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

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

Tuesday, July 19, 2016

8:30 a.m.

Food and Drug Administration

White Oak Campus

10903 New Hampshire Avenue, Great Room

Silver Spring, MD 20993

Reported by: Michael Farkas, RPR/CSR,

Capital Reporting Company

Facilitating Antibacterial Drug Development For Patients With Unmet Needs Volume II

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1 APP E A R A N C E S	1 Peter Kim, M.D., M.S., Medical Officer, Division of
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3 Paul Ambrose, Pharm.D., President, Institute for	3
4 Clinical Pharmacodynamics, Inc.	4 Joe Larsen, Ph.D., Deputy Director (Acting),
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6 Luciana Borio, M.D., Acting Chief Scientist, FDA	6 (BARDA)
7	7
8 Helen Boucher, M.D., Director, Infectious Diseases	8 Thomas Louis, Ph.D., Professor, Department of
9 Fellowship Program and Associate Professor of	9 Biostatistics, Johns Hopkins University Bloomberg
10 Medicine, Tufts University School of Medicine	10 School of Public Health
11	11
12 Samuel Bozzette, M.D., Ph.D., Vice President, Medical	12 Lynn Marks, M.D., Senior Vice President for Projects,
13 Affairs - Americas/East Asia and Global Health	13 Clinical Platforms, and Sciences, GlaxoSmithKline, plc
14 Economics and Outcomes, BioMerieux, Inc.; Adjunct	14
15 Professor of Medicine and of International Relations,	15 Sumathi Nambiar, M.D., M.P.H., Director, Division of
16 University of California, San Diego; Adjunct Professor	16 Anti-Infective Products, OAP, CDER, FDA
17 of Health Policy and Management, University of North	17
18 Carolina	18 John Powers, M.D., Senior Medical Scientist, NIAID,
19	19 NIH
20 Marco Cavaleri, Ph.D., Head of Anti-Infectives and	20
21 Vaccines, European Medicine Agency	21 John Rex, M.D., Senior VP and Chief Strategy Officer,
22	22 Infection Business Unit, AstraZeneca, plc
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1 Edward Cox, M.D., M.P.H., Director, Office of	1 Dan Rubin, Ph.D., Statistical Reviewer, Office of
2 Antimicrobial Products (OAP), CDER, FDA	2 Biostatistics, CDER, FDA
3	3
4 Aaron Dane, M.Sc., Director, DaneStat Consulting	4 John Tomayko, M.D., Chief Medical Officer, Spero
5	5 Therapeutics
6 Dennis Dixon, Ph.D., Chief, Bacteriology and Mycology	6
7 Branch, NIAID, NIH	7 Kert Viele, Ph.D., Director & Senior Statistical
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9 Michael Dudley, Pharm.D., Senior Vice President and	9
10 Head, R&D; Co-Leader, Infectious Disease Global	10
11 Innovation Group, The Medicines Company	11
12	12
13 Ian Friedland, M.D., Chief Medical Officer, Achaogen,	13
14 Inc.	14
15	15
16 John Jenkins, M.D., Director, Office of New Drugs,	16
17 CDER, FDA	17
18	18
19 Nick Kartsonis, M.D., Associate Vice President,	19
20 Clinical Research; Section Head, Antibacterial,	20
21 Antifungals, HIV & CMV, Merck & Co., Inc.	21
22	22

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1	C O N T E N T S		
2	S P E A K E R	P A G E	
3	Edward Cox	362	1 There's conflict of interest disclosures. I
4	Peter Kim	375	2 believe they're on the agenda or at the table out
5	Helen Boucher	380	3 front. So if folks are interested in seeing those,
6	John Tomayko	399	4 they are available.
7	Sumathi Nambiar	418	5 And we also in the afternoon will provide an
8	Marco Cavaleri	445	6 open time for public comment. We wanted to reserve
9	John Rex	453	7 some time for anyone who wants to make any either
10			8 prepared remarks or statements at that point in time.
11			9 I think we do that in the afternoon, if I remember
12			10 correctly. I'll bring the agenda up here in just a
13			11 minute.
14			12 Throughout the course of the day, too, we
15			13 have the microphones. And just like yesterday, if
16			14 folks want to get up, make comments, ask questions
17			15 please feel free to do so and when recognized by the
18			16 - either myself or Dr. Rex. We'll be moderating
19			17 today's sessions.
20			18 And I thought what we'd do today would be to
21			19 start out with panel introductions so you know who's
22			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
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1	P R O C E E D I N G S		1 Consultant.
2	DR. COX: All right. Good morning		2 DR. BOUCHER: Helen Boucher, Infectious
3	everybody, and welcome to Day 2 of our Public Workshop		3 disease, Tufts.
4	series here. It's quiet and it looks like mostly		4 DR. TOMAYKO: John Tomayko. I'm an
5	everybody sat down. It's 8:30, so I think it's time		5 infectious disease physician, work for Spero
6	to go. So we're very glad to see folks back here for		6 Therapeutics as their chief medical officer.
7	Day 2.		7 DR. BORIO: Lu Borio, FDA Acting Chief
8	Today is a slightly different topic, perhaps		8 Scientist.
9	a little bit more challenging than what we even		9 DR. CAVALERI: Marco Cavaleri, European
10	discussed yesterday, and I expect we'll have a fairly		10 Medicine Agency.
11	free-flowing discussion because this is such a		11 DR. NAMBIAR: Sumathi Nambiar, Director of
12	challenging area. I will be very interested to see		12 Division of Anti-Infective Products, CDER, FDA.
13	what folks' ideas are on this topic.		13 DR. REX: John Rex, Internal Medicine and
14	We'll be talking about developing		14 Infectious Diseases, AstraZeneca.
15	antibacterial drugs that target a single species. And		15 DR. COX: All right. Great. Thanks to our
16	as I mentioned yesterday this is a workshop, so it		16 panelists. I was just mentioning, you know, to folks.
17	really is just an opportunity for discussion. It's		17 I mean, there's -- this day took a fair bit of
18	not one to gain consensus. It's not an advisory		18 preparation in preparing the case, and hopefully you
19	committee, but that also should allow folks to feel		19 all had a chance to study it last night. And it was a
20	comfortable to, you know, discuss the issue here and		20 lot of work to get to something that seemed to be, you
21	try to work through some of the scientific challenges		21 know, really as spot on as we could possibly make it
22	we face.		22 in sort of a simulated case.

