming in

3 and being a big issue. So I think you can do that

4 where the pseudomonas is often -- well, that's not the

5 same as here. But the -- you -- so I think you could

6 probably have the meropenem be active against the

7 pseudomonas at least 80, 85 percent of the time.

8   Other questions? Okay.

9   So these are the data that were invented,

10 okay? And it's important to pay attention to both the

11 percent ratios and the absolute magnitude of things

12 like the denominator here. So the nosocomial

13 pneumonia arm, they're 48 and 24 in our microITT

14 analysis. And if you want to pitch them both at about

15 80 percent response -- in fact, 38 out of 48 would be

16 a little closer. I deliberately jittered that away a

17 tiny bit to get the -- to make the delta not so

18 boring. But you know, there's a result that, you know

19 -- it's 20 percent up and down around a delta of zero,

20 more or less.

21   And there you have an intra-ab dataset. And

22 I left those numbers a little closer. You know, 80

1 versus 80, for all intents and purposes. And then

2 there's an open label LTO study, and this is -- I

3 pitch this one to be -- to reflect our experience, as

4 well, with having done a study like this as part of

5 the CAZ-AVI program.

6   You get a lot of UTI. And, you know, people

7 can find those. There's lots of urine to culture, you

8 know. They are identifiable. And it's harder to get

9 intra-abs and nosocomial pneumonias with highly

10 resistant pathogens. It's just harder to pick them up

11 in a way that makes sense.

12   And so just completely fictitious numbers

13 here, just made up that this is what you managed to

14 accrue. And I want to emphasize that these patients

15 are going to be different qualitative than those in --

16 qualitatively from those in the RCT. They're going to

17 have more comorbidities. You won't be really happy

18 with banging them together. In your handout, I add

19 them up if you happen to want to see an integrated

20 summary of efficacy, but I don't really recommend

21 doing that.

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

1   you'll actually get some difficult pseudomonas because

2   that -- why would you be in this? Because you've got

3   a bad one, and so assuming that, you know, about 80

4   percent -- it won't always be the reason, but let's

5   just assume that we get a fair -- so this is a nice

6   feature of this open label. You can say, well, it's

7   an open-label study, how -- lots of complaints. But

8   on the other hand, you know, here's at least, you

9   know, 50 or 60 cases that you can look at and see what

10   do you think happened.

11   Safety. The N on full dose of duration,

12   barring the comment from a moment ago where we could

13   actually get a bigger N, if you just kept it down to

14   those who grew pseudomonas, is about 240 -- 230, 240.

15   You know, you get between 200 and 300 and you're

16   getting really close to having enough for a reasonable

17   safety database at this level of resolution. And

18   unless a major new signal emerges, it's not bad. You

19   know, you can come back to this question. How big of

20   a flashlight do you want? So it's not bad.

21   MR. DANE: John --

22   DR. REX: Yes?

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 1              MR. DANE:  Just --

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

 3     questions.

 4              MR. DANE:  So -- and on the open label

 5     extension data -- I mean, in this example, that looks

 6     fairly supportive.  The response rates are pretty

 7     high.  Given the population we're dealing with, it's

 8     non-comparative small numbers.  It might be worth

 9     discussing what would we do if those response rates

10     were 30 percent or 40 percent, which may not be that

11     outlandish.  It's a small number, and it's a more

12     severe patient population.  So that might be, you

13     know, another test case of -- well, how would we use

14     that type of information then?

15              DR. REX:  I have no good answer to that.  I

16     deliberately pitched those response rates to be lower

17     than in the RCT, just saying that I thought they were

18     going to be more difficult cases.  And you know,

19     that's -- so let's open this up.  And that's a good

20     question.  So open up for questions, comments, and

21     critiques.

22              So, Helen?
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1   MS. BOUCHER: So Aaron, I agree. I think

2   that's a great point, and I think many of us would

3   expect perhaps lower successes in especially the

4   HABP/VABP group and that open label extension. And so

5   that comes back to that notion that we were talking

6   about a little bit earlier, the idea that really

7   looking at each one of those 10 individuals and seeing

8   what was going on is going to be necessary. And we've

9   seen similar examples in the antifungal space. And we

10 saw it a little bit, as Ed alluded to yesterday, in

11 the daptomycin experience of having to look in the

12 cells of each diagnosis, each group, and try to

13 understand what you can learn from what amounts to a

14 collection of cases.

15   But there may be things you could learn.

16 And I don't think there's any shortcuts, and so you

17 come back to the fact that -- was a diagnosis really

18 well-established? Was the outcome really well-

19 established? Do we have drug levels in any of those

20 patients? You know, do we have any other data that

21 might help us feel better or less okay with that

22 message? But in many cases, you might end up with

 1   almost 50-50, or even a little less, in these really

 2   sick people.

 3   The other point I think here is that in the

 4   HABP/VABP population, or if you were lucky enough to

 5   have a group of people with bloodstream infection,

 6   that's a group where their outcome with pseudomonas

 7   infection is pretty clearly very bad in terms of

 8   mortality, and you could look at that data. Again,

 9   with all the caveats about the fact that these people

10   die from other reasons, you know, all those things --

11   and perhaps become either more comfortable or less

12   comfortable with those data.

13   DR. TOMAYKO: John, could I build on what

14   Helen said? In HABP/VABP, I actually think that in

15   this situation it could really illustrate one of the

16   controversies or problems that people see with an all-

17   cause mortality endpoint. And what I mean by that is

18   there's two ways to fail in a -- in that analysis of -

19   - like when you're comparing a non-inferiority type

20   analysis with an all-cause mortality endpoint. You

21   have to realize that untreated pseudomonas pneumonia

22   has a pretty high morality, probably higher than maybe

 1   some other pathogens. And that's crude mortality.

 2   And the reason we like the endpoint is

 3   because there's a lot of improvement you could

 4   demonstrate with a good antibiotic. And if you don't

 5   demonstrate enough, then you could look inferior, so

 6   there are potential to detect an inferior therapy, if

 7   you don't work as well as your comparator. But let's

 8   say you work as well. What are you left with? You're

 9   left with some of that crude mortality that you

10   started with but you couldn't see because so much of

11   it was buried in the pneumonia.

12   So you've got this crude mortality and you

13   have 24 patients on marrow and 48 on ertapenem, and

14   you have to assume that you randomized that and that

15   what's left over you're going to be able to really say

16   that -- you know, this is a problem that I think

17   people have with all-cause mortality because, at the

18   end of the day, you have other things that are also

19   responsible for those remaining deaths. And that

20   might not be handled well here. I don't know if I

21   said that clearly, if anybody has a better way of

22   articulating it, but --

1   DR. REX: Will the left-handed poodle owners

2   be randomized? Right. Will the smokers be equally

3   randomized? Will poodle ownership be equally

4   randomized? You just have no clue.

5   So Helen again.

6   And there's somebody with a question on the

7   mic. Yes?

8   MR. LOUDIT: Yes, so this is Jeff Loudit

9   (ph). So Helen and John are much smarter than I, so I

10   was going to make the same comments. But so quick

11   question, John. That is all-cause mortality that

12   you're showing there with HABP/VABP or is that --

13   DR. REX: Yes, the endpoint for HABP/VABP is

14   all-cause mortality.

15   MR. LOUDIT: That's survival that you're

16   showing there.

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

18   survival.

19   MR. LOUDIT: Okay. So all-cause survival

20   that we're showing there. All right. So I would

21   agree, though, with John and Helen's comment that I

22   think certainly in the open label trial, your numbers

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

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

3   MR. LOUDIT: -- the point is how do you deal

4   with that and put it into perspective? And I think

5   Helen's points are exactly right.

6   DR. REX: Yeah. And so, you know, keep in

7   mind -- you know, if -- cut them in half if you'd

8   like. They're deliberately pitched to be different

9   and not as good. And that's sort of the concept here.

10   DR. CAVALERI: I'm going to just come back

11   before we go.

12   So to John Tomayko's comment, I mean, it

13   sounds like, too, I mean, you know, you're arguing

14   that in a small group of patient you might not have

15   really balanced things out with randomization and the

16   impact that that might have on all-cause mortality.

17   It could affect other endpoints too, yeah. So I just

18   don't -- I mean, I don't know that that's exclusively

19   a problem of all-cause mortality.

20   And these are -- this is a patient

21   population where there's a lot of other things going

22   on, and, you know, some patients will succumb to other

1   conditions that they have. We just can't tell who's

2   who and what the cause is for each of those two

3   things.

4   So, yeah, I just didn't want to -- I mean,

5   so it's not exclusively mortality, but this is a

6   problem that we run into with smaller numbers -- and,

7   yeah, okay.

8   DR. REX: David?

9   DAVID: Yeah, so the issue that I'm

10 struggling with is that we spend an awful lot of money

11 studying an awful lot of patients for an extremely

12 fragile result.

13   DR. REX: I -- And that point is extremely

14 well -- and we actually put up a slide that'll let you

15 talk about this because if you look at -- there's a

16 section, A45, that lists really big risks. And what

17 you're pointing out is number 2 -- that N is tiny and

18 there -- the risk of bouncing off that a little bit is

19 notable.

20   DAVID: Yeah, so I just don't think anybody

21 is going to do this. I think bravo for going through

22 this. I think that this was a really rigorous look at

1   the realities in a way of trying to design a trial

2   like this, but nobody is going to do this.

3   DR. REX: Well, so save that comment when we

4   get to Scenario B because I think you'll maybe want to

5   repeat the comment.

6   MR. HOOFTMAN: Thank you.

7   My name is Leon Hooftman (ph). I'm the

8   chief medical officer, sometimes chief medical

9   scapegoat, of a company that has something like this.

10   So first of all, I would like to commend the

11 panel and FDA and yourself, John, for doing all this

12 work.

13   You know, when you're in clinical trials, as

14 you know, sometimes you're planning for success and

15 always optimistic. Our -- we have done surveys in the

16 Mediterranean area regarding incidence of pseudomonas

17 positivity, and figures are a little bit more

18 optimistic than the sobering statistic that you have

19 presented us with this morning, which is good because

20 often enough you -- you know, you've got the answer

21 because of the hope not because of the fact that

22 somebody says, no, this is not possible.

1   And sorry to come back to the issue of

2   feasibility, but that is the word, you know, with a

3   capital that is high on this agenda. And I agree with

4   the previous person who said this is still probably

5   not feasible. If we would use our positivity data --

6   and it's a survey, and I know you're going to shoot

7   holes through it and it's mainly Mediterranean, you

8   know, our hope would be to enrich the population in

9   countries where this is more prevalent. But we

10   shouldn't fool ourselves because, as you would say

11   yourself, you know, the moment that you start the

12   study, the incidence rates go down.

13   DR. REX: I didn't say that. Louis Lasagna

14   said that. It's a wonderful quote -- Lasagna's Law.

15   So let me just point out these noteworthy

16   risks and then we'll go to the next question -- or

17   just so I've read through the slide. Erta at one gram

18   -- I think I've talked about what I know about that.

19   You know, it doesn't look dumb, but it needs some

20   work. We've just now been talking about the small N.

21   Those margins -- and I would like to have a reflection

22   from our colleagues -- the statistical and regulatory

1   on that.

2   I want to observe that the enrolled N

3   probably needs to be 30 percent bigger, I think, and

4   that there's going to be some unavailable. There's

5   going to be some lost due to meropenem resistance. So

6   if you want to maintain this blinded design, you know

7   -- there are many sins in clinical trials. You could

8   live without the blinded if you wanted to. That would

9   be a best available therapy. But here, if you wanted

10   to do it blinded, which I always like, then you've got

11   to deal with that -- again, the small N with the

12   pseudomonas. And we've not discussed pediatrics at

13   all, so I'm just going to assume that you do something

14   about generating PK data.

15   I want to show this just because it's in the

16   handout. Sometimes it is suggested that we use a

17   larger alpha. Instead of an alpha of 0.05, we use an

18   alpha of 0.1. It's a way of, you know, describing the

19   idea of less certainty. So the mathematical

20   equivalent of that is to use a 90 percent confidence

21   interval. And so here I've recomputed it with 90

22   percent confidence intervals.

1   And so the nice thing about it -- and the

2   numbers were, of course, chosen to do this, right? I

3   -- this -- everything about this is set up to give you

4   the chance to meditate on this.

5   So now the lower bound of the 95 -- 90

6   percent confidence interval is minus 19, so it's

7   inside of FDA's actual M-1 by 1 percent, okay? And

8   ditto the negative 13.6. Okay. So it's inside

9   negative 14 by 0.4 percent. Do you feel any better?

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

11   DR. REX: These are the questions I want to

12   be sure we cover, so.

13   MR. DANE: Yeah, the other thing I would add

14   on that last point, though, is that, although for a

15   specific case when you observe the data, the

16   confidence intervals shift by a few percent, and you

17   could argue about whether that's important or not.

18   Where it can be important is where you're designing

19   the trial and having to figure out how big it's going

20   to be and the feasibility. It can have an impact

21   there as well. So that's where it can help as much as

22   what the result looks like when you get to the end of

1   the study.

2   DR. REX: Right --

3   MR. HOOFTMAN: So it makes it --

4   DR. REX: You're right. So this is powering

5   versus actual data. So here a lot of the power

6   questions are now gone at this point. We've invented

7   some data. You know, we have what we have.

8   MR. DANE: Yeah.

9   DR. REX: Right. So I want to be sure we

10   cover these questions, pros and cons from all

11   perspectives. So we've got to talk about how to deal

12   with two body sites. You know, what do you do there?

13   Come back to concomitant therapy. Is there anything

14   other than erta we could use? There's implicit

15   approach to polymicrobial versus monomicrobial, just

16   to double check. Any other thoughts on MDR

17   pseudomonas and best available therapies? So we've

18   kind of covered some of these, but if you're looking

19   for a question to poke on, be sure we poke on one of

20   these.

21   So there was somebody holding their hand up

22   a minute ago. Yeah, Tom?

1   DR. LOUIS: Tom Louis. Just to comment on

2   the previous discussion on the 95 interval, the 90

3   interval, it becomes endless. And here's a perfect

4   case where, let's say, with uninformative priors on

5   the underlying parameters -- or if you have some

6   knowledge on baseline, just put it in. Compute the

7   posterior probability that the difference in -- the

8   true difference in the parameters is in the range that

9   it needs to be in. I don't know what that number will

10 be in this case, but it's far better than, oh, what

11 about the 90, what about the 95. Just have a direct

12 answer to that underlying question and --

13   DR. REX: So you're getting at the -- a true

14 posterior probability, or in terms that I understand,

15 the likelihood?

16   DR. LOUIS: Well, it would be based -- is if

17 it were uninformative and being, if you like,

18 frequentist, it would be based on the likelihood and

19 would ask the question directly. It would say we

20 don't see the parameters, but we -- there is a true

21 difference. Let's build a model that computes the

22 posterior probability, given the data, that the truth

1   is in whatever range is required, if you like. And on

2   the design side, you can then ask what kind of a

3   sample size would be needed if the true differences in

4   a certain situation so that there's a high likelihood

5   that that posterior probability will be sufficiently

6   large. In other words, you can do -- you can reverse-

7   engineer to do the design question, too.

8   MR. DANE: Yeah, I mean, I would say on

9   that, that's true. You still need -- a company going

10   into a study and investing still needs to have an idea

11   of what's going to be sufficient for approval, though.

12   So, yeah, I agree with everything you say, but in some

13   ways, whether it's an alpha level, whether it's a

14   likelihood, that question still remains, is what's the

15   acceptable regulatory risk in doing some of this in

16   terms of incorrectly approving something.

17   AUDIENCE MEMBER: (inaudible - off mic).

18   DR. REX: Yeah. Well, and I think what

19   you're saying is that we might need to spend some time

20   as a community getting to where we understand -- what

21   you're talking about, I can get a feel for it from a

22   distance, but we'd actually have to be able to

1 understand it broadly enough that even if a pair who

2 is being shown the data is -- you're able to say in a

3 way that actually sort of conveys the feel for the

4 strength of the information. And so that's something

5 to work on. It's a new form of -- you know, because

6 we haven't often -- we have never actually publicly in

7 these conversations done anything other than standard

8 frequentist statistics that we all learned in -- as

9 freshmen in college, you know, that sort of thing. So

10 it's a well-said point.

11   MR. DANE: John, my other point on -- just

12 related to that was that, you know, whether we talk

13 about alpha levels or likelihoods, that the other

14 point is that sometimes they can be useful rather than

15 going to bigger and bigger non-inferiority margins

16 that people become uncomfortable with because we say,

17 well, we can have a margin of 40 percent, for example,

18 because it's feasible. But who's going to be happy

19 saying, well, we could be 40 percent worse, whereas

20 something with a tighter margin -- but you're just

21 saying, well, we've got a big more risk of what we're

22 doing here might be a good balance and a better

1 balance than going that way.

2   DR. REX: And so to say it back to you, in

3 effect, that's what I did here. I made the confidence

4 bound fit inside the margin by picking a different

5 alpha. Actually, I did -- I set this up so that this

6 would be true. But the point is that it's

7 mathematically -- it's -- the underlying data are the

8 same. It's the question of how do you talk about them

9 and whether -- do you want to construe it as margin

10 risk, or is it likelihood of making a certain kind of

11 mistake risk. And -- but mathematically, it's the

12 same. Am I saying it correctly? I mean you -- yeah,

13 okay.

14   AUDIENCE MEMBER: (inaudible - off mic).

15   DR. REX: Well, see, I wanted this case to

16 try to get at these debates. You're right.

17   Okay, so Kenneth?

18   MR. HILLIN: John, thanks.

19   It's an extremely thoughtful and thought-

20 provoking illustration, I think, that you're given

21 here. And I guess there's lots that we could discuss

22 and I'm sure that we will discuss. But as you take a

1   step back and you look at this, I wonder if at some

2   point during today's discussion we might take a vote

3   in the room and ask people to put up their hands if

4   they would be willing to run such a trial because I

5   suspect, although I could be wrong, that they'll be

6   very hands in the room that will go up. And so I just

7   wanted to commend you for sharing this.

8   DR. REX: Okay, well, thank you. We've had

9   a good time putting it together. Lynn?

10   DR. MARKS: Quick question. If you have a

11 big issue (ph) non-inferiority margin and at the

12 bottom of the inverted pyramid you have 20 MDRs in one

13 arm and, I'll say, 25 and 17 and a half in the other

14 arm and there's a descriptive but what some people

15 would call medically interesting difference, would

16 that be able to provide --

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

18 I think, you know, that's helpful.

19   DR. COX: And John, you were asking about

20 this a little bit ago, and Sumathi and I talked some

21 about this. And that is, you know, the margins and

22 sort of setting them, the ones that are in the

1   guidance document. And I think, you know, you're

2   asking a question of how far can you stress M-1. I

3   mean, if you really, you know, look at this very

4   carefully and, you know, the 29 percent, versus the 20

5   percent, versus the, you know, 10 or 12, 5, whatever

6   it is --

7   DR. REX: Use the microphone.

8   DR. COX: Yeah, whatever it is in the

9   situation that you're using it, you move from M-1 to

10 M-2. I mean, it is a good question, and it's probably

11 worth looking back at those numbers a little bit more

12 and seeing, you know, how big things are. And then,

13 you know, just to see, you know, where it is. Those

14 numbers are pretty messy, though, from what I

15 understand. And if I remember correctly, for

16 complicated intra-abdominal, that was like -- I mean,

17 it was not only sort of looking at the numbers, but

18 there was also gymnastics involved in trying to work

19 through that one because we didn't quite have the data

20 that we needed. But we were able to get to something

21 that told us about treatment effect, so --

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

1 that was -- so that you've heard it, the approach

2 taken for intra-ab went as follows. There are no data

3 on placebo therapy of complicated intra-abdominal

4 infection. No one could find any. So something was

5 found that's kind of like that, which is in the '60s

6 and '70s there was a serious question about whether or

7 not you needed antibiotic prophylaxis if you were

8 about to have bowel surgery, so what we would call a

9 clean contaminated procedure.

10   I'm going to open you up. I'm going to

11 transect your gut. So I'm going to spill bacteria.

12 I'm going to sew you back up. Do you need prophylaxis

13 to prevent -- so you didn't have an infection before.

14 Do you develop one post-op?

15   And so there were placebo-controlled studies

16 of that done. What's the rate of preventing

17 development of infections? So it didn't have an

18 infection, didn't develop, versus didn't have and did

19 develop with or without therapy.

20   And so that -- and if you flip that -- so

21 that's the closest anybody could come. And you flip

22 that upside down and you can construe that to be the

1   rate of treating infections.

2   So Mike Dudley is looking at me -- what does

3   that mean? So in -- hypothetically, I've just cut

4   through your wall of your bowel, and I've just created

5   an infection. Let's pretend that I create a little

6   baby infection right at that moment.