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<p>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.</p> <p>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.</p> <p>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</p>	<p>1 such drugs.</p> <p>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.</p> <p>11 So the hope is that if you can target more 12 narrowly maybe you can avoid some of these problems.</p> <p>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.</p> <p>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</p>
<p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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</p>

<p style="text-align: right;">Page 369</p> <p>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.</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 371</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p style="text-align: right;">Page 370</p> <p>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.</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 372</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>22 When do you intervene with the test drug?</p>

<p style="text-align: right;">Page 373</p> <p>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.</p> <p>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.</p> <p>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 an animal rule efficacy guidance document 22 that's out on our web that discusses a lot of these</p>	<p style="text-align: right;">Page 375</p> <p>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.</p> <p>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.</p> <p>12 So Peter welcome to the podium, and walk us 13 through it.</p> <p>14 DR. KIM: Thank you, Ed.</p> <p>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.</p> <p>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.</p>
<p style="text-align: right;">Page 374</p> <p>1 issues, too, that is quite helpful.</p> <p>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.</p> <p>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.</p>	<p style="text-align: right;">Page 376</p> <p>1 X-1 has a new mechanism of action. It acts on a novel 2 ribosomal target unique to pseudomonas aeruginosa.</p> <p>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 doses.</p> <p>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.</p> <p>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</p>

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<p>1 milligram per liter in a recent global survey.</p> <p>2 The MIC distribution for wild type is</p> <p>3 centered on an MIC of .25 milligrams per liter with 5</p> <p>4 percent of isolates at the low and high ends of the</p> <p>5 spectrum. Therefore, both the MIC 90 and MIC 99 equal</p> <p>6 1 milligram per liter.</p> <p>7 The frequency of spontaneous resistance is</p> <p>8 low. Serial passage studies have shown no change in</p> <p>9 the MIC up to 11 passages. Drug X-1 has variable</p> <p>10 activity against other pseudomonas species and no</p> <p>11 activity against other gram-negatives, as we had</p> <p>12 discussed, or gram-positives.</p> <p>13 In animal infection models Drug X-1 wasn't</p> <p>14 effective in treating pseudomonas aeruginosa</p> <p>15 infections based on reduction of colony-forming units</p> <p>16 per gram in the thigh, pneumonia and peritonitis</p> <p>17 models and based on survival in the sepsis model.</p> <p>18 The PK/PD index associated with bacterial</p> <p>19 killing is the percent time that free drug</p> <p>20 concentrations are above the MIC over a dose interval,</p> <p>21 and this index was observed in the hollow-fiber model</p> <p>22 as well as in murine thigh and pneumonia infection</p>	<p>1 concentration ratios of Drug X-1 were approximately 40</p> <p>2 percent and 25 percent in humans and mice,</p> <p>3 respectively.</p> <p>4 Phase 2 proof of concept study. It</p> <p>5 consisted of a 14-day, uncontrolled study conducted in</p> <p>6 patients with non-cystic fibrosis bronchiectasis.</p> <p>7 Drug X-1 was given as monotherapy in 10 patients. At</p> <p>8 the proposed dose, the predicted PK parameters were</p> <p>9 observed. Microbiologic activity was assessed in</p> <p>10 terms of log reduction of pseudomonas aeruginosa in</p> <p>11 sputum. Greater than 1 log reduction was seen in 9</p> <p>12 out of 10 patients, and greater than 2 log reductions</p> <p>13 were seen in 4 out of 10. No adverse events of</p> <p>14 concern were observed.</p> <p>15 And now for perspectives on the development</p> <p>16 program from academia, industry, FDA and EMA.</p> <p>17 Thank you.</p> <p>18 DR. COX: Great. Thanks Peter</p> <p>19 (Applause)</p> <p>20 DR. COX: And now we'll walk through a</p> <p>21 series of perspectives. And first, we'll hear from</p> <p>22 Helen Boucher. And I think many folks know Helen.</p>
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<p>1 models.</p> <p>2 Clinical studies. The sponsor has completed</p> <p>3 some Phase 1 studies and one Phase 2 study. In Phase</p> <p>4 1, the sponsors completed a healthy volunteer study, a</p> <p>5 long ELF study and renal and hepatic impairment</p> <p>6 studies. The sponsor is also planning a thorough QT</p> <p>7 and drug-drug interaction studies.</p> <p>8 Population PK model. Simulations of a</p> <p>9 population PK model based on Phase 1 data showed that</p> <p>10 a 100 milligram IV infusion over one hour every eight</p> <p>11 hours would provide greater than or equal to 40</p> <p>12 percent time above the MIC for an MIC of 1 milligram</p> <p>13 per liter in more than 90 percent of patients using</p> <p>14 parameter estimates from healthy volunteers and using</p> <p>15 a 40 percent inflated variance. Drug X-1 is excreted</p> <p>16 renally, and greater than or equal to 90 percent</p> <p>17 target attainment is possible for varying degrees of</p> <p>18 renal impairment based on dose adjustment.</p> <p>19 Additional data. The terminal elimination</p> <p>20 half-life of Drug X-1 in healthy subjects was</p> <p>21 approximately two hours. No significant drug-drug</p> <p>22 interactions are predicted. The ELF to plasma</p>	<p>1 Helen is current an infectious disease</p> <p>2 physician at the Tufts New England Medical Center but</p> <p>3 also has industry experience in that she was in both</p> <p>4 Pfizer and Cubist over the course of her career. So</p> <p>5 we greatly appreciate her perspective. And she'll be</p> <p>6 providing the perspective, really, from the standpoint</p> <p>7 of a practicing physician/academic physician on this</p> <p>8 situation of developing a drug that's active against a</p> <p>9 single species and providing us some information about</p> <p>10 what she's seeing out there as a clinician these days.</p> <p>11 So Helen, thank you.</p> <p>12 DR. BOUCHER: So much, Ed and Dr. Nambiar</p> <p>13 and Dr. Rex for inviting me. It's a real honor to be</p> <p>14 here to talk some more about this really important</p> <p>15 problem.</p> <p>16 So my disclosures are shown here. And I'm</p> <p>17 also involved with IDSA, as I showed on the first</p> <p>18 slide, and have been working on this problem for a</p> <p>19 number of years with many in this room.</p> <p>20 So as we sort of start to look at this case</p> <p>21 of X-1, I thought we could harken back a little bit to</p> <p>22 some stuff that we talked about yesterday where we</p>