7   So if I then put you on an antibiotic, I'm

8   treating this itty bitty tiny infection. Or I don't

9   put you on an antibiotic. I'm not treating it. And

10 post-response will control some of them. Antibiotics

11 will control some of the others.

12   So that's how it was computed. And it

13 actually showed that there is a benefit of

14 perioperative antibiotics if I'm going to transect

15 your gut wall. I very clearly show that, which, you

16 know, is something we want to do.

17   And you find that there is a difference

18 between -- and you can actually -- the math -- so go

19 read the guide. Now that you've heard the story, go

20 read the guidance document again. You know, I thought

21 it was a -- not a bad approach, and it, you know --

22 show me something better. You guys -- like, all

1   models are flawed. You know, if you don't like this

2   approach, you can't just criticize. You have to

3   solve. So you know, my hat's off for somebody for

4   having found a path.

5   Question?

6   UNIDENTIFIED MALE SPEAKER: Well, I think

7   it's great work, and all the discussion focused on

8   regulatory aspects and on statistical aspects and on

9   evidence. I just want to shed a little bit of light

10   on those patients who actually do not have pseudomonas

11   infection in that study.

12   So first of all, in the arm -- in the

13   experimental arm that -- actually two experimental

14   drugs because the drugs are approved, so probably you

15   needed the DSMB on that arm. And what happens if that

16   ertapenem actually is inferior in the non-PS, which is

17   75 percent of the patients --

18   DR. REX: That's a risk.

19   UNIDENTIFIED MALE SPEAKER: What happens to

20   the study? You're going to stop the study not because

21   the PS isn't working, the pseudomonas. You'll

22   probably stop the study because your adjunctive

1   treatment or your ertapenem isn't working. And how

2   you can send for that in a situation of HBAP/VBAP to a

3   patient where alternative treatments, which actually

4   are approved, are available. So for me, that is one

5   issue.

6   The second issue is that even you have a

7   fantastic new drug called X-1. Actually, that doesn't

8   come for free. There will be safety issues. And some

9   you raised and whatever they are. So you're going to

10 treat 75 percent of the patients in that trial

11 empirically with a useless drug. And they're exposed

12 to safety issues.

13   And you know, I'm 10 years plus chief

14 medical officer of two companies. And I -- in an

15 internal ethical committee, we would have a huge

16 debate whether we would expose these patients to that

17 risk and what type of warning we would give to them

18 and how recruitable would be the study then at the end

19 if you display that information to the participants.

20 And so for me, it's not only a financial feasibility

21 or an evidence issue, it is just an ethical

22 feasibility to get all those patients on board and

1   telling them what their likelihood of benefit versus

2   their likelihood of risk is in that arm.

3   DR. REX: Yeah. Good point, and it actually

4   makes Jeff Loudit's (ph) comment that you ought to

5   keep them on the study more pointed. So if you know

6   it's not pseudomonas, you ought to just keep on

7   running it because now you're at least getting data on

8   how well erta works. And so I had not thought about

9   that aspect of it, but it's a very well -- one of the

10 risks here is that erta is not an approved drug as the

11 combination. But you know, look --come up with a

12 better solution. You know, I didn't like Tigecycline,

13 so, you know, I came down on the side of ertapenem.

14   Jeff and then Ian.

15   MR. LOUDIT: So Dave asked -- Dave said no

16 one would run this study, so I'm going to put my neck

17 out here. I would run this study, Dave, with three

18 caveats.

19   DR. REX: Okay.

20   MR. LOUDIT: One, it's somebody else's

21 money. That would be --

22   (Laughter)

1   MR. LOUDIT: So two -- the second caveat is

2   that the FDA agreed to those non-inferiority modules.

3   The third caveat, though, is the really

4   important one to me, which is the rapid diagnostic

5   test. So there are actually companies that are now

6   developing almost by-the-bedside tests which can tell

7   you within a very short period of time whether you

8   have pseudomonas, acinetobacter, et cetera. And that

9   significantly cuts down your costs of screening and

10   enrollment.

11   So I would be willing to do this study, and

12   we're planning to do a similar study like this, Dave,

13   in the near future with -- I guess it -- I don't have

14   the second caveat agreed to yet.

15   DR. REX: Well -- yeah, that's good. And

16   the thing about the diagnostic, for our purposes, was

17   we were assuming that it wasn't something that

18   required a lot of maintenance. It didn't require a

19   big site -- sort of a user manual at the site. It

20   needed to be something -- because if money is no

21   object, then you can do lots of things. But here,

22   it's for something that you're going to be using

 1   infrequently. You know, I wanted something without

 2   batteries.

 3   So Ian? And then --

 4   DR. FRIEDLAND: I also wanted --

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

 6   he's next.

 7   DR. FRIEDLAND: Thank you for going through

 8   this exercise because it is very useful to take a

 9   practical example and actually look at the numbers.

10   There is a potential way to think about this

11   a bit differently that could try and counter some of

12   the points that are being made, and the one is to

13   consider this a regimen. The regimen you're

14   evaluating is ertapenem plus this drug. And you're

15   not going to try and sort out what the one drug does

16   and what the other drug does -- what the other one

17   does. You know, one drug for one bug gets very

18   complicated.

19   We also don't know -- there could be a

20   really positive interaction between the two drugs. It

21   could be this could synergize with ertapenem and make

22   ertapenem active against carbapenem-resistant strains.

1   And likewise, ertapenem could make this drug more

2   effective against pseudomonas. So I think if we think

3   about this just as a regimen, we're evaluating the two

4   drugs together.

5   And at the end of the day, what you can say

6   -- this is the safety and efficacy of this regimen,

7   and that's the way the drug gets approved. It's in

8   combination with ertapenem just as if we had put the

9   two drugs together in a vial and said this is the

10   product we're developing.

11   DR. COX: Do you want me to comment on that?

12   So, I mean, just one thing to think about, though,

13   too, is I think, you know, this is the opportunity to

14   test the efficacy of X-1. So you know, within that

15   population of patients that are getting the drug,

16   you'll want to be able to discern what was the effect

17   of X-1. And oftentimes, I mean, one of the ways to

18   think about this is suppose that your population of

19   patients you enrolled, you know -- very few

20   pseudomonas aeruginosa. You know, I think it becomes

21   more difficult. So somewhere in there, you'll want to

22   be able to figure out, you know, what X-1 is doing.

1   DR. REX: But there is the intra-ab. You

2   could take Ian's comment and say, well, in the intra-

3   ab component, I get the monotherapy insight. And --

4   but for nosocomial pneumonia, it's labeled as if it

5   was a thing. I mean, I --

6   DR. CAVALERI: Yeah.

7   DR. REX: And I -- part of the assumption

8   that was in the written version of the case was that

9   the sponsor knows that something like that could come

10   in the label, but why would I object to that being in

11   the label, you know?

12   DR. CAVALERI: Right. Yeah, and we have

13   done that -- I mean, if -- some of the drugs that are

14   used in combination with other drugs. But, you know,

15   I'm just sort of saying that the test needs to be sort

16   of a valid way to assess the effect of the drug and

17   that the drug is used with other drugs is not

18   necessarily a problem per se. But if it obscures the

19   ability to assess the effect of the drug, then it gets

20   a little more complicated, so.

21   DR. REX: Okay. So let's look at these

22   questions and be sure that we've -- sorry, Paul

 1 | Ambrose is waving his hand.

 2 | Go for it, Paul. We really have plenty of

 3 | time to discuss, and I don't want any idea to lie

 4 | fallow.

 5 | DR. AMBROSE: All right, I don't have an

 6 | idea, I -- just a comment. Is there any concern that

 7 | ertapenem is being picked here because -- well, it's

 8 | being picked because we think its PK/PD will predict

 9 | as active, right? It's got --

10 | DR. REX: Talk straight into the microphone.

11 | DR. AMBROSE: It's got no randomized

12 | clinical trial in nosocomial pneumonia. It's just

13 | being picked because the PK/PD for it -- forecasts

14 | it'll work. Is there any concern that we're comparing

15 | a new drug to something we don't really understand

16 | would work? For me, I mean, I really believe in the

17 | PK/PD as you -- I put a lot of weight in it, but it's

18 | an interesting precedent that you're setting up.

19 | DR. REX: I think that is a concern. And

20 | you know -- make another suggestion. You know, maybe

21 | as a community, we need to do an ertapenem --

22 | DR. FRIEDLAND: There actually is a clinical

1 trial with ertapenem done in HABP and non-ventilated -

2 - and early-onset VABP. It was just never submitted

3 for reasons other than efficacy.

4   DR. REX: You're kidding.

5   DR. FRIEDLAND: But it actually was a trial.

6 It was actually the very first trial I ever conducted

7 in industry was a VABP -- a HABP/VABP trial with

8 ertapenem. It is published. It was just never

9 submitted for approval.

10   DR. REX: Yeah.

11   AUDIENCE MEMBER: (inaudible - off mic).

12   DR. REX: So I was getting comments from two

13 directions. So you're -- actually, I think -- find

14 those data, you know. And, sir, did you say -- how

15 did it do? I missed that part.

16   DR. FRIEDLAND: It was -- you know, it was

17 done back in 2000 --

18   DR. REX: Back in the year aught, all right.

19   DR. FRIEDLAND: So way -- non-inferiority

20 margins were acceptable, but it was like a 350-patient

21 study versus pip/tazo, and it fell within the non-

22 inferiority margin of 15 percent to 20 percent of --

1   DR. REX: Do you remember offhand if the

2   mortalities were comparable in the two arms?

3   DR. FRIEDLAND: No, I can't remember all the

4   data. The main reason it wasn't submitted was because

5   maybe it did too well, and at the time commercially

6   they wanted to distinguish it from other carbapenems.

7   They didn't want it to look as good as meropenem and

8   ertapenem against, like, really sick patients. So it

9   was a very strange reason why it was never actually

10   promoted or --

11   DR. REX: Well, it's -- so maybe there's a

12   bit more data than we realize. And like I say, you

13   know, the little bit I scrounged up, actually, it

14   looks -- it looked as if it ought to work, you know.

15   Sorry.

16   MR. ARAKOFF: Dmitri Arakoff (ph),

17   divisional and executive (ph) products of DE (ph).

18   Since we have time for discussion, I'd like to address

19   this question of immunotherapy versus dual therapy.

20   Looking at the guidance, it seems that they deem

21   immunotherapies acceptable as long as your drug is

22   active against isolated pathogens. And the reason --

1   we give dual therapies to -- not to prevent

2   resistance, but to make sure that at least one drug is

3   active --

4   DR. REX: Is active.

5   MR. ARAKOFF: -- meaning that if you study a

6   drug supposedly active against resistant pathogens,

7   maybe this criteria not applicable to your product.

8   And it's acceptable to use a new product, at least in

9   this active arm.

10   DR. REX: Yeah, so -- and I think if you

11   felt like you could do that, that would be great

12   upside. I considered the possibility for nosocomial

13   pneumonia of saying -- of doing it the same way I did

14   in complicated intra-ab, which is to say Amikacin is

15   given, but it is blinded versus placebo. So the X-1

16   arm gets a placebo Amikacin, and the meropenem arm

17   gets real Amikacin. And you somehow blind even doing

18   of levels and things like that. And I think you could

19   do that. And if you could, that would certainly help

20   clarify the dataset.

21   I just chose for purposes of this discussion

22   to make us deal with the possibility that there will

1   be a desire for two drugs. And the -- if you look at

2   the IDSA guidelines, you know, what they've said is,

3   oh, wrong way. They really are kind of wishy-washy on

4   this, you know. They -- sometimes they still want two

5   drugs, and so I don't assume to know where the logic

6   is going to go in the future, but your point is really

7   good.

8   MR. ARAKOFF: Because what would be the

9   argument to the second drug? This is my point if it's

10 -- right.

11   DR. REX: Yeah, well, and the argument might

12 be -- you know, Paul Ambrose yesterday said, well,

13 even with a single active drug, there's still a tail

14 of exposures in some subjects. And so, you know,

15 maybe it's nice for that reason. It's not about

16 susceptibility. It's about exposure.

17   Mike?

18   But you're right. Part of this was about

19 not picking -- not making everything always go our way

20 in terms of the analysis. I really wanted stuff that

21 -- to stretch the envelope.

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

1　point I think Ian was making before, though, is what

2　you really are is testing a regimen here. So this

3　regimen is -- of ertapenem plus X-1 is a broad-

4　spectrum regimen. And even though we've got sort of

5　some enrichment or you've got your device and so

6　forth, we're still treating with a broad-spectrum

7　regimen.

8　　　　　　I'm curious about whether or not the

9　labeling would be then specifying that it was -- you

10　know, this drug is being used in combination with a

11　carbapenem, and that what you really did test

12　specifically was a carbapenem combination with this.

13　　　　　　And I think about -- for the -- the example

14　that comes to mind is that piperacillin/tazobactam

15　failed miserably as monotherapy in pseudomonas

16　pneumonia in the initial trials -- miserably. And

17　then when it was -- their trials were repeated in

18　combination with an aminoglycoside, it worked because

19　no -- it prevented resistance from emerging during

20　therapy. So the actual label, I believe, actually

21　states that it's indicated for use with an

22　aminoglycoside and the treatment of pseudomonas

 1 pneumonia.

 2   So I just wanted to clarify would the

 3 labeling in this case -- would be used in combination

 4 with a carbapenem in the treatment of pneumonia or

 5 HABP/VABP. But -- he said yes.

 6   DR. REX: Whatever it is --

 7   DR. COX: Yeah, so, I mean, I think, you

 8 know, that we can do that. We've done that. I'm

 9 thinking of ceftolozane/tazobactam, where we added,

10 you know, to the complicated intra-abdominal we said

11 used in combination with metronidazole. So -- but

12 that's, I mean -- so that's a very easily solvable

13 issue.

14   And it seems like -- and I'm -- in this

15 trial where we're enrolling patients with pseudomonas

16 aeruginosa, we've picked ertapenem because it's whole,

17 and coverage is that it doesn't cover pseudomonas

18 aeruginosa. It seems that what we're really trying to

19 do is -- you know, within this regimen is to be able

20 to test the role of X-1 by isolating it, if you will.

21 And you know, the -- so I think -- you know, that's

22 really what I think we're trying to learn out of this.

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

 2   DR. COX: So we could say use it in

 3 combination with ertapenem --

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

 5 direction.

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

 7 figure out --

 8   AUDIENCE MEMBER: (inaudible - off mic).

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

10   DR. COX: Agree, yes.

11   DR. REX: -- fully expecting E. colis and

12 Klebsiellas and other things. Absolutely.

13   DR. COX: And that's why the ertapenem is

14 there. It's, you know -- there are other things.

15 Either we're going to have patients that we don't

16 culture. You know, it's going to take a while to get

17 the culture back, just like the empiric Amikacin. But

18 what I'm trying to get to is what the -- you know, the

19 primary analysis, it would seem, would be on those

20 patients that have pseudomonas aeruginosa, hopefully

21 not too much concomitant Amikacin, not too much pre-

22 study therapy, to try and isolate the effect of X-1

1   and figure out -- you know, it's only active against

2   pseudomonas aeruginosa to try and figure out how does

3   it perform against pseudomonas aeruginosa because, you

4   know, in subsequent trials in patients with

5   pseudomonas aeruginosa this drug will be used. And

6   this is the chance to figure out whether it works or

7   not.

8   DR. REX: And just for flow of time, we're

9   going to go until 12:15, another seven minutes. And

10 then we're going to take a break, come back at 1:00.

11 So just so you set expectations.

12   The lady right here in the yellow blouse had

13 a question and the gentleman at the mic. So I thought

14 -- you raised your hand. I thought I saw you raise

15 your hand.

16   UNIDENTIFIED FEMALE SPEAKER: Sorry, I'm at

17 the risk of belaboring a point that isn't necessarily

18 shared here. But I can't see how you could ethically

19 randomize a sick patient as was described to a regimen

20 that only included a single possibly active agent

21 against pseudomonas. Your test agent -- you have pre-

22 clinical data. The only clinical data you have are in

1   non-CF-bronchiectasis.

2   It's a very small study with limited, if

3   any, efficacy information. And you're going to

4   randomize a patient to ertapenem plus your

5   investigational agent when we know that the major

6   factor that predicts mortality, which already we know

7   is high, is being initially on appropriate therapy. I

8   just can't see how you could randomize patients to

9   that arm.

10   DR. REX: Well, I think you're asking a very

11   general question. How then can I develop any novel

12   antibiotic --

13   UNIDENTIFIED FEMALE SPEAKER: Yep.

14   DR. REX: -- as monotherapy? And I think

15   that that question -- you know, we can -- we'll come -

16   - we can come back to that after lunch, if you'd like,

17   because there's a lot of thoughtful commentary in the

18   literature on that point. If you say that you can't -

19   - yeah, we do this, and this is how drugs get

20   advanced. And if you're not willing to do at least

21   this much, then we're at a dead stop in more than one

22   area. I mean, I don't know what else to tell you

1   about it. I --

2   DR. TOMAYKO: John, just to add, this is

3   what you're saying. You're rejecting the clinical

4   equipoise argument that would be made, and I'd take it

5   a step further, that that's -- would apply to a broad-

6   spectrum agent as well. It's --

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

8   DR. TOMAYKO: Yeah, it's not limited to a

9   single agent. And what you have to really believe in

10   is that, you know, you could generate PK data. You

11   could generate efficacy data in relevant pre-clinical

12   models, and that you've looked for resistance, that

13   you understand the likelihood that the patient will be

14   infected with the appropriate susceptible isolates and

15   hopefully that you're going to conduct a clinical

16   trial. We will be watching very closely.

17   Now, I will come back and say that I have

18   had the personal experience of a whole country

19   basically saying we're not going to let you do an

20   intra-abdominal study in our country because you've

21   never studied a novel agent in anything and we think

22   that population is too vulnerable and maybe you should

1   go to a UTI study first. But you get a -- the

2   majority of countries were happy to initiate both an

3   IAI and a UTI study.

4   So it is an IRB or a personal kind of

5   determination that has to be made. But you should

6   generate the right data.

7   DR. COX: So just another thought -- and

8   this has come up in discussions, too. It is sometimes

9   when you're trying to advance a drug to treat patients

10   with, you know, more severe infections, with, you

11   know, higher mortality rates, you may try and do a

12   lesser -- less severe infection initially, something

13   with a lower mortality rate, something where there's

14   an opportunity to sort of test the drug and then sort

15   of advance up the scale of things that are more

16   severe.

17   But, I mean, your comment is also

18   interesting, too, in that if you think about what

19   we're talking about here, we're talking about the

20   highly controlled setting of a clinical trial and then

21   advancing a compound to be used out there in the real

22   world. So it also is a very sobering comment with

1   regards to the use of the drug out there. What types

2   of data would we have -- what types of information we

3   have, you know, that would allow us to be comfortable

4   in a clinical trial and what types of information we

5   want to have to be comfortable using this drug outside

6   of the highly controlled setting of a clinical trial

7   when it's out there in the real world? So …

8   DR. REX: Yeah, but you could run the IAI

9   component of this program for a year and have the DSMB

10   look at it and say, yes, it looks like it's working

11   out. Sort of you could eke -- you could ease your way

12   into it because the mortality in IAI -- you can sort

13   of salvage there. The mortality tends to be very low,

14   so a really good question. You know, I pitched it as

15   going together, but you certainly could stagger them.

16   At the microphone?

17   UNIDENTIFIED MALE SPEAKER: Yeah, so just to

18   touch on a point that's already been raised but it's

19   still not clear to me, you're just ignoring the ITT

20   population it seems here. So you have subjects who

21   are potentially being treated three or four days

22   before you come back with culture positivity. And you

1   know, you're talking about the pseudomonas active

2   differential. How would that ITT result factor into

3   your interpretation then at this equivalency?

4   And just -- some of my Merck colleagues are

5   here, too. I didn't work for Merck at the time, but

6   my recollection of ertapenem was there was a grave

7   concern about using that in the ICU because of the

8   lack of pseudomonas activity causing resistance to

9   carbapenems. I think that's why that decision was

10 made not to bring that forward.

11   DR. REX: Yeah, you know, interesting. I

12 think that you would have -- the full ITT would be one

13 of your secondary analyses, and it would at least need

14 to not show anything wildly discrepant, something like

15 that.

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

17   DR. COX: I was going to say, I mean, you

18 know, the reason we're looking at the MITT here is

19 because of the limited spectrum of the drug we're

20 testing -- if it's only active against pseudomonas

21 aeruginosa, you know, patients who don't have

22 pseudomonas aeruginosa that may have something else,

1 you know, I mean, maybe they don't have an infection.

2 Maybe there's something masquerading as nosocomial

3 pneumonia here. It would be hard to test efficacy if

4 they don't have the pathogen of when -- which the drug

5 as active.