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<p>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.</p> <p>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</p>	<p>1 She actually did well that time. She was 2 treated for two weeks with IV tigecycline, 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.</p> <p>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.</p> <p>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.</p> <p>22 And this is what that multidrug resistance</p>
<p>1 really limited options for treatment.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>21 And so this was a case of a 19-year-old 22 kidney transplant recipient who had developed</p>

<p style="text-align: right;">Page 385</p> <p>1 refractory blood stream infection due to 2 <i>stenotrophomonas maltophilia</i> 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.</p> <p>11 So the question to us was does anyone do any 12 special <i>in vitro</i> 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.</p> <p>21 So the last patient I'll share with you is 22 kind of a different category of what we might consider</p>	<p style="text-align: right;">Page 387</p> <p>1 grows now in urine culture greater than 100,000 2 <i>Klebsiella pneumoniae</i> 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.</p> <p>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.</p> <p>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</p>
<p style="text-align: right;">Page 386</p> <p>1 someone with unmet medical need. This is a 47-year-old lady, schoolteacher, who came with pain on 2 urination and some lower abdominal pain. And she was 3 started again by her -- by the doctor at the clinic on 4 oral ciprofloxacin -- again, totally consistent with 5 the guidelines.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 388</p> <p>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 <i>pseudomonas</i> 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 <i>pseudomonas</i> 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?</p> <p>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</p>

<p style="text-align: right;">Page 389</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 391</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>22 So if we contrast this to a more Tier C type</p>
<p style="text-align: right;">Page 390</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 392</p> <p>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.</p> <p>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.</p> <p>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.</p>

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<p>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.</p> <p>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.</p> <p>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,</p>	<p>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.</p> <p>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.</p> <p>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</p>
<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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</p>

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<p>1 still good hope that we'll see that happen.</p> <p>2 So again, in sort of our efforts to use</p> <p>3 these drugs in the most effective way possible,</p> <p>4 stewardship is really, really important. And we're</p> <p>5 very encouraged that antibiotic stewardship programs</p> <p>6 have been proposed as a condition of participation for</p> <p>7 both hospitals and long-term care facilities in the</p> <p>8 United States. And stewardship programs would be the</p> <p>9 best vehicle to make sure that we use these drugs in</p> <p>10 the most appropriate way possible and preserve them</p> <p>11 for as long as possible and for as many patients as</p> <p>12 possible.</p> <p>13 So that sort of brings us back to where we</p> <p>14 started. You know, I think people are asking have we</p> <p>15 come to the pre-antibiotic area, and we didn't even</p> <p>16 get into sort of the most recent kind of scary news</p> <p>17 about MCR-1 and now MCR-2 and the potential of</p> <p>18 plasmin-mediated resistance to colistin and other</p> <p>19 drugs. And I think that is somewhat scary. The cases</p> <p>20 that we looked at certainly highlight the need for</p> <p>21 both parenteral and oral agents to treat specific</p> <p>22 pathogens.</p>	<p>1 useful, if possible. The LPAD mechanism can ensure</p> <p>2 use in this limited population with needed safeguards,</p> <p>3 and stewardship hopefully will ensure that we use</p> <p>4 these antibiotics in the best way possible for the</p> <p>5 patients who need them most.</p> <p>6 So with that, I'll thank the committee again</p> <p>7 as well as Amanda Jezek from IDSA and my colleagues</p> <p>8 here on the panel for the invitation. Thanks so much.</p> <p>9 (Applause)</p> <p>10 DR. COX: Thanks, Helen.</p> <p>11 And now our next speaker is John Tomayko.</p> <p>12 I'm sure many folks are familiar with John, currently</p> <p>13 chief medical officer at Spero Therapeutics and also a</p> <p>14 long history in the field of infectious disease</p> <p>15 development and is an infectious disease physician,</p> <p>16 also, too. John will be providing us his perspective</p> <p>17 from the standpoint of somebody from industry.</p> <p>18 So we appreciate your joining us here today,</p> <p>19 John.</p> <p>20 DR. TOMAYKO: Thank you, Ed.</p> <p>21 Thank you, Sumathi, for inviting me to talk</p> <p>22 a little bit about this important problem.</p>
<p>Page 398</p> <p>1 I think it's fair to assume that we're going</p> <p>2 to be forced to use these drugs with limited data, and</p> <p>3 the cases that -- where we have to use IV and inhaled</p> <p>4 colistin and fosfomycin for ESBL infections, which a</p> <p>5 lot of us have gotten very good at doing with very</p> <p>6 limited data -- tigecycline for MDR infections -- have</p> <p>7 all sort of highlighted this.</p> <p>8 It's very important that, obviously, we keep</p> <p>9 up our efforts on infection prevention and stewardship</p> <p>10 and surveillance. But for X-1, I think we hope to see</p> <p>11 adequate, well-controlled data emerge from either</p> <p>12 small, randomized controlled trials, perhaps with</p> <p>13 wider non-inferiority margins or even some really</p> <p>14 small Tier C type studies, perhaps with external</p> <p>15 controls.</p> <p>16 As we mentioned, you know, strong case</p> <p>17 definitions and the inclusion of the most severe</p> <p>18 infections, I think, are really important. High</p> <p>19 quality data, hopefully from clinical trial networks,</p> <p>20 could advance that.</p> <p>21 For clinicians, I think having information</p> <p>22 about infections at multiple body sites is very</p>	<p>Page 400</p> <p>1 These are my disclosures. And this is just</p> <p>2 my opinion. I don't know that I could represent all</p> <p>3 of industry.</p> <p>4 So the agenda is pretty basic. I'm going to</p> <p>5 just reflect a little bit on some of the success we've</p> <p>6 had in the past and maybe why we're successful. I'll</p> <p>7 review the case, and then I'll give you my perspective</p> <p>8 on how we might develop it. And the end result that</p> <p>9 I'm looking for is a regulatory approval. And since</p> <p>10 this is an FDA workshop, I'm looking for an approval</p> <p>11 in the U.S.</p> <p>12 So the past. I think if you look back you</p> <p>13 can pretty proud of what we've accomplished. We've</p> <p>14 had tremendous success in identifying a number of</p> <p>15 classes of antibiotics. There's two points here that</p> <p>16 I want to make. The first one's obvious because</p> <p>17 there's an arrow there. We haven't had a novel class</p> <p>18 of gram-negatives approved in the U.S., really, since</p> <p>19 the nalidixic acid story began in 1962 with</p> <p>20 fluoroquinolones.</p> <p>21 The other one is that these drugs were</p> <p>22 broad-spectrum agents. And you were able to actually</p>

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<p>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.</p> <p>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.</p> <p>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.</p> <p>21 In a not-so-distant future, I suspect novel 22 science is going to bring us a lot of interesting</p>	<p>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?</p> <p>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.</p> <p>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</p>
<p>1 approaches to managing infection. I can't go through 2 all of this. I'm sure my slides will be available.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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</p>

Page 405 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.	Page 407 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
Page 406 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	Page 408 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 Tigecycline 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

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<p>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.</p> <p>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?</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p>
<p>1 centers, audit those centers, monitor those centers. 2 So the costs are amplified.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>

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<p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>
<p style="text-align: center;">Page 414</p> <p>1 of wide non-inferiority margins and one-sided 2 significance testing.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p> <p>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</p>

<p style="text-align: right;">Page 417</p> <p>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.</p>	<p style="text-align: right;">Page 419</p> <p>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</p>
<p style="text-align: right;">Page 418</p> <p>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</p>	<p style="text-align: right;">Page 420</p> <p>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</p>

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<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>1 patients who only have pseudomonas aeruginosa for 2 specific phenol types. And all-comer pseudomonas 3 aeruginosa population would be acceptable.</p> <p>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.</p> <p>11 Again, this has been highlighted previously.</p> <p>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.</p> <p>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</p>
<p>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.</p> <p>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.</p> <p>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.</p> <p>22 In such a trial, there is no need to enroll</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>

<p style="text-align: right;">Page 425</p> <p>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.</p> <p>6 So I'll just walk you through some numbers.</p> <p>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.</p> <p>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.</p> <p>22 So if one is to do a standard NI trial with</p>	<p style="text-align: right;">Page 427</p> <p>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.</p> <p>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.</p> <p>10 They're not very common. We really need to figure out 11 what the endpoint or the trial design might look like.</p> <p>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</p>
<p style="text-align: right;">Page 426</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p style="text-align: right;">Page 428</p> <p>1 does vary across the different indications.</p> <p>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.</p> <p>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.</p> <p>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.</p>

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<p>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</p>	<p>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</p>
<p>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,</p>	<p>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</p>

<p style="text-align: right;">Page 433</p> <p>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</p>	<p style="text-align: right;">Page 435</p> <p>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 <i>pseudomonas</i> 20 <i>aeruginosa</i>. This could be one or more descriptive 21 study. 22 The plus to this approach is that, you know,</p>
<p style="text-align: right;">Page 434</p> <p>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</p>	<p style="text-align: right;">Page 436</p> <p>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</p>