6   Your point about the ITT, though, we do

7 always look at the ITT because if there's something

8 going in the wrong way, a safety issue, you know, in

9 the overall population, maybe there's something we

10 didn't anticipate or don't understand that's important

11 to know about in patients who are receiving this drug,

12 even though they don't have the target pathogen. So

13 an ITT that was, you know, for some reason going in

14 the wrong way would suggest there was something that

15 we didn't know about that we should know about.

16   UNIDENTIFIED MALE SPEAKER: The reasons we

17 talked about, you know, that the study should be

18 replicating how it's going to be used in the clinic

19 and if what we'll be proposing is a substitution of X-

20 1, you know, into the regimen potentially with

21 ertapenem, if that's what the decision is and the way

22 that the labeling goes, so it is, you know, a broad

1   implication. Are you absolutely going to require the

2   diagnostic before you put them onto therapy? And then

3   it's not being used as it was in the study because

4   it's no longer being used more on an empiric basis but

5   on a confirmed diagnosis, so it's --

6   DR. REX: I guess if I price it high enough,

7   you'll think really hard about using it.

8   MR. DANE: I think the other thing to add

9   there is that in a non-inferiority study, if hardly

10   anybody has got the pathogen you're interested in, you

11   may well show non-inferiority and not have the

12   activity against pseudomonas. So I think you'd want

13   to understand it primary there and just make sure

14   nothing else was going wrong.

15   DR. REX: Yeah, okay. It's 12:15. Let's go

16   have lunch and bring our glucose levels back up. Be

17   back at 1 o'clock, please.

18   (Off the record.)

19   DR. REX: Okay. The last few folks are kind

20   of drifting in. So I show a little after 1:00. My

21   guess is we're going to -- we'll use about the next

22   two hours, approximately. The stated end time is 4

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 1   o'clock.  I just sort of -- my guess is it's going to

 2   be a couple hours of conversation.  If it goes on much

 3   longer than that, we'll stop and take a break.

 4            So let me start by -- just look real quick

 5   at this list of questions and see if there are any

 6   other comments that anybody wants to make about the

 7   themes here -- pros and cons from a clinician's

 8   perspective, an investor's perspective, a regulator's

 9   perspective.  You know, we've heard, you know, the

10   notion that some randomization is better than none.

11   That's where clinicians and regulators, investors very

12   anxious about how big this program is -- since it's

13   very inefficient, you're enrolling a lot of people to

14   get out a very few.

15            Though -- and there's also a risk embedded

16   in this, if you're looking at Bullet 4, about

17   ertapenem.  You know, in effect, we're also testing

18   ertapenem.  But it -- but there may be more data on

19   ertapenem than we've realized.  And you need to dig

20   that out and really test it.

21            I think one of the takeaways I get from this

22   is that really knowing the answer to ertapenem would
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1   be something that we ought to spend some time on

2   because it could be that it's a valuable tool.

3   Data on how to bring the two body sites

4   together -- I've not heard specifically on that. So

5   let's be sure we talk about that.

6   We've talked a lot about concomitant

7   therapy. So if I look at this list, the one that's

8   not as obviously been covered is the data from two

9   body sites. Again, one of our statistical colleagues'

10   comment on approaches to dealing with that, you know,

11   and keeping in mind that the margins are loose. But

12   one of the things that I took some comfort from -- I

13   think it's back here, like, on this slide -- was that,

14   notionally, the program -- the logic for approval has

15   all this stuff built into it, all these different

16   steps, and that I -- the fact that you get a positive

17   result in two subsets, to me, intuitively was

18   attractive.

19   But you want to comment on that particular

20   question, Aaron, Tom?

21   CURT: Sure. Is this --

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

1   UNIDENTIFIED MALE SPEAKER: Hold it close.

2   All right. That's great.

3   DR. REX: Good.

4   CURT: John, could you go back to the slide

5   that had the two -- the data for the two body sites?

6   DR. REX: Oh, sorry. You want, like, this -

7   - like, one of these?

8   CURT: Yeah, like that one.

9   DR. REX: Like that one?

10   CURT: Perfect.

11   DR. REX: Okay.

12   CURT: So you know, there are a couple ways

13   you can go about this. You've got, effectively,

14   separate analyses here. The nice thing that's

15   reassuring is that the data seems consistent between

16   the two body sites -- and it -- not necessarily even

17   consistent on the mortality rates, but the fact that

18   the treatment effect seems to be identical between the

19   two body sites.

20   You know, I often feel uncomfortable about

21   pooling because if you say, a priori, I'm going to do

22   a pooled analysis and then the data doesn't look like

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

2   place.

3   But this gets back to some of the stuff that

4   I was talking about yesterday where if you had some

5   kind of model that said you borrowed dynamically. So

6   the model's set up in advance that if you get data

7   like this, you do something. And I don't know whether

8   it approaches pooling, but you borrow a lot of

9   information between those groups and amplify the

10   similarity. And if you get data that they're

11   different, then you would have to rely on the separate

12   analyses, and it would let that go. But it would get

13   rid of a lot of the risk without pooling but still get

14   you at 30, 40 percent effective sample size boost.

15   MR. DANE: So Curt, how would that work in

16   this type of example where you've only got two body

17   sites? Because I know that performs better with three

18   or more body sites.

19   CURT: So we've done -- it makes a

20   difference. So the more body sites that you have, you

21   get a better idea of the body site variability. If

22   you do it with two -- we've done this in the context

1   of devices where you have, say, two subsets or an old

2   and new device, and we've borrowed between them. Two

3   has more risks than three. But you can at least

4   quantify those in advance about what they are. And

5   you certainly still can do it.

6   And we'd have to say in advance, you know,

7   here are the datasets and here is the potential risk

8   to Type 1 error. And it would have to be agreed on in

9   advance. But you can do something like that.

10   DR. REX: Because otherwise, intuitively, if

11   you've got, like, three out of four pointing in the

12   right direction, that's nice. But if it's one out of

13   two, it's like -- kind of like you've thrown away the

14   one you didn't like and you kept the one you did like.

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

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

17   CURT: -- is to say in advance when you're

18   going to do that so you can quantify the operating

19   characteristics.

20   DR. REX: Okay.

21   MR. DANE: John, it might be the role of the

22   -- what you do with this pool of combined data as

1   well. So is this supportive to each individual body

2   site having a conclusion of non-inferiority as you've

3   got here? Or is that pool dataset the primary source

4   of --

5   DR. REX: Yeah.

6   MR. DANE: -- confirmation? Yeah, so that

7   might make a difference to how you'd view it and how

8   risky it might for -- to Curt's point around the areas

9   you might be making.

10   DR. REX: You know, I think I was just

11   intuitively thinking that if I had, you know, two -- a

12   couple of different observations -- in this case, two

13   -- that were in the same direction, I'd feel good

14   about it. If one of them was really divergent, you

15   know, I'm not -- I -- to my mind, that might have been

16   a dead end for the drug and maybe it's not really

17   working so well. It also would sort of depend on

18   which one was divergent and why and which --

19   MR. DANE: Yeah, and the different endpoints

20   as well that could well be here --

21   DR. REX: All right. I recognize that. So

22   that's why I didn't really talk about any formal form

1 of pooling. It was more sort of if your eyeball can

2 see it, then -- the way I wrote it down was both have

3 to be inside their enormous margins, you know. But

4 having both of them inside is notionally correct.

5   I see Ian at the mic.

6   DR. FRIEDLAND: I have some reservation

7 about IAI as a test for activity against pseudomonas.

8 It's --

9   DR. REX: So do I.

10   DR. FRIEDLAND: -- in the setting of

11 polymicrobial infections. You're not quite sure what

12 role the pseudomonas is playing. And I bet if you

13 looked at drugs that are not active against

14 pseudomonas like ertapenem, Tygecycline, and looked at

15 their activity against the pseudomonas, you might find

16 that you look as active as -- so I think there's just

17 some concern there. We need to know that this

18 actually is a good test of a --

19   DR. REX: I think there's a confounding

20 issue with any microbials in general in intra-ab

21 that's not limited to just pseudomonas. So one of the

22 -- so part of the reason that I suggested doing the

1 two body sites was so that you had two, each one of

2 which had a different flaw. You know, I couldn't

3 think of a better way to get -- you can always do

4 cUTI. But the numbers there -- we saw the numbers

5 again. There -- chasing (ph) pseudomonas there is

6 really hard. And so I took that one off. And I said,

7 well, just take these two with their flaws and see

8 where you get to.

9   Other questions or observations on this? So

10 anything else here that we could -- are there any --

11 is there any options to ertapenem realistically? What

12 else could you do? A bunch of microbiologists in the

13 room -- give me something that has a pseudomonas-sized

14 hole in its coverage.

15   (Crosstalk)

16   DR. REX: That -- you know, that's actually

17 -- we should minute that. That's a really important

18 observation.

19   Was there somebody that raised their hand?

20   Todd (ph)?

21   TODD: What about ceftaroline? I mean, it

22 does have some enterobacteriaceae activity,

1   pseudomonas --

2   DR. REX: It does. It tips over on ESBLs.

3   So you know, may -- this might have been a place for

4   ceftaroline avibactam, which actually has never been

5   developed. It's a developable drug, but it's never

6   been developed. So okay. So but I don't think you

7   can stand ceftaroline up on its own because the ESBLs

8   knock it over.

9   Other ideas?

10   I mean, this for me was one of the harder

11 things about it, was coming up with the fact that I

12 could only find one choice that I was comfortable

13 with. And I -- you know, so I did find the literature

14 on it. And I'm just delighted here there's a study

15 that's not published that might be helpful.

16   On the panel, anybody else have comments on

17 A, questions you want to get at?

18   AUDIENCE MEMBER: (inaudible - off mic).

19   DR. REX: So in the -- so use a quinolone.

20 Use moxy -- so what's the -- I don't have that in my

21 head -- rate of activity in moxy versus pseudomonas.

22 Anybody know?

         1   (Crosstalk)

         2   DR. REX: Very high proportionate resistant.

         3   So that might -- it's a good extra thought. But is

         4   moxy, you know --

         5   AUDIENCE MEMBER: (inaudible - off mic.).

         6   DR. REX: Huh?

         7   AUDIENCE MEMBER: (inaudible - off mic).

         8   DR. REX: But what about nosocomial

         9   pneumonia? No.

        10   (Crosstalk)

        11   DR. REX: Yeah. So you're in the same place

        12   you are with the erta, which is you've got -- I mean,

        13   you might know some -- this -- we can look at it. All

        14   right.

        15   UNIDENTIFIED FEMALE SPEAKER: John, my

        16   question -- or I guess maybe it's to the regulators --

        17   is how do they see data from this type of scenario.

        18   You develop your drug. What's getting in the label?

        19   DR. COX: It might be a little premature. I

        20   mean, we're trying to figure out, well --

        21   UNIDENTIFIED FEMALE SPEAKER: We're supposed

        22   to go and tell this to our management.

1   DR. COX: Oh, yeah, yeah. So I think what

2   we're trying to do is we're trying to figure out, you

3   know, X-1 and its activity against pseudomonas

4   aeruginosa. So I mean -- so it would probably be

5   something along the lines of, you know, X-1 is active

6   in the treatment of or, you know, it can be used to

7   treat the following infections when caused by

8   pseudomonas aeruginosa.

9   Now, if we take, you know, one of these more

10   abbreviated pathways, it's going to have greater

11   uncertainty around it. So I would expect, too, that

12   it would also be a reserve this use for when you don't

13   have anything else, you know, available.

14   And then depending upon where we end up,

15   because we've still got a lot more to discuss here as

16   we work down these various different tiers, the degree

17   of sort of, you know, reservation and whether there's

18   any sort of formal program in place to preserve the

19   drug, I think you'll see that, perhaps, as we start to

20   work through some of these other scenarios where

21   there's even greater uncertainty.

22   So that's off the top of my head because we

1   haven't even worked through all these yet. But if we

2   can get to the -- you know, the information that will

3   help us understand how the drug works, we'll be in a

4   much better position to be able to figure this all

5   out. And it's very hard. I mean, you know, you can

6   see we're all struggling with trying figure out how do

7   you actually discern the -- you know, the efficacy of

8   the drug and then gather safety information.

9   DR. REX: I couldn't imagine anything less

10 than the wording around use in only patients with

11 limited treatment options and get an expert to help

12 you do it.

13   DR. COX: Yeah. Yeah, because these are --

14 I mean, this is really, I mean --

15   DR. REX: Yeah.

16   DR. COX: -- a very, very limited program.

17 So it does seem like the indication would need to

18 have, you know, reservations and maybe even a program

19 around it.

20   UNIDENTIFIED FEMALE SPEAKER: And what body

21 sites are you describing?

22   DR. REX: So --

1   AUDIENCE MEMBER: (inaudible - off mic).

2   DR. COX: So the question is, is what body

3   sites are you describing. And you know, we would want

4   data in the body sites because, you know, at least our

5   experience has been we've showed some of these, you

6   know, past experiences that, you know, there are drugs

7   that don't perform well in some body sites. And

8   sometimes -- I mean, you know, Paul went through a

9   very nice discussion sort of helping us to understand

10 that a little bit more. But sometimes it seems like

11 we find that in the clinical trial.

12   So you know, not having at least some

13 experience to be able to have some degree of

14 understanding about what's going on in a body site

15 would be difficult. And you know, I would think, you

16 know, as part of this, too, as you work towards that

17 body site, you're going to get preclinical information

18 that's relevant to that body site to the extent

19 possible. Understand, you know, tissue levels,

20 whether it be blister fluid or ELF, those sorts of

21 things, to help you sort of as you build, you know,

22 towards doing the clinical trial. And those would be

1   the sort of things you do anyways.

2   DR. REX: Yeah, I should have put in a fake

3   label. I was going to pitch for all three

4   indications. That -- the -- that was, you know -- and

5   in the sense that HABP and the UTI -- and the intra-ab

6   got nice RCT data, UTI, you've only got the open

7   label. And I was going to sort of loosely make the

8   analogy to like (ph) the as (ph) voriconazole approval

9   where you've got a nice big randomized trial in one

10 disease and a related setting, related organism

11 mucormycosis where you've got some open label data.

12 And you sort -- you line it up with urine

13 concentrations being really high and show that, you

14 know, the urine also became sterile and do some stuff

15 like that.

16   I mean, so I was going to pitch personally

17 for all three indications. I should have said that.

18   DR. COX: Yeah. And usually, too, I mean,

19 we have -- you know, had some discussions around this,

20 too. It seems like if -- you know, if you're going to

21 do the multi-body site approach, you don't -- you want

22 to have some, you know, representative amount of

 1   information from each of the several body sites. So

 2   you might want to do -- you know, if you're going to

 3   do two, you might shoot for, like, 50/50. Or, you

 4   know, if you think one particular site be -- might be

 5   a little more difficult, maybe you do, you know,

 6   70/30, or something like that.

 7   But you wouldn't want to end up -- and we've

 8   seen this sometimes in the past with, you know, two

 9   patients in this site, three patients in this site,

10   you know, 100 in this other site and then, you know,

11   expect that you have sufficient information to be able

12   to draw conclusions about the -- what we sort of refer

13   to the onsie-twosies in other sites where you really

14   just don't have enough to be able to say too much of

15   anything.

16   So balancing it out across the sites of

17   interest I think is a good way to think about this.

18   Kenneth? And then we'll pop back over here.

19   MR. HILLIN: I just wanted to make sure we

20   did cover a topic. You specifically requested from an

21   investor perspective. I'm not an investor. But --

22   DR. REX: Well, then --

1   MR. HILLIN: -- I've seen you give nice

2   talks previously to CAC (ph). And I wonder if you

3   could comment from maybe a pharma investor perspective

4   if you think about the cost -- and you talked about

5   that -- and the time and then you think of the

6   probability of technical success, both of the

7   executing the trial -- of the trial, demonstrating

8   what you set up to demonstrate of the regulators

9   approving it, so both the technical and the regulatory

10   success versus the likely commercial return, how you -

11   - when you integrate all those things because that's

12   what an investor thinks about. Do you think that's

13   going to be -- what kind of scenario will that paint?

14   DR. REX: So very briefly, I'll answer one

15   part of it now, defer the others.

16   So can I get a return on this product if I

17   had it developed? I think the answer to that is yes.

18   This meets all the criteria for a new kind of fire

19   extinguisher for which there should be a value. And

20   I'm going to -- if I can get it developed at a

21   reasonable price, I get I can make a reasonable return

22   on this one. I'd be willing to make the case.

1   The question of would I actually run --

2   would actually spend the money, ask me that question

3   after we've looked at Scenarios B and C. You know,

4   let's get a little further along because I want to

5   highlight a particular problem that we've pointed at,

6   but I'm going to make it really painful.

7   Have the mic? Go for it.

8   UNIDENTIFIED MALE SPEAKER: Can I see the

9   statistics again, please, the chart?

10   DR. REX: Oh, sorry.

11   UNIDENTIFIED MALE SPEAKER: So what --

12   DR. REX: I keep going the wrong way. There

13   you go.

14   UNIDENTIFIED MALE SPEAKER: Yeah. So here

15   in the HABP/VABP only, we cross the 20 percent margin

16   by 2 percent, and that is already a wide margin. Now,

17   what type of discussion would a sponsor face in front

18   of, you know, NDA submitting these data and wanting a

19   label for HABP/VABP and cIAI, given that only the

20   pooled, or borrowed, matter, whatever, analysis meets

21   the 20 percent margin but not the single ones with a

22   numerical inferiority, which is just the patient,

1   actually. But that is issue of small numbers.

2   So what type of risk do we actually take as

3   a sponsor? Also, imagine that probably only 36 or 48

4   may respond. And then we're at 28, or whatever. You

5   know, we're five over. So what type of discussion

6   would we face for that indication then?

7   DR. REX: And can I suggest --

8   UNIDENTIFIED MALE SPEAKER: You know, what

9   is the risk?

10   DR. REX: -- the -- I'm going to -- let's

11   hang on to that question because -- but did everybody

12   hear what he just said? If we look at the numbers

13   again, if that 37 over 48 becomes 38 over 48, then the

14   difference -- because at 48, every one is worth 2

15   percent. So now the delta goes down to, like, minus

16   .1, and the confidence interval shrinks a teeny, tiny

17   bit. And I will tell you that it comes in right at

18   minus 20 -- deliberately done to make this point.

19   So this is pitched to be out by the tiniest

20   bit, and I can make that go away if you'd like by

21   using a different alpha. And that was Aaron's point,

22   was that if you're -- if you say, well, I can't have a

1   drug that might be as much as 20 percent worse, okay,

2   well, about -- or as much as 22 percent worse, can you

3   have one that might be as much as 19 percent worse?

4   Would you feel better about half a point? I just want

5   you to be aware of the choices we're making

6   numerically, all right?

7   So I'm going to -- let's push on because I

8   think we have covered these questions.

9   So Scenario B, this one is chosen so the

10 meropenem results have -- are unchanged. What's

11 happened is that on the X-1 arm in both cases I've

12 nudged the response rate down for X-1 as low as you

13 can go and still have the computed 95 percent

14 confidence bound to be within 30 for HABP/VABP and 25

15 for intra-ab. And remember, it was 37. It actually

16 would -- it would probably help to see. So it's 37

17 and 55 is what gets you neutrality. 34 and 50 puts

18 you in a worrisome place.

19   So now, would you like to have this drug?

20   Dr. Boucher?

21   DR. BOUCHER: Is this --

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

1 other thing. Look at the -- the HABP/VABP is all-cost

2 survival, so -- the endpoint. So the mortalities are

3 29.2 percent on the left and 20.8 percent on the

4 right. That's 150 percent higher mortality on an

5 absolute basis, okay?

6   Now Dr. Boucher?

7   DR. BOUCHER: So this really comes back to

8 what we talked about earlier. The issue will become

9 what is going on. It's five patients who have moved

10 here now. And the data are the data, right? We have

11 numerically lower survival and success in this

12 scenario. And so we're going to have to understand as

13 well as we can what's going on there.

14   And I think it's quite possible that there's

15 a real problem that suggests that there is a drug

16 either efficacy or safety. I think, really

17 importantly, what if there's a toxicity, either

18 something we could have predicted or something we

19 might not have predicted, playing a role or an

20 apparent lack of efficacy -- efficaciousness, I should

21 say, based on serum concentrations in these patients

22 or other things we could ascertain. But it's going to

1   take a look at all 48 and 24 HABP/VABP patients and 69

2   and 34 cIAI patients. And it will come back to how

3   strong -- how clear are we in what was going on in all

4   of those individuals.

5   So there's really no room for poor quality

6   data. There's no room for question about what --

7   whether the diagnosis is what we thought it was or

8   whether the outcome is what we think it is. But it's

9   a risk.