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<p>1 approve the product under the animal rule.</p> <p>2 And the post-approval study would really</p> <p>3 face the same -- likely face the same challenges that</p> <p>4 you encountered pre-approval. And I think for us a</p> <p>5 bigger issue from a policy standpoint is what kind of</p> <p>6 a precedent we might set for other clinical conditions</p> <p>7 of low prevalence, so a lot of issues to work through</p> <p>8 but certainly an option worth discussing.</p> <p>9 Here's some examples of products. I just</p> <p>10 have the list of drugs. I don't have the list of</p> <p>11 biologics here that have been approved using the</p> <p>12 animal rule. For infectious diseases, we have three</p> <p>13 products approved for plague and three approved for</p> <p>14 inhalational anthrax. There are also other products</p> <p>15 available for non-infectious disease conditions, you</p> <p>16 know, products that might help for radiologic nuclear</p> <p>17 incident, cyanide poisoning or nerve gas poisoning.</p> <p>18 So next, I'll walk you through the plague</p> <p>19 example, you know, just sort of to, you know, let you</p> <p>20 know that this is -- it's really not that</p> <p>21 straightforward. But it's doable, I suppose, if we</p> <p>22 all decide this is the way we are going.</p>	<p>1 laboratory test standpoint, they had leukocytosis,</p> <p>2 abnormalities in the liver function test, coagulation</p> <p>3 abnormalities.</p> <p>4 The duration -- the onset of bacteremia was</p> <p>5 quite variable from 30 hours to 94 hours, and they had</p> <p>6 radiologic infiltrates as well. On hystopath, there</p> <p>7 was evidence of fibrinosuppurative hemorrhagic</p> <p>8 pneumonia, so not really different from what one</p> <p>9 expects in animals.</p> <p>10 So here's -- in the next two or three tables</p> <p>11 I tried to compare how the disease looked like in the</p> <p>12 AGM compared to what we know about human pneumonic</p> <p>13 plague. So the challenge agent in the AGM model was</p> <p>14 Y. pestis CO92. In humans it's Y. pestis. The CO92</p> <p>15 strain was isolated from a human with pneumonic</p> <p>16 plague.</p> <p>17 The pathogenic determinants of the organism</p> <p>18 are the same monkey are to humans. The root of</p> <p>19 exposures in AGM was aerosol, had only exposure. In</p> <p>20 humans, it tends to be aerosol exposure as well,</p> <p>21 generally, when there's close contact with the --</p> <p>22 another individual with pneumonic plague are in the</p>
<p>1 So the African green monkey model of primary</p> <p>2 pneumonic plague was developed to provide a platform</p> <p>3 for testing various therapeutic intervention.</p> <p>4 Mortality outcome was assessed in AGMs with</p> <p>5 symptomatic disease, and this was done in more than</p> <p>6 one lab. The progression of the disease was</p> <p>7 described, and the potential triggers for therapeutic</p> <p>8 intervention were also evaluated.</p> <p>9 And we had some human data available. I</p> <p>10 mean, they were not perfect, so one could compare the</p> <p>11 disease in the AGMs with that in humans. So here,</p> <p>12 naïve -- experimentally naïve AGMs healthy male and</p> <p>13 female was studied. The Colorado 92 strain of</p> <p>14 Yersinia pestis was used, and this was the exposure</p> <p>15 target. The AGMs were monitored clinically, and</p> <p>16 laboratory tests were also monitored. And then the</p> <p>17 AGMs that succumbed to disease, pathology both gross</p> <p>18 and microscopic were assessed.</p> <p>19 So when these studies were done, the</p> <p>20 exposures did range a fair bit. AGMs clinically had</p> <p>21 fever, loss of appetite, respiratory distress,</p> <p>22 lethargy and increased respiratory secretions. From a</p>	<p>1 unfortunate setting of a bioweaponized aerosol.</p> <p>2 The exposures are quantified in the AGM. It</p> <p>3 ranged -- but as long as you got more than 20 LD50,</p> <p>4 the animals all succumbed. The infectious inoculum in</p> <p>5 humans varies. It depends on the contact and the</p> <p>6 degree of exposure.</p> <p>7 From a pathophysiology standpoint, there</p> <p>8 were a lot of similarities between the disease you saw</p> <p>9 in AGMs and humans. The time to onset of disease of</p> <p>10 condition ranged from one to three days, slightly</p> <p>11 longer duration in humans. Time to death, again, it's</p> <p>12 not very different.</p> <p>13 Signs and symptoms were fairly similar.</p> <p>14 There's fever, lethargy, tachypnea tachycardia. There</p> <p>15 was evidence of neutrophilic leukocytosis, coagulation</p> <p>16 abnormalities. Radiologic evaluation showed</p> <p>17 infiltrates. In humans, it's very similar --</p> <p>18 consolidation cavities bronchopneumonia and the</p> <p>19 pathologies hemorrhagic pneumonia in both.</p> <p>20 Both AGMs and humans are highly susceptible</p> <p>21 to the disease and uniformly fatal if untreated. The</p> <p>22 trigger to intervention in humans was based on them</p>

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<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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</p>
<p>1 available on the website if you look for an advisory 2 committee in 2012.</p> <p>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.</p> <p>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.</p> <p>21 So I know I walked you through a lot in the 22 short period of time. But you know, just my sort of</p>	<p>1 clinical conditions being considered for development.</p> <p>2 Thank you.</p> <p>3 (Applause)</p> <p>4 DR. COX: Thanks, Sumathi.</p> <p>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.</p> <p>10 Marco?</p> <p>11 DR. CAVALERI: Thank you, Ed.</p> <p>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.</p> <p>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</p>

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<p>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.</p> <p>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.</p> <p>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.</p> <p>21 And of course, one of the goal will be to 22 try to reduce the amount of patient that are enrolled</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>22 So clearly, there is some benefit in</p>
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<p>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.</p> <p>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).</p> <p>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.</p> <p>20 But of course, here, we will not be overly demanding</p> <p>21 And is said by others, it's very important 22 for conducting trials with this kind of drug to go</p>	<p>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.</p> <p>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.</p> <p>13 Nevertheless, it could be a good opportunity to try to 14 make the clinical development more efficient.</p> <p>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.</p>

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<p>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.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>20 The last option will be an uncontrolled 21 study, including the major indications as highlighted 22 before with infection specific clinical outcome at</p>
<p>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.</p> <p>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).</p> <p>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.</p> <p>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.</p>	<p>1 test of cure as primary endpoint. And here, it would 2 be essential to have adequate and convincing external 3 and historical control.</p> <p>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.</p> <p>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</p>

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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 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 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 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

<p style="text-align: right;">Page 457</p> <p>1 what I meant about a field study.</p> <p>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.</p> <p>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.</p> <p>16 So yes. And if that is 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.</p> <p>21 DR. REX: It looks like Helen has a question 22 and then Ed.</p>	<p style="text-align: right;">Page 459</p> <p>1 we get to that point.</p> <p>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.</p> <p>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?</p> <p>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</p>
<p style="text-align: right;">Page 458</p> <p>1 DR. BOUCHER: So maybe I'll just follow up 2 Sumathi.</p> <p>3 So in that scenario, what would the label 4 look like?</p> <p>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?</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 460</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>