10   DR. REX: So Dr. Tomayko, you're an ID doc

11   at the mic. You talk --

12   DR. TOMAYKO: Yeah.

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

14   DR. TOMAYKO: I guess if I was still out in

15   the field I'd be less interested in understanding

16   everything here than in the last example. But still,

17   now that I have the added experience of working for a

18   company and looking at data, you know, the first thing

19   I would do is focus on the word you have up there,

20   which is the punch line and the message that I had in

21   my presentation.

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

1   sit down and look at a bunch of HABP/VABP studies and

2   bring a statistician and say how much heterogeneity is

3   in there and are these just sample variation issues.

4   And if they are, then, you know, we're really stuck

5   with a big problem, you know, I mean, as I think we're

6   all trying to illustrate. If you can't reliably do a

7   small sample and get an answer that tells you that

8   this is a good drug, then you have a problem. And

9   that's --

10   DR. REX: So --

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

12   at here.

13   DR. REX: So I didn't call up a statistician

14   to do that, but I did do the study a second time. And

15   this time, the results came out like this. So now X-

16   1's -- X-1 and meropenem have basically traded places.

17   I'm going to put them side by side on the next slide.

18   But notice that they've now basically traded places.

19   And so here they are side by side. At the

20   top is the tilt to the right. X-1 looks a wee bit

21   better. And at the bottom is the tilt to the left.

22   X-1 looks a wee bit worse. It depends on how you

 1   define wee, I suppose.

 2   Since you were just about to talk yourself

 3   into X-1 not being a very good drug when I just showed

 4   you the bottom scenario, is X-1 a superior agent in

 5   the top scenario?

 6   Kenneth?

 7   MR. HILLIN: This is -- and it's relatively

 8   straightforward. This is just a tyranny of small

 9   numbers --

10   DR. REX: Tyranny of the dichotomous mind.

11   MR. HILLIN: -- and the ability of

12   randomization in the scenario to take care of the

13   imbalances which are inherent in the kind of design

14   you have here.

15   So I think it's -- when you get down to

16   small (ph) end (ph) streams, things happen.

17   So and as Helen said, actually, then you're

18   driven by the individual characteristics of every

19   single patient when you get down to small numbers. So

20   it would be a statistical --

21   DR. REX: Well --

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

1   MR. DANE: Well, I would just add it's not

2   just imbalances. It could be perfectly balanced and

3   you could still see this just from random variability.

4   So --

5   AUDIENCE MEMBER: (inaudible - off mic.)

6   MR. DANE: So I mean, in some ways, you

7   can't avoid that. You can't magic up more precision

8   than you've got, you know. And I mean, that's the

9   risk with these programs, as far as I can see, unless

10 you can supplement it with something else.

11   MR. HILLIN: I think they -- what would be

12 criminal would be if you had a great drug that was

13 truly superior and you didn't observe it and the drug

14 was never approved. That's what we want to -- also

15 one of the things we want to -- we don't want to miss

16 if it turns out we have a better drug and we can't

17 figure out how to get it approved.

18   DR. REX: Yeah. And this is one of the

19 places where my decision to do two-to-one was

20 beginning to bite me because now the meropenem arm,

21 every movement of one is almost 4 percent. And so

22 that -- you know, it's painful, right? You know, I --

1   it was -- you know, I had a reason for doing the two-

2   to-one. But now it's biting me in the tail.

3   And so you know -- and you look at how

4   little the numbers have to move for this sort of a

5   shift to occur. And I found that to be disturbing.

6   So sort of the same sorts of questions, you

7   know, because, you know, Kenneth, you asked the

8   question how do I feel about the risk. Now Tom's

9   going to come to the microphone and give me some

10 insight.

11   DR. LOUIS: Question on the numbers changing

12 only a little, two points -- one is, properly done,

13 the confidence interval knows that. We all know that,

14 that it tries to reflect exactly that. But maybe a

15 point that does directly relate to the -- if you only

16 were to change one number is the strong need for high-

17 quality data and that any kind of miscodes or anything

18 like that can also be tilting this balance, especially

19 in a small setting.

20   DR. REX: And also, if you would really like

21 to -- I don't know how to maximize bacteremias and so

22 forth, but you'd like to have a sort of maximum

1 severity of cases. And I -- you know, you could

2 arbitrarily seek people with APACHEs course (ph) about

3 some threshold, I suppose. That would just further

4 shrink your pool. You know, every one of these

5 choices just gets -- digs you a different kind of a

6 hole.

7   Yes, ma'am?

8   UNIDENTIFIED FEMALE SPEAKER: Yeah, I'm just

9 thinking about the previous comment by Tom --

10   DR. REX: Into the microphone. Sorry.

11   UNIDENTIFIED FEMALE SPEAKER: Sorry. Just

12 about the previous comment by Tom, yes, you -- it --

13 there is definitely a huge component of quality. But

14 especially with the point you're making, John, as you

15 move up in the severity index, as these patients get

16 sicker, then their comorbidities start to come into

17 play. And not only do you see what John Tomayko was

18 talking about with that affecting all-cause mortality

19 as your endpoint, but you -- it also starts to play

20 over into your other endpoints, right, because you're

21 not going to call a patient a clinical cure from their

22 cUTI or their cIAI if they died. You're going to have

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 1   to ascribe those patients to failure.  So now, this is

 2   all spilling over into your other endpoints as well.

 3   So it becomes a real issue.

 4            DR. REX:  Right.  Sort of the same questions

 5   -- and as -- let me see if I can back up to this.  So

 6   the questions for the -- to be sure we discussed on B

 7   are the same as for A, basically.

 8            And does anybody see anything up there that

 9   they, you know -- I think the big one for me was about

10   the investor perspective because this was the, you

11   know -- I was thinking about that question as I built

12   these scenarios.  And you know, John Tomayko's phrase

13   was, you know, it's okay to understand risk.  How do I

14   manage risk?  And if the drug fails, you know, that's

15   the deal.  The drugs fail.  But if it fails for

16   reasons that don't have anything to do with the drug,

17   then, you know, you're unhappy.

18            And here, where it's -- you know, this is

19   really pushing the limits, particularly since our

20   endpoints are dichotomous, not continuous.  We

21   actually are -- you know, there's not anything else,

22   really, to look at.
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 1   Any other wisdom or -- Marco looks like he's

 2   about to say something.

 3   DR. CAVALERI: Yeah. Well, I think I agree

 4   with the previous comment that, at the end, with such

 5   small datasets, you would need to look at the data one

 6   by one, subgroup and try to understand what is

 7   happening. So it's not just merely into the

 8   statistical analysis of the entire dataset -- so it's

 9   -- because we acknowledge that there is this risk that

10   the statistic might not tell us exactly the whole

11   truth about the product.

12   So it's very important to look at this data

13   really capillary (ph), looking at the patient of the

14   subgroup, try to understand what would be the

15   imbalance at baseline and any other factor that could

16   have contributed to showing a difference. And that's

17   what we would do, and that's also why sometimes in the

18   small dataset running after, you know, inferential

19   testing might not be helpful at the end of the day.

20   And that's why we're open to alternative approaches.

21   And so it's the entirety of the evidence

22   that matters. And we have to look at all aspects.

 1   DR. REX: Yeah. And if you could maybe do a

 2   Paul Ambrose-ish pharmacometric analysis and see if

 3   you felt like there was a response in there that you

 4   could identify.

 5   MR. DANE: Yeah, John, because -- to me,

 6   scenario where you -- or Scenario B, the investor

 7   aspect is the same in the investor aspects at the

 8   start before you've even done the study. And I think

 9   it's all about the risks you've got that you're not

10   going to be able to support what you're trying to do

11   because you've got more uncertainty and you don't

12   quite know where you're going to end up. And yes,

13   that stays somehow captured in the confidence. It's

14   for -- but you know, it's got more potential to move

15   around.

16   DR. REX: Yeah, I just spent a year raising

17     $60 million for a drug where the story was not nearly

18   this hard to understand. And that -- I -- that year

19   was hard work.

20   Okay. So Scenario C. So what's happened

21   here is that the -- or excuse -- back up. I want you

22   to lock something into your brain. Lower bound --

1   look at the left scenario. Lower bound is minus 29

2   and minus 24.5, so just inside my hypothetical -- huge

3   margins, right?

4   So in Scenario C, the selection device has

5   failed, and you get just the natural rate of

6   pseudomonas. You get 10 percent on intra-ab, and you

7   get 15 percent in nosocomial pneumonia. And the

8   sponsor sees this coming because, you know, you can

9   have blinded -- a blinded rate of pseudomonas as

10   you're -- you can know that about the trial. But

11   there's no more money. You know, we've just got to

12   take what we get, okay?

13   So now we do -- so we run it, and it comes

14   out like this. And now this is assuming the two drugs

15   really match very, very tightly. And I've got a minus

16   29 up top and a minus 20.8 on the bottom. Now, look

17   at that for a second and notice that it is 22

18   successes and 34 successes.

19   I'm sorry. Where did it go? Excuse me.

20   That's going to come in a minute. It's a different

21   analysis.

22   So this one, the margins are the -- the

1   lower bounds are kind of like in B but with the deltas

2   being centered on zero. I mean, it is -- so this is -

3   - you know, you didn't even get the high quality of A

4   because you couldn't get your device to work. So this

5   is the problem of -- you know, and we take -- instead

6   of enrolling 1,000, you'd have to enroll 1,600 in

7   order to get at this if the device just flat out

8   failed.

9   Comments on this? Because this, for me,

10   really amplifies the investor concern. I don't know

11   how this device is going to work. I -- if I've had to

12   invent this device for my trial, goodness gracious,

13   you know, I have no idea how it's really going to

14   work.

15   MR. DANE: John, I think the thing I would

16   say is that, although it may -- when you get -- this

17   is what the data could look like. It might not be any

18   worse. The time you've got an issue is that if your

19   diagnostic doesn't work and you get this many fewer

20   patients, your power is 50 percent, not 85 percent

21   because what this is telling you is you've got 50/50

22   chance of showing something like that even if the two

 1 drugs are actually the same.

 2   DR. REX: Now, every movement of -- on the -

 3 - in HABP/VABP arm of one patient is 3 percent on the

 4 X-1 arm and 6 percent in the meropenem arm. It's

 5 enormous. Move one patient, and those number -- so

 6 this just gyrates like crazy if you start to play with

 7 it.

 8   Other insights or comments?

 9   Okay. So we've now done A, B and C in

10 which, you know, you can kind of sort of see, if you

11 look sideways, a non-inferiority study buried in here.

12 And there are other variants. You could put more

13 energy into the nosocomial pneumonia arm and just sort

14 of focus there.

15   But that actually -- Amy's question before

16 the break was are you really comfortable doing that,

17 right? And so -- and also, you'd like to have --

18 you'd like to un-confound where you can. And so I

19 liked having the intra-ab as part of this program,

20 even though it, too, has its flaws. As Ian pointed

21 out, you know, it's very, you know -- inter-ab is

22 confounded by surgery. And yet there is -- there's

1   some sort of an effect there.

2   So let's go on to Scenario D. So inhale,

3   exhale because now it gets awful. The culture-

4   positive rate is now about 5 percent, and there's

5   absolutely nothing I can do about it. You know, I

6   just -- that's it.

7   So the program size explodes. At a 30

8   percent margin and one-to-one, I might get down to

9   1,276 for any one indication in order to get the same

10   kind of crummy margins that we were getting in

11   Scenario C. So you understand, that's -- that -- it

12   would take 1,300 patients to get at data as bad as

13   Scenario C.

14   If I bring the margin down at all, the sizes

15   go up north of 2,000 patients. And maybe I could

16   really enrich (ph) for high-reach cases -- for high-

17   risk cases such as renal failure and more co-

18   morbidities. But this, I think, is where the animal

19   rule question becomes of interest.

20   So Sumathi and I went back and forth on this

21   a little bit. And this model doesn't exist. But

22   there's no reason to believe you couldn't do it, which

1   is you can take a large enough mammal -- a piglet or a

2   rabbit -- you can put it on a ventilator and give it

3   nosocomial pneumonia. You know, I've got to assume

4   that I could create something that looks a little like

5   the human disease. But you know, Tom Walsh (ph) has

6   been doing rabbits like this for years, and they

7   produce a very human-like pattern. I don't really

8   have reason to believe you can't do it. And then you

9   actually get into the notion of the clinical trial

10   being, effectively, a field trial. And you -- maybe

11   you can throw in some informational (ph) control data.

12   So here's the results. We've -- we did it.

13   Sumathi and I got together and did a ventilated piglet

14   model somehow.

15   UNIDENTIFIED MALE SPEAKER: You've been

16   busy.

17   DR. REX: Yeah, I'll tell you what. We've

18   been busy. It's been a -- we've had a busy month

19   since she suggested that I write this case. All

20   right.

21   So in the ventilated piglet model, 18 to 20

22   survival with X-1 and 0/10 with placebo, P equals

1   .005. And then we do the Phase 3 in nosocomial

2   pneumonia alone, so just picking one indication,

3   picking the most -- the important one. And we assume

4   the things that are shown there that I won't read to

5   you.

6   And at the end of the day, I get, after

7   enrolling, 726 subjects. I have 24 and 12 on X-1 in

8   control with my target pathogen. And there are my

9   made-up results. And if I want -- if I'm using a

10   boundary of negative 30 as my margin -- isn't that

11   what I said? Where -- did I write a margin down?

12   UNIDENTIFIED MALE SPEAKER: Thirty-five.

13   DR. REX: Thirty-five. Right. If I move

14   one patient -- instead of it being 19 to 24, it's 18

15   to 24 -- I actually exceed the 35 percent non-

16   inferiority margin. Sorry I didn't write it down. So

17   -- and I'm not doing inferential statistics. I'm

18   signing up for no math, okay -- none. Instead, I'm

19   signing up for the P of .005.

20   So now the discussion. Do these things

21   together create Tier C minus or D plus? Discuss.

22   DR. TOMAYKO: John, is there any chance that

 1   you would be able to tell us whether or not target

 2   attainment was achieved?

 3   DR. REX: Oh, well, absolutely. The desired

 4   exposures were hit. And so it's like in Scenario A.

 5   You know, we hired a really good PK-ologist, and we

 6   nailed it in our clinical program. And maybe we --

 7   it's picking up on the idea that we actually dosed a

 8   couple of people with HABP, with VABP with single

 9   doses before we started the program just to be sure

10   that we were comfortable with our exposures. You

11   know, you can do all those things. It's all right.

12   Absolutely, the drug -- and the drug gets

13   into the ELF, might or might not be able to do the

14   non-CF bronchiectasis study, depending on -- like, if

15   we're doing acinetobacter, I don't think I've ever

16   seen acinetobacter colonize in that. It might not be

17   a study, like, that you can do. But I can sure enough

18   do an ELF.

19   DR. TOMAYKO: But you're basically saying

20   that all of these folks for the MIC of pseudomonas,

21   which is I think going to be something less than one,

22   all the achieve (ph), the target exposure that they

1   needed --

2   DR. REX: Let's assume that.

3   DR. TOMAYKO: Okay.

4   DR. REX: Let's assume that we've got a good

5   exposure and that Paul Ambrose puts up one of those

6   plots like the other day and says, you know, it looks

7   like it's in the right spot, you know. It's not a

8   guarantee, but it looks like it's in the right spot.

9   I think you must assume that.

10   David (ph)?

11   DAVID: I just think -- I mean, again, it's

12   a huge amount of work, and you're amazing for having

13   done it. But I think it shows that you can't do non-

14   inferiority for this sort of indication. The data

15   just become too fragile at the end of the day, and the

16   risk is too high. So I would reject the non-

17   inferiority design for this sort of program.

18   DR. REX: And so let me be clear that I'm

19   not actually going to propose a statistical

20   hypothesis. I'm just going to say it's a control and

21   it's small. And I'll bring you some external

22   controls, and I'll show you that people in the past

1   with pseudomonas died a lot.

2   DAVID: I think -- but again, I think if you

3   put in the context of a different design approach,

4   then it gets a lot easier in a way -- in some ways.

5   DR. REX: What is that design?

6   DAVID: A superiority approach using

7   external controls and other controls, again, not

8   necessarily powered at P .05.

9   DR. REX: Well, let me be sure I've heard

10   what you said because you said use the external

11   control to show superiority. So I can do that right

12   now because I can tell you that, in the historical

13   data, people with untreated nosocomial pneumonia or

14   incorrectly treated nosocomial pneumonia have a all-

15   cause survival of about 30 to 40 percent.

16   DAVID: Yeah. So --

17   DR. REX: So I -- so it's -- so that's

18   buried down deep in here. And I bet I could do that

19   with contemporaneous controls.

20   DAVID: Right.

21   DR. REX: I bet I could that with some --

22   like, the Di Carlo data --

1   DAVID: But so I think what you -- yeah, I

2   think what you'd have to do -- I mean, I could go

3   through kind of a design that we went through thinking

4   about this particular sort of drug a while ago if this

5   is the right time to do that. Or I could wait until

6   later or not --

7   DR. REX: Oh, no. There's no better time

8   than now. So go ahead.

9   DAVID: Okay. So what we were thinking

10   about was a superiority design where you had your

11   drug, X-1. And this would -- could either be combined

12   with ertapenem or even meropenem, depending the

13   sensitivity of your investigators to a new drug for a

14   dangerous infection like pseudomonas. And I can tell

15   you that you do get pushback from investigators when

16   you go out and talk to them about this in real life.

17   So and you treat these patients. You try

18   and enroll patients with pseudomonas. You do all-

19   comers if you like. I would do all-comers. And

20   within that population of pseudomonas -- and you have

21   to be careful about what centers you pick because if

22   you do the trial in centers where there are very high

1 rates of carbapenem resistance, then everybody gets

2 put on colistin. So you actually don't want to do

3 your trial there.

4   You want to do your trial where you have UDR

5 rates of carbapenem resistance, which is on the order

6 of 15 to 20 percent kind of globally, and their

7 physicians are still using carbapenem mostly to treat

8 pseudomonas aeruginosa infections.

9   So you then look -- so you treat everybody

10 with your drug plus ertapenem or your drug plus

11 carbapenem. But you specifically look from among that

12 group --

13   DR. REX: This is open label --

14   DAVID: It's open label, yeah.

15   DR. REX: This is open label, one arm.

16   DAVID: Yeah, it's one label, one arm and

17 historically controlled. And I'm going to get to this

18 controls because you have to do a lot of work on the

19 controls up front to make this all work. And I

20 actually don't know the numbers because nobody's ever

21 done the work that I'm -- that I have in mind.

22   But you treat everybody up front with this

1 combination. And then your historical control should

2 be contemporaneous. It could either be done by a

3 retrospective analysis similar to what the medicines

4 company people did. It should be done in centers that

5 are going to participate in your trial. And it should

6 be done using the inclusion-exclusion criteria that

7 you plan to use for your trial, which I would argue

8 would have to be fairly broad.

9   Then what you would need -- so that would

10 give your control. What you're looking for is the

11 control levels of response of people initially treated

12 with carbapenems who have carbapenem resistant

13 pseudomonas aeruginosa. That's the control number you

14 want to get.

15   And then what you have to do --

16   DR. REX: So to play it back, what you're

17 going to do is seek people who would have met the

18 inclusion-exclusions of this trial.

19   DAVID: Yeah.

20   DR. REX: You didn't actually ask them to

21 consent. But at least on paper, they could have

22 consented. And then you're going to look for the

1   response rate in the carbapenem resistance subset --

2   DAVID: Yes.

3   DR. REX: -- of that group.

4   DAVID: Right. Right. So then the other

5   issue is monotherapy or where, you know, are you going

6   to add Amikacin. The centers that we talked -- when

7   we talked about this would have added Amikacin. So

8   you'd probably have to do that so you don't answer

9   that you're still stuck with that. But again, looking

10   at the carbapenem resistant group gives you at least a

11   look at the activity you want to look at.

12   So then what you have to do is you actually

13   have to validate your previously constructed control

14   group during your trial. And you can do that in two

15   ways, or both ways, one of which is you do a

16   prospective observational study of people who don't

17   get enrolled. Again, and/or -- and/or -- you have

18   something like a four-to-one randomization in your

19   trial.

20   DR. REX: So to play it back, what you're

21   saying is that after you've constructed this

22   hypothetical -- your developed data on a response rate

1   of MDR pseudomonas in a group that meet inclusion-

2   exclusions. And now you're doing the real trial. And

3   you either observe people who didn't go into your

4   trial, or you do a very disproportionate

5   randomization.

6   DAVID: Right.

7   DR. REX: So --

8   DAVID: The idea is to try and get numbers

9   to support the historical control that you started

10   with, so to avoid the Ellenburg effect of having

11   inadequate historical controls, if you like.

12   DR. REX: Okay.

13   DAVID: So that was kind of the design in a

14   nutshell of what we looked at for a drug like this.

15   And the problem that you run into is that when you

16   actually get crunch -- start crunching numbers,

17   depending on what those controls look like, you might

18   get down to a point where you don't have an adequate

19   inferential test at .05. So it might have to be .1 or

20   .2 or something, and you might have to use additional

21   data. You'd have to rely very heavily on PK/PD data

22   both in people and in animals.

1   But I believe that that sort of program all

2   together might provide a way forward for the smaller

3   patient populations. And it avoids a lot of the

4   issues that you run into in the non-inferiority

5   designs.

6   DR. REX: So Ian Friedland, where are you?

7   You're summoned to the microphone.

8   So help us out here. This sounds -- so just

9   sort of feel your way into this. It -- you know, in

10   many ways, this is a little like what you did, though

11   -- I mean, there are clear differences. But you are -

12   - this is about seeking the super-resistant bugs. And

13   Sumathi did the math to suggest that 1 in 122

14   pseudomonases would be resistant to two drugs, which

15   would --

16   DAVID: No.

17   DR. REX: No? Sorry. One -- no, it's the

18   rate of dual resistance --

19   DAVID: These organisms are only resistant

20   to the carbapenem. They don't have to be resistant to

21   Amikacin in the study. You accept -- you do the same

22   thing you did in your study. So --

1   DR. REX: Okay.

2   DAVID: -- patients are treated for --

3   DR. REX: But they have to have been treated

4   -- but in order to get a control group, it has to be

5   those treated only with the carbapenem in order to get

6   the response rate for carbapenem-resistant

7   pseudomonas.

8   DAVID: Most of the patients that you'll

9   find when you do your little study are going to get

10 carbapenem plus an aminoglycoside for pseudomonas --

11   DR. REX: So they will have actually had --

12 so I guess I say again if I want to get a placebo

13 response rate, I have to find people who didn't get an

14 active drug.

15   DAVID: No, what you want is a control rate

16 that matches the controls that you'll have in your --

17   DR. REX: But I have to beat the control.

18 So if the controls --

19   DAVID: Yeah.

20   DR. REX: -- have gotten an active drug, why

21 am I going to be superior to an active drug?

22   DAVID: Because Amikacin alone is not very

1   good is what we find.

2   DR. REX: I -- boy howdy. Okay. I'm now

3   not buying the risk, but --

4   AUDIENCE MEMBER: (inaudible - off mic.)

5   DR. FRIEDLAND: I agree. The concern would

6   be the Amikacin because, if you treated just Amikacin

7   alone, maybe you would, but they're not going to do

8   that. As soon as they get the ceftaroline (ph),

9   they're going to switch to another drug. So they're

10   going to give you an Amikacin plus an active drug. So

11   it's basically the 24, 48 hours in which maybe they're

12   not covered with a --

13   DAVID: That's --

14   DR. FRIEDLAND: -- effective butolactam (ph)

15   or some other --

16   DAVID: Right. But that's why the controls

17   are mainly -- it's historical or external controls.

18   So that's -- so you're not -- so the four-to-one

19   randomization, you would have to deal with this

20   confounding issue. Or you do the prospective

21   observational study where, again, you're not treating

22   the control group.

1   DR. REX: All right. So that's an idea that

2   fits into Scenario F of an approach that wasn't

3   considered and which I -- we're going to come to that

4   in a minute. We're looking for other ideas.

5   Can I get a little more conversation on the

6   animal rule-ish support for this? So it's not the

7   sun, the moon and the stars. And it's a pretty small

8   flashlight.

9   Dr. Boucher?

10   DR. BOUCHER: I mean, I think again we'll

11   work with what we have to work with. And if this was

12   a drug Scenario D that worked in acinetobacter or some

13   new place where we're really up against it, I think

14   it's possible to work with that. You know, ideally, a

15   little more clinical data would be nice.

16   And so in -- I sort of hesitate to say this.

17   But from the clinical perspective, it still would be

18   helpful to see those patients with the worst -- you

19   know, with the blood stream infections or, you know,

20   some places where clinically, even if it's individual

21   cases, there was some evidence that the drug was

22   effective.

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 1            DR. REX:  So --

 2            DR. FRIEDLAND:  I'll comment on the animal -

 3  -

 4            DR. REX:  And -- well, actually, the two of

 5  you -- Ed asked the question of me a second ago, and

 6  I'm going to phrase it because I'd like the two of you

 7  to respond to this.  How will you use this drug in the

 8  clinic?  How often do you think you'll use it?  Why

 9  will you use it?  Because that goes in to the question

10  of risk, benefit and labeling.

11            Ed, do you want to amplify it all in a

12  question for them before we let them loose on it?

13            DR. COX:  Yeah.  I know we're still

14  struggling.  And this is why I asked John.  I said is

15  it too early to ask this question.