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1	DR. REX: Helen again.	1 Box, and I think it's self-explanatory for today.
2	DR. BOUCHER: So to that end, some things	2 If you look at your handout, what we've done
3	that have been discussed as part of the carb effort	3 here is several of us have kind of collaborated on
4	have included, you know, improved monitoring of	4 this. We've built up a series of approaches, and
5	antibiotic use in general through the CDC and HSN and	5 we're going to talk about, first, three scenarios that
6	other mechanisms really directed at stewardship. But	6 are an attempt to eke out a path to a non-inferiority-
7	it may not be crazy to think that those types of	7 based approval. Just see what -- you know, what does
8	mechanisms might work here where, you know, a new drug	8 it take. Kind of do a little wiggling around.
9	for very a specific special population came out and	9 And then Scenarios D and E are -- put you --
10	could be monitored in that way with some kind of	10 sit down into a further corner where you just conclude
11	feedback whereby, you know, it's more real world. And	11 that either you can't do it, or it's crazy for one
12	so the quality of the data, you know, it may not be	12 reason or another. And then Scenario F is going to be
13	exactly what you're looking for, but it would -- could	13 that I'm looking for one of you guys to have a
14	be a way to monitor and understand more about the	14 brilliant insight in the course of the day. Audience
15	potential utility and/or risks of these new agents.	15 participation. What did we overlook? What else could
16	DR. COX: And just thinking about things	16 we have done?
17	too, I mean, you know, there will be, you know, a fair	17 In terms of timing, I'm going to use -- it's
18	-- you know, an animal rule-based approval does have,	18 just now 11 o'clock. We're going to go till about
19	you know, a certain degree of uncertainty. And you	19 12:15. I think that's probably going to be enough to
20	know, those that have worked with animal models and,	20 walk through some of the Scenario A, basically. And
21	you know, how they're developed -- and they're sort of	21 then we will come back and walk through the remainder
22	developed to actually show an affect. I mean, that's	22 -- remaining stuff and have a moment for -- and along
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1	sort of why you, you know, develop the animal model in	1 the way it's very, very informal. So you can take off
2	the way that you do. So getting that sort of second	2 your tie.
3	component of predicting human efficacy, I mean, there	3 That's the other thing to know, okay? Yeah,
4	is a degree of uncertainty.	4 I do tie it. If you can't tie it, you shouldn't wear
5	So the animal rule does have with it, you	5 it. Stop there.
6	know, restrictions to ensure safe use. And it would	6 (Laughter)
7	seem that, you know, some of the conditions that are	7 DR. REX: But I am -- with that said, it
8	described might be very reasonable to consider in a	8 would going to be scary to go further. All right. So
9	circumstance like this because the drug would be --	9 --
10	you know, patients are out there. They're having	10 AUDIENCE MEMBER: (inaudible - off mic).
11	infections, you know, from day to day. And you know,	11 DR. REX: Yeah. No pressure here. It's
12	the appropriate therapeutic role for such a product,	12 just -- all right.
13	you know, this may be an appropriate area to think	13 So here are the constraints. So as we were
14	about some of those restrictions and how the product	14 developing this case and the approaches, the goal was
15	would be used appropriately in order to balance, you	15 to make this very real, okay? So you're not permitted
16	know, what's the uncertainty the -- you know, so that	16 any imaginary thing, so -- and also excluded sort of
17	the product is used safely out there in the real	17 the BFMI solutions which is an acronym for me, brute
18	world, so.	18 force massive ignorance, okay? So enroll 10,000. No,
19	DR. REX: Any other questions for	19 we're not going to do that.
20	clarification sort of on the context in the setup?	20 We don't assume any kind of a perfect
21	Okay. So let's move forward then.	21 diagnostic. I don't have an instant susceptibility
22	So I've always like this quote by George	22 for all the pathogens in the sputum. I don't have

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<p>1 instant knowledge that only pseudomonas aeruginosa is 2 present. I don't have that.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>22 We -- there's an implicit assumption just</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>
<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>22 What we know is the preclinical signals are</p>

<p style="text-align: right;">Page 469</p> <p>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.</p> <p>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.</p>	<p style="text-align: right;">Page 471</p> <p>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.</p> <p>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.</p> <p>21 There's a place where they talk about what 22 do you do for empiric therapy. "We suggest</p>
<p style="text-align: right;">Page 470</p> <p>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</p>	<p style="text-align: right;">Page 472</p> <p>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</p>

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<p>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 is 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.</p> <p>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.</p> <p>21 You know, in two years from now, people 22 might really be saying it even more often. Other</p>	<p>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 <i>pseudomonas aeruginosa</i>. 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.</p> <p>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.</p> <p>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.</p> <p>21 There are probably some more modeling that could be 22 done to get comfortable with it, you know, and also</p>
<p>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.</p> <p>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.</p> <p>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 <i>pseudomonas</i> and 22 you'd like to take a shot at it with X-1. That's sort</p>	<p>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.</p> <p>7 But as it stands right now, it looks to me 8 like entrapenem for non-<i>pseudomonas</i>, 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.</p> <p>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 ertapenem 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 get given to the 21 X-1 arm. So it's Amikacin versus placebo.</p> <p>22 For nosocomial pneumonia, made the decision</p>

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<p>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?</p> <p>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.</p> <p>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.</p> <p>21 And then the ertapenem or placebo -- 22 everybody gets one dose of that a day because</p>	<p>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.</p>
<p>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.</p> <p>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.</p> <p>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.</p> <p>21 So the stats will be -- the primary analysis 22 will be in the microITT population. That is the</p>	<p>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-</p>

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<p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>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.</p> <p>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.</p> <p>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.</p> <p>15 But you know, it's that kind of data because 16 you've actually -- can go look for some modern data 17 tell you whether or not you've got a problem. That's 18 as close as I get to using a miracle.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>20 I'm trying to do it -- yeah, don't do that, 21 right.</p> <p>22 So here's the actual study that, of course,</p>