16            But you know, we're struggling with trying

17  to figure out how we evaluate the efficacy of this

18  drug.  And at the end of the day, I mean, there's

19  going to be tremendous uncertainty around this.  And

20  you know, maybe this drug is active against baumannii,

21  and maybe other drug is active against pseudomonas

22  aeruginosa.
```

1   I mean, it would be interesting if folks

2   have insights. You know, how would this drug actually

3   be used in the clinical arena. I mean, would it be,

4   you know, your institution had some tremendous problem

5   with resistance among pseudomonas aeruginosa in

6   patients. And could you identify risk factors? Or

7   you know, there's an outbreak of acinetobacter

8   baumannii in your ICU and, you know, available --

9   based on what you know about resistance testing from

10   the first case or the first couple of cases, you don't

11   have good options. So you're -- you know, that --

12   this is going to be the instance where you, you know,

13   reach for an alternative.

14   I'm just trying to figure out where does

15   this fit or how does this -- how would it be used.

16   Any thoughts or insights on that?

17   DR. TOMAYKO: I'll take a stab. I -- as I

18   said yesterday, I'm pretty impressed with the

19   surviving SES (ph), this experience where we really

20   learn to pay very careful attention to infections and

21   manage them appropriately, be it source control or be

22   it rapid onset of appropriate therapy.

1   And I believe Anon Kumar (ph) has now

2   followed up on his database. And he's no longer just

3   looking at one-hour intervals increasing mortality by

4   7 percent. I think he's got it down to 15 minutes.

5   So you know, I would take -- if I had a

6   problem in my institution and I was in my ICU and my

7   patient was in septic shock -- because that's what he

8   studied -- and I was concerned about pseudomonas, I'd

9   give them whatever I had to treat pseudomonas before

10   this drug was approved. And then I'd add this on it.

11   And if I came back just like I do with my

12   Amikacin in the clinical program and found out that

13   everything else is there and I have great evidence,

14   then I would drop the drug X-1. If I didn't, I'd be

15   gathering data to submit to the company that was kind

16   enough to invest in the program and say hey, your X-1

17   really made a difference today.

18   DR. COX: And I'm not being critical. I'm

19   just trying to understand a little bit more.

20   So if I'm understanding correctly, you would

21   use this as part of your empiric regimen in the ICU

22   for sick patients that you suspected pseudomonas

1   aeruginosa so it would be empiric use, given the

2   importance of initial therapy. So it could be a fair

3   volume of usage that this drug would see --

4   DR. TOMAYKO: Well --

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

6   that --

7   DR. TOMAYKO: I think you're getting to the

8   point. I'm not arguing that.

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

10   DR. TOMAYKO: Let me tell you --

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

12   DR. TOMAYKO: Let me tell you that we have

13 some safety data on the drug, and we have a lot of

14 preclinical safety data. I mean, that equation might

15 change dramatically if the drug was like colistin or

16 worse. But if it was better than colistin in terms of

17 safety and the data was supportive, then I'm thinking,

18 well, the big problem here is that the efficacy isn't

19 good enough, but I don't have anything else, or I have

20 colistin. I'd have to make a decision there. That

21 animal data might look better. I wonder if you could

22 study colistin in that model and see what that looks

1   like.

2   So there's a lot of information that you

3   could craft together. I'm kind of interested to see

4   what Helen would say. But I would not be afraid to

5   start the drug in a person where it could make a huge

6   difference and I could actually advance our

7   understanding of whether or not the drug could have an

8   impact if it could make that difference. If nothing

9   else was treating that patient and that patient in

10   septic shock got better, I think you'd want to hear

11   that data.

12   DR. COX: Yeah. So before -- and just

13   because this is helpful to me, let me just -- so I'm

14   assuming, John, sort of there's two cases that are

15   coming to mind. Within your institution, it sounds

16   like you have, you know, patients who are infected

17   with pseudomonas aeruginosa that, you know, have, you

18   know, very resistant organisms. So that's sort of one

19   situation. The other situation I'm thinking about is

20   the situation that Paul mentioned, which is the

21   variability and exposure.

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

1   only were to use it in situation where the institution

2   had a significant rate of resistance to, you know,

3   available therapies, you know, that would be a more

4   restricted population. If there's concern more

5   generally about, you know, patients where there's

6   going to be significant variability of exposure -- so

7   this is, in essence, a third agent being added in --

8   then the use of the drug could be quite significant, I

9   would think. Fair?

10   DR. TOMAYKO: I don't know. It's been a

11   while. How many patients in my ICU are in septic

12   shock and have some of the risk factors that would

13   predispose them to pseudomonas? How many of the units

14   on my hospital have this? And again, you know, if I

15   don't need it, I'm going to stop it.

16   But the other place I would use it is when

17   for some reason I got it wrong but the patient's still

18   alive and I want to rescue them. So I would

19   definitely use it there. But you know, you're going

20   to have the biggest impact on an infection if you

21   start antibiotics early. And I think that it's really

22   what we're trained to do.

1   One last comment, on that animal data that

2   John showed, I'd certainly want to know whether or not

3   Paul saw anything in the exposures in the animals that

4   might not make the data look pretty robust because it

5   did look pretty robust. You know, it was a lethal

6   model, and the drug had a profound effect in that

7   study, so.

8   DR. COX: Yeah, and I don't disagree with

9   that. I'm just trying to figure out, you know, the

10   development program, what the, you know, clinical data

11   are that you accrue during that program and then what

12   usage might look like for such a drug that was really

13   based on a database that had a fair degree of

14   uncertainty. And I don't disagree with what you're

15   saying.

16   DR. TOMAYKO: No --

17   DR. COX: I'm just trying to anticipate what

18   this might look like because I think that's important

19   for us to understand.

20   DR. TOMAYKO: No, this is important, too,

21   because you just gave me a great idea for a field

22   study.

1   DR. COX: Do tell.

2   DR. TOMAYKO: Well, I mean, if the drug's

3   approved and I want to do something that's meaningful,

4   then I get a protocol out there and, you know, figure

5   out how to get it disseminated. I think if it's an ID

6   program, I'd have a lot of support from my IDSA

7   colleagues. And I would make it a pragmatic-type

8   protocol, and I would collect rigorous data, including

9   PK data, on this population of patients in septic

10   shock where I could manage a real-time significant

11   effect. And then I would pull that together and do

12   what I can with it and submit it.

13   DR. COX: No, that's fair. I mean, you

14   know, and I think, you know, one of the things we

15   talked about this some during the preparation of the

16   cases, is that, you know, if the overall rate of

17   infections caused by pseudomonas aeruginosa doesn't

18   really change, you may end up with a very large "ITT"

19   population. You may learn something important there.

20   You could certainly get PK, and PK would be valuable.

21   And then you know, it's also -- and I was

22   thinking about this a little bit. I was sort of

1 asking, you know, are there studies that you could do

2 after a drug is approved that might become somewhat

3 more feasible. And it sounds like you're hinting at

4 that may be something that, in fact, would be true.

5 And I'm -- there, I'm focusing on the MITT population

6 and recognizing that the patients were probably

7 getting a variety of other drugs that may make it

8 difficult to evaluate the test drug unless there are

9 certain resistant -- certain resistance profiles that

10 allow you to isolate that. But there may be

11 opportunities to try and figure out how to study the

12 drug.

13   So I'm just trying to think through it.

14   DR. DUDLEY: Yeah. Mike Dudley. The

15 medicine's coming out.

16   John, you sort of flipped the card that I

17 think I was thinking of as well. And the new

18 commissioner actually made some comments a few weeks

19 ago about use of registries in the post-approval smart

20 process and really was encouraging use of that kind of

21 information.

22   So I -- where I thought David was going to

1 go and which I think was on the superiority side is --

2 is that you may -- what we may want to be thinking

3 about, in fact, the multi-drug-resistant situation

4 here, not for inferential testing and -- but perhaps

5 for trying to see signals of superiority because if

6 the drug has a big enough treatment effect, that's

7 probably the population where you're going to be

8 seeing that.

9   So I never thought I'd see myself arguing

10 for a superiority, but I do think that if the

11 properties that were described in the case, that of

12 being able to go where you think the biggest treatment

13 effect may be.

14   And then thirdly, I was thinking about the

15 population. And you know, the anti-PCRV (ph) antibody

16 work that's been done with pseudomonas, the trials

17 that were done in 40 hospitals in France enrolled 30

18 patients with pseudomonas infections in nine months.

19 And so perhaps maybe specifying a patient population

20 that's particularly high risk, which they identified

21 as having tracheal bronchitis, might be a population

22 where we could go and see that treatment effect.

1   But I vote for the animal rule.

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

3   DR. REX: Sorry. So sort of Helen and then

4   David. Sorry. We're going to go back and forth.

5   DR. BOUCHER: Okay. So I would just say as

6   much as I agree with a lot of what John said, from a

7   clinical perspective, especially in Scenario D, I

8   think that the way the drug would be used would be in

9   those settings like my first patient that we talked

10 about where we know that we've got nothing else to

11 offer, or we know that --

12   DR. REX: Okay. But you're talking about

13 your first patient from your presentation --

14   DR. BOUCHER: From my presentation.

15   DR. REX: -- from this morning.

16   DR. BOUCHER: The lady with the MDR

17 Klebsiella that was resistant to everything except

18 colistin, including the two new agents, where this

19 drug might offer something that's potentially

20 tolerable to this woman for whom colistin really

21 wasn't an option and that, through our stewardship

22 program, we would gain some experience in people with

1   known infections because this dataset is small. And

2   that's something that our community looks at when we

3   decide to bring these drugs in.

4   And then perhaps -- the next place I could

5   see early use would be in -- if, God forbid, there was

6   an ICU kind of problem where we had a particularly

7   nasty organism that we knew about that was

8   circulating, you know, that that would be another

9   place where -- thank Heavens I haven't had to do that

10   -- but we -- where you could envision tapping into

11   something like this.

12   But we'd want to see more clinical data,

13   whether that's Phase 4 -- you know, however we got it

14   before we moved on. And I think that's largely what's

15   happening, at least in our hands and in those around

16   the country with the two new agents, even though

17   they're kind of relatives of drugs we know well with

18   the ceftolozane/tazo and the ceftazidime/avibactam.

19   You know, we're using them in individual cases with

20   the best susceptibility testing we can get and getting

21   experience with them before we think about broader use

22   -- in stewardship programs, you know, in a very kind

 1   of -- in a way that probably our sponsor colleagues

 2   don't like to hear. But that is what's happening, I

 3   would say.

 4   So I think the answer to your question on

 5   the prior example maybe is a little more difficult.

 6   But I find it hard to imagine in 2016 with the way

 7   things are working where I work that we would be able

 8   to think about using this stuff empirically at this

 9   point.

10   DR. COX: So that's helpful, Helen. So that

11   sounds like situations where culture results tell you

12   that you essentially don't have options or in the

13   setting of ICU outbreaks with the particularly

14   problematic organisms circulate around where you have

15   a resistance profile that tells you you don't have

16   other options or you have very, very, very few what --

17   other options.

18   Okay. Thank you.

19   DR. REX: We need to talk about the

20   economics of that at some point.

21   So David?

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

1   question about how it would be used. So I work in a

2   70-bed hospital. I think 70 percent of U.S. hospitals

3   are under 200 beds. Most of those small hospitals

4   don't have big resistance problems. In the four years

5   that I've been working there, we had our first case of

6   VAP just last year. And it was pseudomonas aeruginosa

7   but a susceptible strain.

8   So if you extrapolate that across the United

9   States, I don't think there's going to be a huge

10   amount of empiric use. It'll be mainly in academic

11   centers where resistance is going to be a problem.

12   So I don't -- and also, the -- in order for

13   anyone to make money on this, which I think is

14   someplace John was going to go, the price in the

15   United States is going to have to be pretty high. And

16   stewardship programs are going to clamp down pretty

17   hard on people who use very expensive drugs

18   empirically for no good reason, so.

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

20   introduce yourself.

21   MR. WARREN: So Travis Warren (ph) from the

22   U.S. Army.

 1   Could you go back to the previous slide from

 2   this one? It's the one where you introduced the

 3   animal model.

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

 5   MR. WARREN: Next one.

 6   DR. REX: Yeah. Well, so I've got some

 7   made-up data with the animal model here.

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

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

10   --

11   MR. WARREN: There was the one --

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

13   -

14   MR. WARREN: There was a bullet point about

15   the -- generating the validated pig model. And so I

16   think there's a possibility you may have violated your

17   requirement for the miracle less than one on that one.

18   And you know, I --

19   DR. REX: Oops.

20   MR. WARREN: -- I say that tongue in cheek.

21   But it's an important point because I think it's

22   important to emphasize that I'm not familiar with the

1 pseudomonas models that are out there. But it's been

2 alluded to that there's not a good animal model that's

3 out there. And I don't want especially sponsors who

4 were considering potentially using this type of thing

5 to think if there's not already -- if there's not a

6 model that's already out there -- it's not a plug-and-

7 play system where you choose the species you're

8 interested in and the pathogen you're interested in

9 and put them together and, voila, you've got the

10 disease that's indicative of the human disease.

11   So it's -- I think that if this is -- as

12 sponsors are thinking about potentially using this

13 pathway, it seems possible that there would be as much

14 regulatory interaction just around validation and

15 trying to have -- give the FDA confidence in that

16 animal model because they're going to be scrutinizing

17 those data very, very carefully, I would anticipate.

18   DR. REX: I want to say thank you for

19 standing up and saying that. That's something I -- it

20 was on my list to comment on. And Dr. Nambiar will.

21   DR. NAMBIAR: Yeah, I thank you for your

22 comment. And that's what's probably (ph) was the last

1 point on my slide as well. Even though the animal

2 model seems like an approach, there is a lot of work

3 to be done between now and getting to it. And then

4 certainly we're talking about one model. But ideally,

5 we need more than one model. And the disease in the

6 animal has to be reflective of human disease.

7   And I think your comment is right. There's

8 a lot of interaction, a lot of back and forth before

9 we get to a model that we are comfortable with to

10 decide the trigger and I think, as I mentioned, what's

11 the inoculum, what's the organism. With bio-threat

12 agents, it is -- it was easier because we used one

13 strain of Y. pestis. You know, with pseudomonas, I

14 mean, we have a lot more issues.

15   So even though there's an appeal to the

16 animal rule, I think it's fair to say that it's a lot

17 of work done. And the years and time spent in getting

18 that to fruition, you might be able to do clinical

19 trials. I think we have to keep that in mind.

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

21 Ed.

22   DR. BORIO: And I know you asked the

1   question, John. But I'll ask a question to Sumathi,

2   which is, you know, if you two can comment on the

3   appropriateness of a placebo in the control arm in

4   this model, you see a very dramatic treatment effect.

5   But the control is based on a placebo. Can you

6   comment on that? When was the last time you had an

7   animal rule in a pivotal -- the efficacy studies that

8   relied on a placebo control?

9   DR. NAMBIAR: It will -- so I think the

10   approval for levofloxacin was levofloxacin versus

11   placebo.

12   DR. REX: So was the answer that you

13   typically do it this way?

14   DR. NAMBIAR: Yeah.

15   DR. REX: Right, since this is the model you

16   made up. So I was --

17   DR. NAMBIAR: Like --

18   DR. REX: -- hoping it was --

19   DR. NAMBIAR: -- in humans.

20   DR. REX: -- correct.

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

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

1   -- the example that you showed in the real-world

2   example of the African green monkey, you kind of had

3   data like this at the end of the day.

4   DR. NAMBIAR: Yeah. I think maybe off by a

5   couple of numbers, but it was --

6   DR. REX: Or less. Right.

7   Ed?

8   DR. COX: Yeah. I just wanted to thank the

9   folks that were daring enough to postulate or

10   speculate on how the drug might be used.

11   And you know, the reason I'm asking is I

12   think that, you know, everyone recognizes that there's

13   tremendous uncertainty around this data. And so you

14   know, if it -- you know, if we think about, you know,

15   managing the risk of a product out there, it seems

16   like there would need to be some sort of program or

17   some sort of restriction on use. And just -- it helps

18   to have some insights into how the product might be,

19   you know, envisioned being used to help to understand,

20   you know, how you might put some sort of program in

21   place to, you know, restrict the use to certain

22   settings where it was appropriate to use it, you know,

1   where the safety and efficacy, essentially, were --

2   you know, whether it was balance of benefit risk and

3   then also thinking about how do you gather more data

4   to figure out what is going on with the product. Is

5   it -- you know, is it working well in the situation

6   out there in the real world? Or have we uncovered

7   something that we didn't anticipate from the premarket

8   data in that -- you know, either with regards to

9   safety or efficacy? So --

10   DR. BOUCHER: So Ed, I agree 100 percent. I

11 think that, you know, tying it in to sort of the

12 overall strategies that we're working on in the carb

13 efforts, you know, the stewardship kind of being more

14 universal in the United States as well as monitoring

15 of antibiotic use in general but especially for these

16 type of antibiotics seems like a very appropriate and

17 timely kind of systems-type measure to help with this.

18 And that's something that, you know, in our carb

19 efforts there's a lot going on in this area. And more

20 hospitals are using the NHSN antibiotic module

21 already. That's capturing all the antibiotics that we

22 use.

1   So that's a system that exists. Now, it may

2   not be 100 percent acceptable for all the need. But

3   it's a -- it's evidence that there is a U.S.-based

4   systematic approach to all antibiotic use, but

5   especially for these really precious agents.

6   DR. TOMAYKO: And I just want to say that

7   there are settings where we've done things in the past

8   under a protocol. So that's what you were getting at.

9   Maybe there should be restrictions on how the drug is

10   used in the general sense based on that data. But

11   maybe it really is.

12   I was kind of thinking on the fly. But

13   maybe it really does become kind of a registry or a

14   field study. And you know, we make it -- take

15   advantage of diagnostics to try to minimize any issues

16   and whatever. But collecting that data is critical.

17   DR. COX: Yeah, and I agree, John. I think

18   we're all thinking on the fly today, and that's part

19   of what makes this interesting. But yeah, you know, I

20   appreciate everybody's comments and willingness to

21   hazard an opinion on this as we try and work through

22   it -- very helpful.

1   DR. REX: So I want to be sure that we've

2   thought about what this means economically. So what

3   does it cost to run the plant that makes an injectable

4   antibiotic 100,000 doses a year? My number is $20

5   million.

6   UNIDENTIFIED MALE SPEAKER: Is that a

7   combination product of two --

8   DR. REX: Well --

9   UNIDENTIFIED MALE SPEAKER: -- of different

10   types --

11   DR. REX: It's --

12   UNIDENTIFIED MALE SPEAKER: I mean, what --

13   DR. REX: This is a general -- I asked my

14   guys for a general number for having a facility. And

15   it definitely went just like this. Yeah, if you're

16   making a monoclonal, it's more expensive. It sort of

17   is. This was a general number, all in. And it

18   doesn't mean -- it doesn't assume you have had to be -

19   - it assumes you don't have to build your own

20   facility. You can actually work in somebody else's,

21   you know, shed, so to speak.

22   But to have the staff to make -- to have the

1   runs to, you know, sort of take it in and out of

2   production, that's the warm-based kind of a minimum

3   cost if kind of the wind is to your back.

4   It can be more expensive than that depending

5   -- it still depends on how much you want to make. You

6   know, the actual physical cost of each vial begins to

7   be relevant after a while. You know, making 100,000

8   vials or something even at 5 bucks, you know, that's

9   half a million dollars right there -- boom, done. And

10 that's -- it doesn't count stuff that goes in and out

11 of date. And the occasional run, you know, sterile

12 injectable manufacturing -- oh, my God, well, at least

13 once a year, some batch blows apart and you lose

14 50,000 vials. And you -- everybody just goes bananas.

15   So the part -- the difficulty with what we

16 just discussed is that if the drug is being used in

17 the United States 100 times a year and in Europe -- so

18 Europe -- the population of Europe is three times all

19 of your -- even whether you -- it's in or out, it's a

20 little over three times the United States.

21   So let's pretend 500 courses a year. What

22 do I have to charge for each course to have the warm

 1   base exist so that Helen can do her experiment? I

 2   mean, I -- ouch. I just want to observe that.

 3   So this -- you know, this is why I spend a

 4   lot of time on the pool models. I would want to treat

 5   this as a better fire extinguisher and argue that some

 6   countries should pay a certain access fee to guarantee

 7   that the drug exists in the pharmacy so that you can

 8   have it on an as-needed fire extinguisher-like basis.

 9   But you know, I look this, and I wonder

10   could I convince somebody to pay for this fire

11   extinguisher. You know, and I'm not saying that I

12   like my answer when I say that. You know, it doesn't

13   make me happy. But this is the problem -- this was

14   the reason for the case.

15   I don't see any hands go. So let me just

16   show the very last slide. So this is Scenario E.

17   It's like in Scenario D. But the animal model is --

18   I've pointed out it's hard. I don't know that I can

19   do one. Well, so we tried, and it -- couldn't do one.

20   Absolutely. The pseudomonas, piglets, rabbits -- none

21   of it really looked like human beings.

22   So now we're down to can't do it, can never

1   do it. What do -- and yet X-1, honestly, looks like

2   it ought to be of some value. I mean, honestly, it

3   does.

4   So discuss. I told you the cases were going

5   to get harder. Everybody take a deep breath.

6   MR. DANE: You know, I guess it ranks (ph)

7   to some of the earlier discussion, John, is that when

8   we're in this situation, it's -- yeah, it's hard

9   whatever we do. And in one way, the idea of open

10   label trials with external control may sound

11   appealing, but the trouble is are they really

12   comparable. And you'd have to do a lot of work to be

13   sure they were unless you had a very big effect. So

14   if you had a very big effect, you could be a bit more

15   confident that, actually, you had the benefit.

16   Otherwise, it's just all getting mixed up in noise.

17   But at the same time, yeah, it normally

18   (ph)randomize. But if you've got a small number of

19   heterogeneous cases, does it really help you? So it

20   avoids the bias of treatment choice, but it doesn't

21   necessarily give you balance in your groups.

22   So I'm not sure I've given any answers there

1 other than more problems. But I think it was -- it's

2 just the caution around this idea of external controls

3 can solve all our problems. We just have to be a big

4 careful with that and make sure that's sufficiently

5 comparable to be able to do something with that.

6   DR. REX: So let's talk a little more about

7 external controls. I mean, I -- you're right. I'm

8 teasing you a little bit to -- the -- no, you didn't

9 help me at all there. So I'm still stuck. Okay.

10   So I've got this thing. And the -- really,

11 the best thing I can imagine is I'm going to go find

12 folks who they've grown it. And now I'm going to --

13 maybe it's acinetobacter, you know, right? Now I can

14 kind of do this with acinetobacter, that, well, you

15 see one of those, pretty high frequency of I don't

16 have any drug at all that works. And I could do an

17 open label case series.

18   What about -- you know, David Shlaes was

19 pointing at the idea of some sort of a contemporaneous

20 control group. I mean, is there anything -- and I

21 know there are strong allergies to external controls

22 because previous datasets have been really messy.

1   Marco's smiling at me fixedly. And Ed and

2   Sumathi are in deep debate.

3   So opine on agents approved based solely on

4   external controls.

5   DR. COX: So yeah, we were talking about

6   something else.

7   (Laughter)

8   DR. NAMBIAR: Well, I can reveal what that

9   is, is I was asked to find another job.

10   (Laughter)

11   DR. REX: Well, at least we all share the

12   pain here. That's the good thing.

13   DR. COX: So yes, I mean, we do use external

14   controls and historical controls. And the times we

15   use them are in situations where, you know, the

16   outcome is -- you know, I like to use the term -- you

17   saw it on my slides today -- lights on, lights off,

18   for it's -- you know, it's dependable. It happens all

19   the time, and it doesn't really change that much. And

20   you're not quite as susceptible, you know, within the

21   group that you're looking at to variability with

22   regard to outcomes.

1   You know, I've talked some with my

2   colleagues in oncology, and I asked them about, you

3   know, the situations where they've used historical

4   controls. And you know, they'll sometimes say to me

5   so, like, you know, tumors just don't get smaller on

6   their own. They just don't do that. So if you have

7   something that makes tumors get smaller on their own,

8   you know, that as a surrogate (ph) endpoint, helps us

9   to understand that we think we have an active drug.

10   And then some other studies can happen, you know,

11   longer term that tells us more about the effect of the

12   drug clinically.

13   So when you -- so there are some infectious

14   disease conditions where, you know, the progression is

15   invariable and, you know, unfortunately, I mean, it's,

16   you know, the really bad diseases. And you know, we

17   have used historical controls in those sort of

18   circumstances where we think we've got a situation

19   where, you know, progression will be essentially

20   relentless if you don't have an active drug.

21   And I think the last time we did something

22   like that was for isavuconazole, which is approved for

1   invasive aspergillosis and also for mucormycosis. And

2   we focused in on that -- in that application. You

3   know, it was very helpful to have data form the

4   invasive aspergillosis study. And then you know, we

5   recognize these are different agents, and I mean the

6   agent causing the infection.

7   But with mucormycosis, we were able to look

8   at patients with hematologic malignancies, a group

9   that we thought would have, essentially, relentless

10   progression if they didn't see an effective antifungal

11   agent. And you know, we looked at that group of

12   patients and saw something that we thought wouldn't

13   have happened absent an effective antifungal drug.

14   So there are scenarios where such an

15   approach is, I think, informative. There are, you

16   know, many other scenarios where, you know, the

17   outcome and can change tremendously. You know, the

18   variability and outcome may be as large as the

19   treatment effect that you might expect, depending upon

20   who gets in the trial, what their, you know, baseline

21   conditions and comorbidities are. And when you're in

22   that scenario, it can be very difficult to,

1   essentially, you know, sort out, you know, what --

2   whether the drug is having an effect or not.

3   And you know, we've seen situations, too,

4   where, you know, despite thinking that we understand

5   the factors that impact upon outcomes, you know, the

6   patients that actually end up in a clinical trial do

7   better. And that's not just us, but that's an ICHE

8   (ph) tend that essentially says that, you know,

9   patients that end up in a control group within a

10   historic -- within a clinical trial typically do

11   better than their historical counterparts.

12   So I mean, that's what makes it really hard,

13   is when there is this variability. If it's lights on,

14   lights off, something that never happens, then

15   historical controls, you know, can be a good and

16   reliable way to do this. If it -- if there's a lot of

17   variability and it's hard to understand all the

18   factors that impact upon that variability, it can be

19   really tough.

20   DR. REX: Have you ever seen anybody do what

21   David described, which isn't -- it isn't just the last

22   50 cases with X, but rather, they've been filtered.

1   And at least you've looked at them at the level of I

2   think they could have been enrolled in the trial had I

3   been in that hospital at the right time. Have you

4   ever seen that done?

5   DR. COX: So I don't know that we've seen

6   exactly what David's described. But we have seen

7   people make a fairly valiant effort to pull together

8   historical controls. And you know, it usually -- it -

9   - this is not the way to do it. But usually, it's

10   done sort of after the fact, and it's sort of, you

11   know, where can I go and sort of pick through a

12   collection of patient records and find some patients

13   that I think, you know, could have been enrolled in my

14   trial and trying to get to something similar. And

15   it's -- that is very, very difficult.

16   So I think, I mean, you know -- and

17   everybody, you know, who I think advises on what you

18   ought to be doing if you're trying to put together an

19   external control will be talking about, you know,

20   trying to be in the same institutions, trying to have

21   the same protocol, trying to do it at a similar time

22   period to get patients that are as comfortable as

1   possible so that you're reducing the likelihood that

2   your historical control is not, you know, related --

3   is not comparable to your patients that you're

4   actually getting your therapeutic.

5   And we've also heard a couple of times, I

6   think, from our statistical colleagues the idea of

7   having, if at all possible, some concurrent controls,

8   even if the randomization is disproportionate so that

9   you can do some techniques to try and understand who's

10 in the trial and how they might relate to the external

11 controls, too.

12   So I mean -- so external controls, I think,

13 you know, are useful in certain situations.

14 Understand the characteristics of a particular disease

15 that you're studying. But you also do have to be

16 careful of situations where they may not be, you know,

17 as helpful as you might hope they would be.

18   DR. REX: Yeah. And Jack (ph) then one made

19 -- once made the observation to me about people with

20 cryptococcal meningitis that got into the early

21 protocols. He said they were unusual because they

22 lived long enough to make it to the NIH. You know,

1   and so they were a selected subset.

2   Marco, do you have any comment?

3   DR. CAVALERI: Well, I think, yeah, indeed,

4   as Ed said, in the antifungal space, we had a number

5   of cases, isavuconazole as being the last one for us,

6   too. And you know, at the end, we went positive as

7   well for mucormycosis, despite we were not really

8   overenthusiastic about how historical control were put

9   together. So it could have been better, frankly.

10   Yeah, I think, indeed, there is a lack of

11   this idea of setting up robust external or historical

12   control that could be used for the sake of

13   interpreting, you know, single on (ph) trials. And

14   that is a matter where maybe there is a need to think

15   about what could be the option. And now we can do it

16   better in order to make them useful in a setting like

17   this one.

18   MR. DANE: I do wonder is whether there's --

19   I'm not sure this is even feasible. But could you set

20   something off prospectively that? And, yes, under a

21   similar type of trial program that a sponsor would

22   conduct, you have something that runs, you know, maybe

1 a bit more like a network so that you -- you're

2 generating data an on ongoing basis. Then it's all

3 under the same protocol. And the prospectives, you've

4 got those issues of comparability still. But at least

5 you're doing it all under the same banner, if you

6 like, rather than going back and trying to do it.

7   DR. COX: Right. You know, thanks, Aaron.

8   Yeah, you know, this is -- I mean, we've

9 talked some about this. But the idea of a clinical

10 trial network, I think, is sort of an ideal sandbox to

11 try and work through some of these questions. You

12 know, if you just slightly change, you know, the

13 inclusion-exclusion criteria within a trial, if you

14 change the institutions where the trial is taking

15 place, if the comparator drug changes over time, you

16 know, we may not sort of fully take that into

17 consideration when we're looking at the outcomes of

18 Trial A to Trial B to Trial C.

19   So it is possible that if you had a clinical

20 trial network this would -- you know, where you've got

21 a protocol that's stable, you're at similar or the

22 same institutions over time, it might give you some

1 important insights into what -- you know, what is

2 happening with regards to patient outcomes and

3 whether, you know, I mean, what is the degree of

4 variability. We see the variability. I'm not sure we

5 fully understand it.

6   And the question is, is could -- I mean,

7 could you, using, you know, those sorts of -- if -- I

8 don't know -- using a network, could you figure that

9 out in a way that, you know, you could convince

10 yourself that things were sufficiently consistent and

11 sufficiently reliable over time that they didn't

12 change. I think it's a good question and one where,

13 you know, data would help us through that. And a

14 clinical trial network could help tremendously.

15   DR. REX: Lynn?

16   DR. MARKS: We talked a good bit about what

17 I think -- I don't know what the right term is -- but

18 augmented control arms so that you do have a small

19 randomization number -- let's -- I'll make it up -- 10

20 to 1. So it's very disproportionate. And then you

21 run in the same time frame, same institution, et

22 cetera, to get that baseline.

1   But then you get into that small numbers

2   part because in the -- and you have so much belief

3   that the one that's in the real trial is the real

4   number. So if it deviates in the wrong way from this

5   larger body of data, sometimes, you know, your mind

6   goes to the fact, well, those were just sort of the

7   fake controls and this is the real control and one

8   person in that kind of disproportionate stuff. So I'm

9   not sure it makes you -- it makes a heck of a lot of

10 difference.

11   Now, if everything goes in the right way,

12 then life's good. And then you have these kind of

13 trials because most of the time we've focused on the

14 non-inferiority downside as opposed to the non-

15 inferiority upside. But then again, since I'm up

16 here, I'll say I have a hard time thinking of that

17 non-inferiority drug because that's not how I was

18 planning on using the drug in the real world to what

19 you guys talked about. I mean, this is something

20 that's on top of something else to make sure that your

21 percent susceptibility or that difficult to treat or

22 that outbreak or that scenario's there rather than

1   just I've got something else I'm going to add in.

2   MR. DANE: So on the augmented control, I

3   don't know if maybe Kert wants to make a comment, but

4   I would agree that in this setting -- so when we -- we

5   tend to look at that when you've got a few hundred

6   patients and then you've still got a reasonable amount

7   and a reasonable amount of precision to compare with

8   your external dataset, whereas here, if you're only

9   talking -- I mean, in that example, it was 12. And if

10   you did a more extreme randomization ratio, it's less.

11   So it seems a lot more difficult to actually do

12   something that formal. Yeah, exactly.

13   UNIDENTIFIED MALE SPEAKER: John, going back

14   to the estimate that you were saying where we are

15   treating 100 patients in the U.S. and maybe 500 in

16   Europe, I just cannot fit it with some statistics that

17   I've seen. So CDC estimates that there are 51,000

18   total cases of so the --

19   DR. REX: Oh, sorry. But wait. I'm sorry.

20   In D and E, I've drifted -- pseudomonas is

21   definitely more frequent than this. So like, maybe

22   this is acinetobacter. Maybe this is

 1   stenotrophomonas, you know, something that's even less

 2   common. So it's no longer pseudomonas, necessarily.

 3   UNIDENTIFIED MALE SPEAKER: Okay. Okay. So

 4   you were not --

 5   DR. REX: Is that --

 6   UNIDENTIFIED MALE SPEAKER: -- talking about

 7   pseudomonas.

 8   DR. REX: No, because we know we can get --

 9   we know we got the slightly higher numbers. And so I

10   made this -- and I suppose you could --

11   UNIDENTIFIED MALE SPEAKER: No, no. I was

12   talking about the scenario --

13   DR. REX: No, no. You are correct.

14   Pseudomonas is definitely more frequent than that --

15   but acinetobacter, stenotrophomonas, things of

16   interest.

17   UNIDENTIFIED MALE SPEAKER: Fine.

18   DR. REX: Thank you.

19   UNIDENTIFIED MALE SPEAKER: Bye.

20   UNIDENTIFIED MALE SPEAKER: Hi. At the risk

21   of going really sideways here, instead --

22   DR. REX: Well, actually, let me say this is

1 the time to go sideways because we're to Scenario F

2 and you're the first up.

3   What else?

4   UNIDENTIFIED MALE SPEAKER: Right. So we

5 know some standard drug works, at least to some -- at

6 a level of efficacy that we like, right? Maybe it's

7 meropenem against pseudomonas. It has a certain

8 probability of hitting an effective exposure, does it

9 not? So why not compare for our new drug, new

10 regimen, its probability of hitting those effective

11 exposures? And that's where comparing those exposure

12 distributions, knowing that, for the drug we know,

13 that exposure distribution is tied to an efficacy

14 level that we like. And that's really what we're

15 making our comparison on.

16   DR. REX: So if I play it back, you're

17 proposing approval on the basis of adequate PK with

18 the definition of adequate being really pretty

19 sophisticated. It's tied into an exposure --

20   UNIDENTIFIED MALE SPEAKER: But we know that

21 --

22   DR. REX: -- response curve.

 1   UNIDENTIFIED MALE SPEAKER: We know that

 2   exposure is associated with a certain level of

 3   efficacy.

 4   DR. REX: Right. And we -- it's tied into

 5   the animal responses, and it's tied into the risk

 6   factors and familiarity (ph), you know, and the

 7   changes in PK due to underlying diseases.

 8   And so Dr. Cox?

 9   DR. TOMAYKO: That's the animal rule, isn't

10   it? You know, you do the good animal data to show

11   it's an antibiotic. And then you know what the target

12   exposure has to be. And then you show in the target

13   population that you achieve those exposures in a

14   certain percentage of the population. I think that's

15   -- that sounds great. That's what I'm advocating for.

16   UNIDENTIFIED MALE SPEAKER: It's the human -

17   -

18   DR. TOMAYKO: It's the human version of it,

19   yeah.

20   DR. COX: So I think --

21   DR. REX: It's the large animal rule.

22   DR. COX: So I think, you know, John, when

1   you're bringing up -- you know, one of the criteria

2   for the animal rule is when you have the outcome in

3   the animal model. And then what you're trying to do

4   is to, you know, link the exposure from the animal to

5   the exposure in the human. If you look at our animal

6   rule guidance document, it actually recommends, you

7   know, that you try and exceed that exposure with the

8   human exposure that would exceed the animal exposure

9   by some multiple, if at all possible, recognizing that

10   sometimes we run into safety issues.

11   And I think, Paul -- so what you're

12   describing is -- so you've got -- and I'm going to say

13   you've another carbapenem and you have an idea of what

14   your exposure target is for carbapenem. And you're

15   trying to -- so you've now got another drug from the

16   same class. And you're trying to, essentially,

17   achieve a similar target for this new agent that's

18   also from the same class, if I understood correctly.

19   Is that fair?

20   UNIDENTIFIED MALE SPEAKER: They could be

21   from the same class or a different class,

22   theoretically.

 1   DR. COX: If you get to a different class,

 2   it gets a little tougher, though, doesn't it, because

 3   you don't actually have -- you don't actually know

 4   exactly where you're going.

 5   UNIDENTIFIED MALE SPEAKER: Yeah, but you do

 6   know that, you know, your chances of curing the

 7   pneumonia go up with killing bacteria. So you're

 8   picking an exposure threshold target that's associated

 9   with a certain --

10   DR. COX: Okay.

11   UNIDENTIFIED MALE SPEAKER: -- killing of

12   cells.

13   DR. COX: Okay. So you're picking the

14   target from other drugs, yeah.

15   I mean, so I don't know that I would replace

16   what it is that we're talking about here, trying to

17   replace a clinical outcome. But I think what you're

18   describing could be very helpful in deciding, you

19   know, what dose to use. Fair?

20   UNIDENTIFIED MALE SPEAKER: I'm not saying

21   replace.

22   DR. COX: Okay.

 1   UNIDENTIFIED MALE SPEAKER: You've got this

 2   study in which you show one at 74 percent in a couple

 3   fistfuls of patients and the other at 77. And you're

 4   worried that it's -- that there's not enough evidence

 5   there.

 6   DR. COX: Yeah.

 7   UNIDENTIFIED MALE SPEAKER: Well, maybe

 8   because we know so many other factors cause failures

 9   in this disease state that you've all pointed out,

10   right -- their protein status, all the other things

11   that we all know --

12   DR. COX: Right.

13   UNIDENTIFIED MALE SPEAKER: -- and you're

14   worried that the new regimen looks a little bit lower

15   than the old regimen, and it's stressing you out. I

16   think the way to not be stressed is to look at the

17   exposures you achieved and are you hitting things you

18   know.

19   DR. COX: Yeah. So I mean, I think, you

20   know, throughout all the discussions, you know, I

21   think the importance of PK and getting the dose right

22   is, you know, clearly there. I -- some of the

1 examples from yesterday I thought were particularly

2 striking and really underscored the importance of

3 doing that.

4   And I think, you know, to your point of will

5 we still be stressed if the clinical outcome data

6 looks a little bit lower. I think our stress will

7 continue. But I don't think that takes away anything

8 from the importance of, you know, trying to do the

9 best you can with the PK.

10   DR. REX: Mike?

11   MIKE: Yeah. So you -- maybe it was covered

12 in Scenario XY, or something, and may -- as on the

13 cutting room floor. But I'm curious. I was trying to

14 think about dose response as a form of control and has

15 been used for some programs. But I was trying to come

16 up with whether or not that's more efficient than

17 using sort of a simultaneous control but perhaps in

18 the setting of the external controls, which I think

19 everyone sort of is feeling is a little bit more

20 doable.

21   So it -- maybe you could talk a little bit

22 about dose response control, where there we're not

1   trying to meet certain margins. Or what are the

2   criteria where in a dose response control are you --

3   you're not looking for necessarily statistically

4   significant differences between groups? Or are you?

5   And obviously, we would pick our doses to be

6   informed by PK/PD so we're not unnecessarily exposing

7   patients at risk to sub-therapeutic doses just to

8   squeak out a control group.

9   DR. COX: Do you want to do this one, John?

10   DR. REX: Oh, I just -- I was going to

11   suggest we -- my comment is I left dose response out

12   deliberately because I don't tend to see how I can

13   choose two doses, both of which are going to be

14   efficacious, and have them be meaningful different

15   because my general sense is I have to -- doses have to

16   be quite different going (ph). One mg per kg versus

17   five mgs per kg will get really separate exposures.

18   One mg per kg versus one and a half, you know, the --

19   MIKE: Yeah, maybe like --

20   DR. REX: And -- sorry. The last thing is

21   the one mg per kg has to be acceptable.

22   MIKE: Yeah. So let me clarify a little

1   bit.

2   So I think what you're -- what you want to

3   do is you want to be -- there's going to be

4   variability. So what the dose response curve

5   essentially does is it spreads your exposure response

6   out over a greater period -- a greater number of

7   exposures. Obviously, you could have somebody in the

8   high-dose arm be among those patients that had

9   actually the lowest exposures because of variability.

10   So I think the dose response is, more or

11 less, just sort of spread the field. You'd obviously

12 not be wanting to choose the lowest dose that would be

13 getting you 90 percent of your patients having a sub-

14 therapeutic exposure --

15   DR. REX: No, I just said that I --

16   MIKE: -- but it would be --

17   DR. REX: -- would not be willing to sign on

18 to the one -- to even the one mg per kg having a low

19 target attainment because that sets me up for public

20 shaming. You know, I --

21   MIKE: Well, I --

22   DR. REX: -- I'm just not willing to do

 1   that.

 2   MIKE: I don't think it has to be -- you

 3   know, again, I don't think it has to be, you know, low

 4   target attainment. As I've -- as we've talked about

 5   before, we always -- we pot our doses up to get 100

 6   percent target --

 7   DR. REX: Right.

 8   MIKE: -- attainment. So --

 9   DR. REX: But then you're --

10   MIKE: So I think you could --

11   DR. REX: -- Paul and -- but Paul -- what

12   Paul said was that I'm picking them both to be

13   efficacious. I mean, I -- it's -- you're asking for

14   both sides of this simultaneously.

15   MIKE: But again, the objective of trying to

16   get, you know, information about safety as well as

17   efficacy in that population having dose response or

18   exposure response as the ultimate analysis plan, that

19   would do that compared to a simultaneous external

20   control group. What are the thinking about dose

21   response or exposure responses in control?

22   DR. TOMAYKO: Mike, can I just ask a

1   different way? Because yesterday, Paul presented a

2   number of examples. And I think some of them were

3   related to pseudomonas -- the doripenem (ph) data, the

4   Ceftobiprole data, maybe some Tigecycline data. And

5   if you do a pharmacometric analysis and you see that

6   when you achieve exposure, if you have those failures

7   already and you could make an argument that those

8   failures are dose-related, well, it just basically

9   says I didn't have an antibiotic here.

10   So you can get a pretty good estimate of

11   what it's like not to treat one of these patients. I

12   mean, is that not correct, Paul? I mean, do you --

13   DR. AMBROSE: Yeah, I think what you're --

14   what you may be referring to is when you model the

15   exposure response and you can basically use the

16   intercept of the no exposure as kind of your

17   equivalent placebo by extrapolating back to that.

18   That then allows you to estimate the magnitude of the

19   treatment effect.

20   UNIDENTIFIED MALE SPEAKER: And between what

21   Paul -- I guess I'm taking it one step further. He

22   showed it -- made the point in a number of different

1   programs. And FDA probably has a number of different

2   databases where maybe we could even fortify that

3   learning. And that could be useful information, and

4   it may be better than an external control.

5   UNIDENTIFIED MALE SPEAKER Yeah. Well, I

6   think you use -- you may be able to use the intercept

7   if you're doing that intercept pharmacometric method

8   to be able to compare that to the external control

9   data just to sort of see where you are in terms of

10   your treatment effect.

11   DR. REX: Ed. Sorry. We kind have been

12   going around.

13   DR. COX: Yeah. So I think our experience

14   has been, you know, similar to the debate that you and

15   John were having, which is, you know, most folks going

16   into the serious infection, you know, the dose that

17   they pick is going to be one that's going to be

18   ideally on the flat part of the curve. So I think

19   that's one part of it. I understand you're asking

20   about a second part.

21   So the -- you know, the idea of doing a

22   second dose, I mean, and most -- it seems like most

1 people would be shooting for that flat part of the

2 curve where the likelihood of showing it -- an effect

3 is going to be, you know, not so great.

4   Now, if there's equipoise and you pick two

5 doses and you get the degree of variability that Paul

6 shows with your low dose, that's -- you know, there's

7 equipoise for doing that and you happen to find a

8 difference there for those two dose groups, then I

9 mean, you've got something that, you know, suggests --

10 I mean, you've got, essentially, a superiority design

11 where you've shown a clear effect.

12   Obviously, with serious diseases, you want

13 to have a DSMB in place. I mean, you couldn't -- I

14 don't think -- you couldn't plan to do this, is what

15 I'm thinking. You can't plan to give patients with

16 serious infections sub-therapeutic doses.

17   So is that -- that's part one of your

18 question, I think, right?

19   UNIDENTIFIED MALE SPEAKER: I think that's

20 right. I mean, I think that what Paul's data showed

21 vividly there --

22   DR. COX: Yeah.

 1   UNIDENTIFIED MALE SPEAKER: -- in the best

 2   laid plans --

 3   DR. COX: Right.

 4   UNIDENTIFIED MALE SPEAKER: -- there are

 5   still going to be patients who have low exposures

 6   and/or higher (inaudible - off mic) ranges.

 7   DR. COX: Right.

 8   UNIDENTIFIED MALE SPEAKER: So unless you're

 9   doing a concentration control trial because you're --

10   that's the only way that you're ever going to prevent

11   that.

12   DR. COX: Right. And you know, it's hard

13   because, as you start to learn that, you have to push

14   the dose because you have this concern that with this

15   variability you're going to have some patients that

16   are sub-therapeutic. It becomes hard not to try and

17   push the dose to get to something that's on the flat

18   part of the curve, you know, to, essentially, create a

19   scenario where the likelihood of showing this

20   difference is going to decrease to some extent.

21   Is that fair? Have I answered your

22   question? Or was there another part to it? I

 1   couldn't tell if you were getting to sort of, you

 2   know, exposure response, what happens in the trial and

 3   trying to sort through that. Is that your other

 4   question?

 5   UNIDENTIFIED MALE SPEAKER: Yeah, I think I

 6   --

 7   DR. COX: Okay.

 8   UNIDENTIFIED MALE SPEAKER: But I think it's

 9   more of --

10   DR. COX: And John, you're going to have to

11   cut us off in a moment because I think some other

12   folks might want to ask some questions.

13   UNIDENTIFIED MALE SPEAKER: -- more of like,

14   you know, can we use -- I think Paul's getting at

15   this, was the exposure response --

16   UNIDENTIFIED MALE SPEAKER: Yeah.

17   UNIDENTIFIED MALE SPEAKER: -- relationship

18   that would come as part of a dose ranging trial. I

19   absolutely agree that, you know, you're not going to

20   try and sign this. We all have limitations. I mean,

21   I haven't seen very many 10-gram doses of carbapenems,

22   although I know a 10-gram dose of carbapenem would

 1   clearly get concentrations where we need it. So --

 2   DR. COX: Right.

 3   UNIDENTIFIED MALE SPEAKER: -- there's

 4   always limitations that you're always going to have on

 5   these things.

 6   But I think that's the nature of the trials,

 7   are going to give you an exposure response curve. And

 8   therefore, by modeling that effect, is that evidence

 9   of a treatment effect, therefore, when reflected

10   against external controls, that give you evidence of

11   efficacy?

12   DR. COX: Right. So --

13   UNIDENTIFIED MALE SPEAKER: And so --

14   DR. COX: And you said dose ranging trial,

15   which again makes me think you're talking about going

16   in with different doses.

17   UNIDENTIFIED MALE SPEAKER: Yeah. I --

18   DR. COX: Okay.

19   UNIDENTIFIED MALE SPEAKER: I would say that

20   we would pick doses that --

21   DR. COX: Yeah.

22   UNIDENTIFIED MALE SPEAKER: -- are above,

1 based upon the Phase 1 data that are above the

2 expected therapeutic effect. One, you know, is at

3 therapeutic effect and then some multiple of that,

4 knowing that we're going to have variability and

5 exposures in those patients and in ELF if we're doing

6 a HABP/VABP trial. And therefore, we would de-

7 convolute that as part of the analysis plan and then

8 be able to show then those exposure response or

9 evidence of an --

10   DR. REX: So to play it back, you might

11 deliberately use a range of doses in order to ensure

12 that you got a reasonably broad range of actual

13 exposures and then hope that you have enough cases to

14 fill in some of the cells at the lower end of the

15 exposure, which gets into how many of those you've got

16 to have, which might -- makes to be a reasonably good-

17 sized program, which maybe you could do something

18 else.

19   So I -- good. So we're -- so --

20   DR. COX: Maybe just one last quick comment

21 and then I'll stop.

22   It's just the issue of -- I mean, if you

 1   were, you know, allocating patients to different dose

 2   groups, then you've got comparisons between dose

 3   groups and you're trying to show superiority of one

 4   group to the other. If the exposures happen, you

 5   know, and you're trying to look at the exposures that

 6   actually happen to patients compared to outcome. You

 7   know, there's always the question of is the reason

 8   that the exposure is low in a particular patient also

 9   something that's associated with the poor outcome.

10   And that's the difficult question.

11   DR. REX: The exposure --

12   DR. COX: So the de-convolution is very

13   difficult.

14   DR. REX: So we're going to move on.

15   UNIDENTIFIED MALE SPEAKER: We've heard that

16   argument before, and there's not a lot of evidence

17   that have that because you're going to be able to de-

18   convolute that. There is --

19   DR. COX: So you -- so --

20   UNIDENTIFIED MALE SPEAKER: So you're saying

21   that are there patients that are at greater risk for a

22   bad outcome that just have goofy pharmacokinetics.

1   DR. COX: Yeah. I mean, are the patients

2   that, you know, are hyper-metabolizers that clear the

3   drug more quickly? Are there -- is that somehow

4   associated with a worse outcome?

5   UNIDENTIFIED MALE SPEAKER: Yeah,

6   biologically.

7   DR. COX: Yeah, yeah, yeah.

8   DR. REX: Because the exposure is --

9   DR. COX: Yeah, and you say there's no data

10   for that.

11   UNIDENTIFIED MALE SPEAKER: Not really --

12   DR. COX: Okay.

13   UNIDENTIFIED MALE SPEAKER: But --

14   DR. REX: Yes, ma'am?

15   DR. COX: All right. So a topic for a

16   longer discussion.

17   DR. REX: All right. So I've accumulated on

18   my list for Scenario F things like think about

19   exposure response, the Shlaes case control model. And

20   I've also jotted down Bayesian prior.

21   So yes, ma'am? On to you.

22   UNIDENTIFIED FEMALE SPEAKER: Okay. So the

1 difference between X-1 and some of the other things

2 that we're looking at to treat multidrug-resistant

3 organisms is that X-1 and a couple of other things

4 that some of us are more familiar with don't have any

5 effect on other organisms. And that's makes the

6 challenge because if you've got something like

7 isavuconazole, you have got clinical data and you've

8 got something to base your efficacy on.

9   DR. REX: Right.

10   UNIDENTIFIED FEMALE SPEAKER: If you have

11 new aminoglycosides, if you have new versions of

12 classes which are expanding, they are completely

13 different from what we're looking at with X-1.

14   Now, what I am going to suggest, which might

15 be that we could look at the sort of thing with --

16 that we did with isavuconazole where we looked at

17 Fungiscope, which is a registry of rare fungus

18 diseases where we got the data from that we used for a

19 lot of the case controls.

20   And I'm just going to ask if -- particularly

21 from Helen -- whether actually we ought to be keeping

22 a registry of these difficult cases like the first

1   case you presented because that's exactly what we do

2   with things like Fungiscope. We collect these cases.

3   We track them. We look at the outcome. Obviously,

4   with fungal infections like mucor, they're much longer

5   conditions.

6   But perhaps that's what we should be doing

7   and not trying to get our safety and clinical data

8   separately in more conventional trials for those

9   programs and look at using external controls from the

10 data that, perhaps, those kind of registries could be

11 set up so that we're not trying to push the envelope

12 and spend an awful lot of money looking at the edges

13 of very good drugs in other ways but actually have

14 been expanded a little.

15   For those things that are -- have no other

16 activity, I think we should be going to John looking

17 at what they bring in addition to what is there

18 already, which is the adjunctive elements of those

19 projects. So I kind of think we should be looking at

20 this rather differently, looking at what we're trying

21 to achieve in terms of the clinical things with the

22 established products that we can get data on other

1   areas. And for those that are completely novel, look

2   at the adjunctive programs in a completely different

3   way because we are looking there. I think we can't

4   get away from superiority studies against placebo and

5   normal control because we are trying to do something

6   different to support those patients.

7   So I would advocate the registry element if