<p style="text-align: right;">Page 485</p> <p>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.</p> <p>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.</p>	<p style="text-align: right;">Page 487</p> <p>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.</p> <p>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</p>
<p style="text-align: right;">Page 486</p> <p>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.</p> <p>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.</p> <p>9 Okay. Yes, Kenneth Hillin (ph), I'm having 10 to pick him up off the floor.</p> <p>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?</p> <p>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</p>	<p style="text-align: right;">Page 488</p> <p>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.</p> <p>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?</p> <p>9 Yes, question.</p> <p>10 UNIDENTIFIED MALE SPEAKER: John, can you 11 run that by me again? You said you got 16 percent 12 (inaudible - off mic) study?</p> <p>13 DR. REX: Right, but we're using my device.</p> <p>14 UNIDENTIFIED MALE SPEAKER: Using the 15 device.</p> <p>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.</p> <p>22 UNIDENTIFIED MALE SPEAKER: But I'm</p>

<p style="text-align: right;">Page 489</p> <p>1 confused. How does the device increase the incidence?</p> <p>2 DR. REX: It doesn't. It just means I only</p> <p>3 enroll the ones who have pseudomonas -- of the people</p> <p>4 I enroll, they're more likely to have pseudomonas.</p> <p>5 Right. And you can argue about where is the cost.</p> <p>6 Actually, the cost isn't just in the enrolled</p> <p>7 patients. It's in the maintenance. You know, 250</p> <p>8 sites means I've got to visit 250 sites once or twice</p> <p>9 a year and replenish their IDP, and, oh my gosh, okay?</p> <p>10 It gets really expensive just to have 250 sites open</p> <p>11 for three years.</p> <p>12 That might -- I don't have a good -- if</p> <p>13 anybody has a good feel for the ratio of true per-</p> <p>14 patient to site running costs underneath -- you know,</p> <p>15 I've got a whole range of estimates from my group.</p> <p>16 I'm happy to have any ratios there you come up with,</p> <p>17 but that's the notion, okay? And, once again, why</p> <p>18 those particular numbers? Because it fits inside</p> <p>19 1,000 patients.</p> <p>20 You know, I have played exhaustively with</p> <p>21 this, and you can come up with other variations. I</p> <p>22 didn't go to one-to-one because I needed the safety</p>	<p style="text-align: right;">Page 491</p> <p>1 four weeks, so there are holes in it.</p> <p>2 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>3 DR. REX: Sorry, say it one more time</p> <p>4 please.</p> <p>5 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>6 DR. REX: No, because empirically, you don't</p> <p>7 know at moment zero on Day 0. So at Moment 0, Day 0,</p> <p>8 you randomize and you start Amikacin on everybody, so</p> <p>9 everybody is going to have had that in this design.</p> <p>10 Other questions? Question?</p> <p>11 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>12 DR. REX: It's based on the cultures coming</p> <p>13 back. You know, by the end of the second day, you</p> <p>14 often have -- because what you all -- what you care</p> <p>15 about is the susceptibility of the pseudomonas.</p> <p>16 So if it grows on Day 1, then you'll have</p> <p>17 susceptibility by Day 2, and that happens with</p> <p>18 Pseudomonas, but it might also take to Day 2 and then</p> <p>19 Day 3 to get it. Pseudomonas is not a particularly</p> <p>20 slow-growing organism. It's not, you know -- it</p> <p>21 doesn't hide. And anything better than this or worse</p> <p>22 than, you know -- okay, so it's three days on average,</p>
<p style="text-align: right;">Page 490</p> <p>1 database on X-1, so I wanted more cases there.</p> <p>2 Didn't, you know -- one-to-one increases the -- it's -</p> <p>3 - your best statistical power is always at one-to-one.</p> <p>4 Any deviation from one-to-one costs you. But here I</p> <p>5 chose to accept that cost because I wanted the safety</p> <p>6 database, okay?</p> <p>7 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>8 DR. REX: No, but they don't all get it for</p> <p>9 full dose and duration. So only the 48 and only the</p> <p>10 69 are going to stay on X-1 -- are -- because if you</p> <p>11 don't have pseudomonas, you come off the study. You</p> <p>12 know what? I didn't say that. That's a good point.</p> <p>13 You could leave them on the study if you wanted to and</p> <p>14 you learn about ertapenem. That's a good point.</p> <p>15 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>16 DR. REX: Why not? Well, it's a good point.</p> <p>17 You could -- I'd implicitly assumed that,</p> <p>18 you know, if you didn't -- in terms of safety, you</p> <p>19 actually could have way more than enough safety here.</p> <p>20 It's a good point. Thank you. Thank you for the</p> <p>21 clarification.</p> <p>22 This case was busily invented over the last</p>	<p style="text-align: right;">Page 492</p> <p>1 you know.</p> <p>2 I -- but I sort of was thinking about what</p> <p>3 does it often feel like to me, and I often have some</p> <p>4 hint of it by the end of the second day. The morning</p> <p>5 of the third day, I can get rid of the Amikacin. You</p> <p>6 know, and maybe that's two and a half days, you know,</p> <p>7 that sort of thing. Good question.</p> <p>8 Yes, sir?</p> <p>9 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>10 DR. REX: Sorry, say that one more time.</p> <p>11 I'm trying to repeat the questions, but it's tricky.</p> <p>12 UNIDENTIFIED MALE SPEAKER: All right. So</p> <p>13 the drop-off rate applies for the total MP population</p> <p>14 and not necessarily to the one who have pseudomonas,</p> <p>15 right, and get the test drug. So for those, let us</p> <p>16 say, to assess what the confounding effect of Amikacin</p> <p>17 on test track would be, those rates would be higher</p> <p>18 because those who have pseudomonas let's say probably</p> <p>19 4 or 5 days -- 80 percent right?</p> <p>20 DR. REX: What we're -- what I have assumed</p> <p>21 is that you're willing to drop down to monotherapy, so</p> <p>22 it goes a little bit against the IDSA guidelines.</p>