8   Helen thinks that's viable.

9   DR. REX: A long-term registry after the

10   fashion of Fungiscope. Okay.

11   MR. DANE: So I suppose my only question

12   comes back to the external control again. Is it

13   comparable or not? So and it comes back to whether

14   you just (ph) pay a big benefit over that external

15   group, I think.

16   DR. BOUCHER: You know, there's been a lot

17   of discussion over the years. So Ed and I go back to

18   the voriconazole days and caspofungin, which was

19   approved on 61 cases with historical control. So you

20   know, we've come full circle in some ways.

21   But in discussions both in the fungal space

22   and the antibiotic space, there's been a lot of, I

1 would say, healthy debate about the benefit of

2 registries. I mean, I think in a lot of ways, I mean,

3 academic. You know, I love to learn about these thing

4 -- you know, there's a lot of upside to learning about

5 the natural history of these diseases. And I think

6 groups in the IMI and other places are taking little

7 pieces of this in the ARLG here in the U.S.

8   But the consensus that I've heard has been

9 that a registry, per se, wouldn't meet the criteria

10 that we need for the external control, necessarily.

11 So that's been part of the reason for the lack of

12 enthusiasm in funding. It's very expensive.

13   So the question would come down to, well,

14 who pays for this. The NIH? You know, it gets to --

15 the sponsor has an interest for his or her compound

16 for that period of time, but not in perpetuity.

17   DR. TOMAYKO: So Helen, you mentioned IMI.

18 And before I left GSK, I was working with Jesus

19 Rodriguez-Bano. And I've presented this before. And

20 IMI was sponsoring and designing and, I presume, still

21 executing a study that was -- it was looking at a very

22 sophisticated way of collecting the natural history

 1 data of carbapenem resistance in Europe.

 2   And my hope was, is that that could be, you

 3 know, initiated and completed before the natural

 4 history or the natural -- the management changes

 5 dramatically. I'm sure they'll figure out ways of

 6 incorporating what -- what's changed from polymyxin-

 7 based therapies to Avycaz when it becomes available

 8 and some of the other products we've heard of.

 9   But I think combining all of these things, I

10 mean, thinking Bayesian. You know, if you have the

11 exposure response data that Paul's already presented,

12 you know what, you know, a placebo effect might look

13 like from a pharmacometric approach with some of this

14 stuff. The data -- the understanding probably gets

15 strong and stronger. And then maybe it helps us if

16 the treatment effect, as Aaron said, is big enough,

17 which we would think it might be with an antibiotic --

18 that was what makes adjunctive work so hard -- you

19 know, maybe you could get comfortable with small

20 datasets if you could start to believe what all this

21 other data is telling you.

22   MR. DANE: Yeah, it might help you

 1 understand the area rather than be a direct

 2 comparator. That's what I could imagine. So you --

 3 yeah, you understand your risk factors and things like

 4 that. It's that comparison, that direct comparison,

 5 that becomes more challenging.

 6   DR. REX: Kenneth?

 7   Sorry. Did you have a follow-up? No, you

 8 didn't. Okay.

 9   Kenneth?

10   MR. HILLIN: I think one of the things

11 that's become very clear to me is that, for these

12 types of drugs, you won't have evidence of --

13 substantial evidence of safety and efficacy for these

14 drugs for the purposes of approval. And I have lots

15 of questions about the animal model and even how

16 biologics and small molecules might behave differently

17 in those models which are intrinsically human.

18   So if we can't get to the stage where we

19 have substantial evidence of safety and efficacy, is

20 there a different way to get these drugs approved and

21 available so that we can study them further? In the

22 oncology world and in many other places, you have, for

1   example -- it would be different from this -- but

2   accelerated approval. And I lived through the pain of

3   Avastin being approved for breast cancer based on PFS

4   and then having to be -- that label be withdrawn for

5   breast cancer. So I know it doesn't always work out

6   well.

7   But I wonder if there would be a way to have

8   a two-step approval based on a minimal dataset. And

9   that could be defined relatively well. It could, you

10   know, include preclinical as well as clinical data so

11   you actually have some safety data. And then there

12   will be a commitment. And I think this in the world

13   of anti-infectives would have to be in conjunction

14   with the government in some ways. So perhaps that

15   clinical trial network actually continues to help to

16   study the drug beyond then. And then a further

17   dataset would be brought back to the FDA for, perhaps,

18   a full approval.

19   So it would be a two-stage process. And you

20   would put in place restrictions both in terms of the

21   label and also the use, perhaps even the types of

22   centers. Maybe the CDC, based on the monitoring, says

 1   it's actually only these centers that would be

 2   eligible for this drug based on the resistance levels.

 3   You know, I don't exactly know how that

 4   would work, but perhaps a two-stage approval process

 5   because we can't get to substantial evidence of safety

 6   and efficacy as part of the statute.

 7   DR. REX: So both Ed and Marco should

 8   comment.

 9   DR. COX: Yeah. So you know, the

10   accelerated approval still is substantial evidence of

11   efficacy, but it's based on the surrogate marker. So

12   and I see, Kenneth, I mean, you're already recognizing

13   that.

14   So you know, and usually, it's used in

15   situations where the clinical outcome for the disease

16   is sometime removed. So you may see something like,

17   you know, a reduction in tumor size or, you know, a

18   decrease in HIV viral load or hepatitis C viral load,

19   whatever the case may be. And you know, some of these

20   surrogates are, you know, very, very well correlated

21   with the clinical outcome that may happen many years

22   down the road.

1   You want to amend your question, I see.

2   MR. HILLIN: Well, I was actually -- we did

3   -- at Genentech, we did lots of analysis about the

4   correlation between PFS and overall survival. And

5   actually, I think killing the pathogen is actually a

6   much better surrogate than reduction and shrinkage of

7   a tumor, so.

8   AUDIENCE MEMBER: (inaudible - off mic).

9   DR. COX: Which is? We'll give Marco a

10 chance to talk in just a minute.

11   AUDIENCE MEMBER: (inaudible - off mic).

12   DR. COX: Sorry?

13   MR. HILLIN: We're choosing a way what is

14 the standard for anti-infectives in Europe, which is

15 test of cure, which is basically looking at the

16 microbiological response, which could be -

17   DR. COX: Most tests of cures are a clinical

18 response. The patient's better.

19   AUDIENCE MEMBER: (inaudible - off mic).

20   DR. COX: It's a clinical response. Yeah,

21 yeah. Okay.

22   So just to clarify that issue, so usually,

 1   with accelerated approval, you're looking at a

 2   surrogate. And oftentimes, the diseases that you're

 3   using those surrogates in are outcomes that have been

 4   some time removed.

 5   So if you think about what happens in an

 6   acute bacterial disease, you may have, you know, a

 7   particular biomarker that you're looking at. But you

 8   also usually have the clinical outcome staring you

 9   right in the face before you. And you don't -- I

10   mean, you know, there's not necessarily a one-to-one

11   correlation with these two events. And so you end up

12   in the somewhat awkward scenario of saying I believe

13   the biomarker, but I don't believe the clinical

14   outcome.

15   And I know it's tough because there are

16   patients, obviously, that succumb to their underlying

17   illness. And the issue becomes it's difficult to

18   understand, you know, in whom that's true and in whom

19   that's not true. So it creates a little bit of an

20   issue.

21   So I'm not -- you know, so that's why we

22   have not -- you know, in acute bacterial diseases

 1 where you achieve the clinical outcome within a -- you

 2 know, within a couple of weeks or, you know, you're

 3 looking at Day 28 mortality, we haven't looked so much

 4 at, you know, clearance of biomarkers or, you know, a

 5 microbiologic endpoints alone because if there is a

 6 discord and you're going to let the biomarker trump

 7 the clinical outcome, it's a little bit of a -- you

 8 know, it's a little bit of an odd scenario in some

 9 ways.

10   MR. HILLIN: No, thanks. And I appreciate a

11 lot of that. I actually wasn't advocating for

12 accelerated group. It would be a new mechanism

13 because accelerated approval is absolutely on a

14 surrogate, as you spoke about.

15   But in some ways, if you think about it, why

16 do we approve things for accelerated approval when you

17 could actually just wait until the outcomes mature for

18 overall survival, wait two years, find out the

19 outcome? It's because of the feeling in oncology of

20 the urgency to have these new therapies be made

21 available for patients who have few options. And

22 we're in the scenario where we have patients, as Helen

 1   so, I think, described it very in a sort of

 2   heartbreaking way, the patients that she sees.

 3   And so is there a way to have options

 4   available in a controlled way until such time as we do

 5   gather more data in the future. That was my point.

 6   Could we come up with a new way, not called

 7   accelerated approval, but specific for anti-bacterials

 8   targeting pathogens, particularly from multidrug

 9   resistance.

10   DR. COX: Right. So it sounds like, you

11   know -- I mean, everybody feels the urgency. That's

12   why we're trying to figure out ways to do this.

13   There's no question about that. It sounds like what

14   you're almost describing -- and David Shlaes I see

15   back there. We talked about this not too long ago.

16   And he brought up the idea many years ago and, you

17   know, I -- you know, the idea of some sort of gray

18   approval or some sort of conditional approval.

19   And you know, right now, I mean, the options

20   that we have are sort of standard, full approval,

21   accelerated approval using a surrogate marker,

22   availability under IND, you know, usually not the

1   scenario here that we're talking about, but, you know,

2   in the setting of, you know, a national emergency --

3   we've got emergency use authorization. But that

4   really doesn't seem to fit here either.

5   So could somebody do this? Yeah, somebody

6   could do this, I mean, you know, change the way you

7   look at approvals and such. And I think that's what

8   you're getting at. You're getting at more sort of a

9   conditional sort of situation.

10   And it -- given that's what you're asking

11   about, maybe Marco wants to make some comments.

12   DR. CAVALERI: Yeah. Indeed, as I explained

13   yesterday, we have tools in Europe for this early

14   access regulatory route. And of course, the condition

15   marginalization (ph) is the lead one, indeed, where we

16   stayed, that the benefit of having other drug

17   available earlier outweighs any risk associated with

18   the uncertainties that will derive from the data that

19   will be initially submitted. So that is pretty clear

20   and is a pathway that could be used.

21   Of course, it is very important to see what

22   can come next because the condition of marginalization

1   is it's quite serious, you know, requiring that post-

2   approval specific obligation are committed to and that

3   dataset are provided. And if we are in a situation

4   that then these data are not provided or delayed or

5   even come out with negative result, that is a big

6   problem and could put us in a very difficult

7   situation. But of course, it's a tool that is not

8   being used for antibacterial so far. And maybe it's

9   the time to think about whether there are situation

10   for which it can be used.

11   The alternative, of course, will be the

12   exceptional circumstances which may be fitting into

13   situation for which the new drug is supposed to be

14   working just in rare populations. So why not also

15   considering that? And on top of that, also, as said,

16   we have the new pharmaco-regional (ph) legislation

17   which allows us to pose even in the context of a full

18   marginalization to the sponsor to conduct post-

19   authorization safety or efficacy study. And I think

20   the receftor (ph) is a good case because, you know, we

21   received recently positive opinion from the CHMP. And

22   there was a post-authorization efficacy study imposed,

 1   which essentially is the (inaudible) nosocomial

 2   pneumonia study.

 3   So we have a lot of tools to look into

 4   having more data come in the post-authorization phase.

 5   And we should look seriously about how can we improve

 6   these mechanisms so that new drugs that have a

 7   potential of addressing on a need (ph) can reach

 8   patient needs earlier with enough certainty about what

 9   it can do, but them supplement it after authorization

10   (ph) with other data that could bring us to a full

11   understanding of the benefit risk.

12   And registries, of course, are an important

13   area. And I think they should be disease or pathogen

14   registries. And it would be very important to think

15   about a mechanism worldwide, or at least in the U.S.

16   and in Europe, about setting up this registry because

17   this will be extremely useful information for

18   everybody, including sponsors.

19   DR. REX: So we're going to try to wrap up

20   in about the next 15 minutes. And before we leave

21   this one, everybody should look up marketing

22   authorizations under exceptional circumstances. And

1 then put in the word V -- V as in Victor, O-S-S-E-N.

2 It's a man's name -- Vander (ph) Vossen. It's a

3 lovely paper about four drugs that got approved under

4 exceptional circumstances and about how miserably they

5 did in the marketplace. And that's the story.

6   So John and then Dave.

7   UNIDENTIFIED MALE SPEAKER: So I guess it

8 was kind of getting at my question. But I was going

9 to ask about the role of an expanded access program

10 and as far as generation of data and what that could

11 ultimately -- how that can be looked at.

12   And secondly, how the -- potentially the

13 clinical trials network could be involved because know

14 -- so Helen, when I looked at your -- when I think of

15 your patients, I think of the patient that you sent to

16 hospice because you had nothing else available. And

17 if there was something that was being developed

18 clinically, if there -- if you could utilize that in

19 whatever outcome and how that could be utilized

20 because I think back to, putting back my clinical hat

21 on, when we were developing these problems when you

22 had a patient like that, what you did was go around

1   fishing to all these different pharmaceutical

2   companies that were doing something and trying to find

3   someone who had something to be able to give this

4   patient the chance.

5   If there was an opportunity to go to a

6   network of people who are -- all knew all the

7   different studies that were ongoing and if you could

8   figure out a way to get that patient tapped in,

9   generate some data but then, most importantly, how

10   that data could be utilized.

11   DR. REX: Well, I have lived that. Expanded

12   access programs -- you can't ask for clinical data as

13   a condition of receiving the drug. You just can't.

14   And so you end up -- and the problem then is also drug

15   supply and having to give away drug supply that you

16   need to actually run your Phase III program. It's

17   less useful than you think. And it's really better to

18   have an open label study that you stick people in so

19   you can gather data.

20   UNIDENTIFIED MALE SPEAKER: Yeah, but the

21   problem, I guess, becomes, is that if it's an open

22   label study in an institution, what happens is you get

1   the phone call from the hospital that's not

2   participating in your study.

3   DR. REX: So we put a study kit in a box,

4   and we hired a company called Clinigen to have depots

5   around the world so that we can actually do that in 24

6   to 48 hours, any country in the world.

7   So Dave?

8   DR. COX: To your second point, too, about a

9   clinical trial network, I mean, it may -- I think it -

10 - I would expect it would help. And I think it would

11 push forth the threshold of what it is that is

12 achievable. And you would be able to study things

13 that, you know, were on the cusp previously. And it -

14 - you know, it may also be a mechanism, too, if

15 there's the need to do studies after a drug is

16 approved to be able to further understand how the drug

17 is performing.

18   So and I agree completely --

19   DR. REX: Yeah.

20   DR. COX: -- with John on the expanded

21 access part. It's -- you know, it's hard to do much

22 of anything there. But the clinical trial network is

 1 promising.

 2   DR. REX: Yeah. That's actually one of my

 3 summary points, is that if you have this warm base

 4 network running, you drop a diagnostic in and you

 5 start playing go fish for the cases of pseudomonas.

 6 Then it's efficient to be looking for pseudomonas at

 7 all these sites. And the investigators have other

 8 things to do.

 9   Dave?

10   DAVID: I just wanted to go back to this

11 idea of conditional approval and the differences

12 between Europe and the U.S. and see if there are ways

13 we could think about this.

14   So along the lines of what Marco was

15 suggesting, actually, so going back to that

16 conversation that we had, which was 15 years ago now,

17 I think, but I think we talk -- more recently talking

18 about this, the idea would be that you would do a full

19 approval based on small datasets. You would require

20 some post-market studies. But then you would pre-

21 specify some review, which could be an advisory

22 committee review, or something. I mean, you can

1 always ask for more data and another review.

2   So that would be one -- I would think one

3 way maybe you could ask. I guess the question is

4 would that be one way. Is that an option for you?

5   And then I was going to ask -- the other

6 issue is if one went to Europe and got a conditional

7 approval in Europe, gathered more data, then that

8 would bolster the dataset you could then present to

9 the FDA, I would think. So --

10   DR. COX: So maybe just to an overall

11 comment, which is, you know, most of the time what we

12 end up doing in the U.S. pretty much mirrors what

13 happens in Europe. And you know, Marco was talking

14 about ceftazidime and avibactam and, you know, similar

15 circumstances, similar approaches, similar outcomes

16 for that application here.

17   You know, the reason that we're talking

18 through all this today and trying to figure out how to

19 handle these difficult situations is a recognition

20 that it's going to be hard to get much data here. And

21 you know, we can look at substantial evidence in terms

22 of, you know, the degree of unmet need, what we can

1 actually, you know, accrue.

2   And so I think that there are ways to work,

3 you know, with what we are -- you know, with what we

4 have, the tools, you know, to be able to evaluate a

5 product, recognizing the limitations of what's

6 achievable.

7   And then, you know, I think, David, you're

8 asking about -- you know, and we've talked some about

9 how a drug might be utilized. There may be some sort

10 of program about its availability and a recognition

11 for the need for additional data, which can be done

12 through post-marketing commitments, post-marketing

13 requirements.

14   So there are ways to gather additional data

15 and -- you know, after a drug is approved for its

16 initial indication. And it's -- you know, I mean, I'm

17 -- you guys already know this because you're the ones

18 doing it for the most part. And that is, is that, you

19 know, oftentimes, a drug will get an initial

20 indication, but further study will follow to further

21 understand the therapeutic role of the drug, whether

22 it be in other indications.

1   And with regards to opportunities to look at

2   a drug at some later point in time, you know, have an

3   advisory committee discussion, I mean, sure. I mean,

4   those things could be an option. I mean, obviously,

5   once a drug is out there and it's approved, you know,

6   it is an approved agent. It can be used. And you

7   know, I think Kenneth, who's now left was talking some

8   about, you know, some of the experiences with Avastin.

9   So we won't get into the -- those situations.

10   But you know, the hope is, is that, you

11   know, if a drug gets out there, there's further study,

12   it will help to further characterize its safety and

13   efficacy. We hope that everything looks good. And

14   you know, the usual scenario, at least in the

15   antibiotics base, has been when a drug -- when the new

16   data becomes available about an indication or an agent

17   that, you know, has safety problems that are, you

18   know, significant or major or significant efficacy

19   issues are uncovered in a subsequent study, usually,

20   that leads to either that indication going away or

21   that drug going away because there's mutual

22   recognition that there's a problem here and it's not

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 1   an appropriate agent for being out there, so.

 2              DR. REX:  All right.  So I've got six things

 3   that I'd like to offer as a summary of stuff I've

 4   learned today.  And then I'd like to turn it over to

 5   Ed to talk about what's kind of the next step in this

 6   conversation.

 7              So actually, first, is thanks to all of you

 8   for participating in this.  We had no idea how this

 9   was going to work out.  The fact that you've all been

10   so energized and bring so many ideas, I'm really

11   grateful for it.

12              So the first thing I learned is that all

13   approaches that we've discussed are flawed, including

14   the approach of not having an approach.  And that's

15   actually a really important thing to say, is that it -

16   - that not having an approach is as flawed as

17   everything else.  And actually, it could hurt us over

18   time.  But you know, that's -- sometimes you have to

19   point stuff out like that to make it clear why we have

20   to make some other tradeoffs.

21              The second thing I've learned is that

22   everything is going to be based on having fabulous
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1   pharmacology and PK understanding and that you're just

2   going to have to presume that you're going to have to

3   do a lot more work there than at other times in the

4   past.

5   The third thing is that a clinical trial

6   network doing ordinary studies could be the foundation

7   that enables us to study less common things. So I

8   could fully imagine running a HABP/VABP clinical trial

9   network, having a diagnostic running for

10   acinetobacter. And it's not efficient to search for

11   those rare cases of acinetobacter and put them into a

12   clinical program that could accrue with reasonable

13   efficiency. And I think it's -- suggest to me it's

14   possible.

15   The fourth thing I've learned is there's no

16   easy way out of this. The animal rule is really --

17   you look at D and E, and you go, wow, that would be a

18   tough sell. And the open labels with external or

19   historical controls or external contemporaneous

20   controls, you know, that, too, causes a great sucking

21   in of breath and is not satisfactory. You know, it's

22   -- somehow we have to get at least a little clinical

1   data.

2   Number five is we need to validate

3   ertapenem. Somebody needs to help me figure out how

4   to do that.

5   And number six is we have got to get the

6   pool incentives working so that people will pay for

7   these things as fire extinguishers because paying for

8   them on a per-use basis, that's going to be $100,000 a

9   course in order to make it make sense. And that's not

10   going to fly.

11   So those are my six quick observations from

12   today.

13   So again, thanks to all of you for your

14   participation.

15   Ed?

16   DR. COX: Thanks, John.

17   And thanks to everybody who joined us. And

18   you know, we really do appreciate, you know, the

19   continued attention to development in this area. We

20   think it's an important area. There's patient needs

21   out there that need to be met currently, and we expect

22   that will continue to be the case in the future, just

1 given what we know about microbes and their ability to

2 evade our therapeutics. So many thanks.

3   Many thanks, too, to all the panelists who

4 gave up their time both before the meeting and during

5 the meeting and to the many, many people who made the

6 meeting possible.

7   In particular, I want to thank Sonita (ph),

8 too, who also helped us tremendously with our workshop

9 and getting it together.

10   You know, this is a difficult problem. I

11 mean, the easy problems we don't bring to you because

12 we can solve those. So we bring you the difficult

13 ones because we're having, you know, significant

14 challenges we -- as we work through them.

15   I -- somebody asked me yesterday what did I

16 think about the workshop. And I said I thought it was

17 going to be good, but it exceeded my expectations.

18 And I find the same here today, too. I mean, these

19 are difficult discussions, and I appreciate

20 everybody's willingness to express their opinions and

21 to, you know, offer suggestions and ideas.

22   We're all working through this, you know, at

 1   this present time. So not everything has been

 2   completely figured out. But the willingness to sort

 3   of talk about things I think helped us to move the

 4   field forward.

 5   You know, this is clearly an important area

 6   of development. You know, there are folks out there

 7   with compounds. The ability to not destroy the -- you

 8   know, the normal flora of the GI tract and the

 9   consequences that can result thereafter seems like,

10   you know, a very important therapeutic area to try and

11   explore and develop products.

12   You know, we -- this is really sort of the

13   first real public discussion we've had about these,

14   you know, more narrow-spectrum drugs, you know, drugs

15   targeting a single species. And clearly, you know,

16   our goal here is to get to a pathway so that there is

17   a pathway for development. And we recognize, too,

18   that the problem is, you know, not so much in areas

19   where -- you know, the example I used in my slides,

20   staph aureus and skin infections -- it's typically for

21   gram-negative rods and more serious infections like

22   HABP/VABP, complicated -- abdominal-complicated UTI.

1   So you know, we're committed to continue to

2   work on this to get to the point of, you know, having

3   a pathway and trying to figure out exactly how this

4   will work. And you know, some of this will need to

5   continue to be worked out because we had some

6   discussions about how would such a product be

7   available. How do people see this product being used

8   clinically?

9   And I think it's important that we also

10   think about, you know, how the product would be

11   available -- you know, restrictions for use, those

12   sorts of things, which seem commensurate with a

13   product that this degree of uncertainty, which is

14   considerable but also is some way to essentially have

15   such products have a pathway for developing.

16   And clearly, you know, as we work through

17   the science, I mean, if the -- and I'm sure all of my

18   fellow panelists are somewhat tired and probably more

19   tired -- humbled by the science and what the biology

20   continues to teach us day to day as we continue to

21   work through these difficult problems.

22   So I want to thank everybody. And we will

1   continue to work on this. If you have a product and

2   you're targeting something, you know, like, you know,

3   a species that occurs rarely, please do come in and

4   talk to us. The particular cases in hand help us to

5   sort of work through these situations.

6   You know, we will continue to try and, you

7   know, have discussions within our group and look

8   forward, perhaps to additional public meetings and/or,

9   you know, putting out, you know, pathways on how you

10   might approach this situation because there clearly is

11   a need. And to the extent that we can get to, you

12   know, approaches that have been, you know, described

13   and articulated, I think that's the best situation for

14   everybody. It helps everybody to sort of know where

15   they're going.

16   So thank you very much for participating in

17   the challenging discussion that we've had over the

18   last day and the day prior.

19   And with that, any final words, John? Or --

20   all right.

21   We will close the meeting. And thank you.

22   And we wish you all safe travels back to home and look

1   forward to seeing everybody again sometime soon.

2   So thank you.

3   (Proceedings concluded at 3:15 p.m.)

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1   CERTIFICATE OF NOTARY PUBLIC

2   I, Michael Farkas, the officer before whom the

3   foregoing proceeding was taken, do hereby certify that

4   the proceedings were recorded by me and thereafter

5   reduced to typewriting under my direction; that said

6   proceedings are a true and accurate record to the best

7   of my knowledge, skills, and ability; that I am

8   neither counsel for, related to, nor employed by any

9   of the parties to the action in which this was taken;

10   and, further, that I am not a relative or employee of

11   any counsel or attorney employed by the parties

12   hereto, nor financially or otherwise interested in the

13   outcome of this action.

14

15

16   Michael Farkas

17   Notary Public in and for the

18   State of Maryland

19   My commission expires: 6/27/18

20   Notary Registration No.: 256324

21

22

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3   I, Karynn Willman, do hereby certify that this

4   transcript was prepared from audio to the best of my

5   ability.

6

7   I am neither counsel for, related to, nor

8   employed by any of the parties to this action, nor

9   financially or otherwise interested in the outcome of

10   this action.

11

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14   07/27/2016   Karynn Willman

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