<p style="text-align: right;">Page 493</p> <p>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.</p> <p>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?</p> <p>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.</p> <p>20 Yes, ma'am?</p> <p>21 UNIDENTIFIED FEMALE SPEAKER: How do you 22 account for the risk for CRE in the comparator arm?</p>	<p style="text-align: right;">Page 495</p> <p>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.</p> <p>8 Other questions? Okay.</p> <p>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.</p> <p>21 And there you have an intra-ab dataset. And 22 I left those numbers a little closer. You know, 80</p>
<p style="text-align: right;">Page 494</p> <p>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.</p> <p>10 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>11 DR. REX: Yeah, I'm with you. I want to 12 work there, too.</p> <p>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.</p> <p>22 Remember, the ICUs are trying very hard to</p>	<p style="text-align: right;">Page 496</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>22 And I'm guessing that here's a place where</p>

<p style="text-align: right;">Page 497</p> <p>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.</p> <p>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.</p> <p>21 MR. DANE: John --</p> <p>22 DR. REX: Yes?</p>	<p style="text-align: right;">Page 499</p> <p>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.</p> <p>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</p>
<p style="text-align: right;">Page 498</p> <p>1 MR. DANE: Just --</p> <p>2 DR. REX: So now we're going to do 3 questions.</p> <p>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?</p> <p>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.</p> <p>22 So, Helen?</p>	<p style="text-align: right;">Page 500</p> <p>1 almost 50-50, or even a little less, in these really 2 sick people.</p> <p>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.</p> <p>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</p>

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<p>1 some other pathogens. And that's crude mortality.</p> <p>2 And the reason we like the endpoint is</p> <p>3 because there's a lot of improvement you could</p> <p>4 demonstrate with a good antibiotic. And if you don't</p> <p>5 demonstrate enough, then you could look inferior, so</p> <p>6 there are potential to detect an inferior therapy, if</p> <p>7 you don't work as well as your comparator. But let's</p> <p>8 say you work as well. What are you left with? You're</p> <p>9 left with some of that crude mortality that you</p> <p>10 started with but you couldn't see because so much of</p> <p>11 it was buried in the pneumonia.</p> <p>12 So you've got this crude mortality and you</p> <p>13 have 24 patients on marrow and 48 on ertapenem, and</p> <p>14 you have to assume that you randomized that and that</p> <p>15 what's left over you're going to be able to really say</p> <p>16 that -- you know, this is a problem that I think</p> <p>17 people have with all-cause mortality because, at the</p> <p>18 end of the day, you have other things that are also</p> <p>19 responsible for those remaining deaths. And that</p> <p>20 might not be handled well here. I don't know if I</p> <p>21 said that clearly, if anybody has a better way of</p> <p>22 articulating it, but --</p>	<p>1 are going to be significantly lower than that. And --</p> <p>2 DR. REX: So feel free to knock them down.</p> <p>3 MR. LOUDIT: -- the point is how do you deal</p> <p>4 with that and put it into perspective? And I think</p> <p>5 Helen's points are exactly right.</p> <p>6 DR. REX: Yeah. And so, you know, keep in</p> <p>7 mind -- you know, if -- cut them in half if you'd</p> <p>8 like. They're deliberately pitched to be different</p> <p>9 and not as good. And that's sort of the concept here.</p> <p>10 DR. CAVALERI: I'm going to just come back</p> <p>11 before we go.</p> <p>12 So to John Tomayko's comment, I mean, it</p> <p>13 sounds like, too, I mean, you know, you're arguing</p> <p>14 that in a small group of patient you might not have</p> <p>15 really balanced things out with randomization and the</p> <p>16 impact that that might have on all-cause mortality.</p> <p>17 It could affect other endpoints too, yeah. So I just</p> <p>18 don't -- I mean, I don't know that that's exclusively</p> <p>19 a problem of all-cause mortality.</p> <p>20 And these are -- this is a patient</p> <p>21 population where there's a lot of other things going</p> <p>22 on, and, you know, some patients will succumb to other</p>
<p>1 DR. REX: Will the left-handed poodle owners</p> <p>2 be randomized? Right. Will the smokers be equally</p> <p>3 randomized? Will poodle ownership be equally</p> <p>4 randomized? You just have no clue.</p> <p>5 So Helen again.</p> <p>6 And there's somebody with a question on the</p> <p>7 mic. Yes?</p> <p>8 MR. LOUDIT: Yes, so this is Jeff Loudit</p> <p>9 (ph). So Helen and John are much smarter than I, so I</p> <p>10 was going to make the same comments. But so quick</p> <p>11 question, John. That is all-cause mortality that</p> <p>12 you're showing there with HABP/VABP or is that --</p> <p>13 DR. REX: Yes, the endpoint for HABP/VABP is</p> <p>14 all-cause mortality.</p> <p>15 MR. LOUDIT: That's survival that you're</p> <p>16 showing there.</p> <p>17 DR. REX: Excuse me, it's -- it is all-cause</p> <p>18 survival.</p> <p>19 MR. LOUDIT: Okay. So all-cause survival</p> <p>20 that we're showing there. All right. So I would</p> <p>21 agree, though, with John and Helen's comment that I</p> <p>22 think certainly in the open label trial, your numbers</p>	<p>1 conditions that they have. We just can't tell who's</p> <p>2 who and what the cause is for each of those two</p> <p>3 things.</p> <p>4 So, yeah, I just didn't want to -- I mean,</p> <p>5 so it's not exclusively mortality, but this is a</p> <p>6 problem that we run into with smaller numbers -- and,</p> <p>7 yeah, okay.</p> <p>8 DR. REX: David?</p> <p>9 DAVID: Yeah, so the issue that I'm</p> <p>10 struggling with is that we spend an awful lot of money</p> <p>11 studying an awful lot of patients for an extremely</p> <p>12 fragile result.</p> <p>13 DR. REX: I -- And that point is extremely</p> <p>14 well -- and we actually put up a slide that'll let you</p> <p>15 talk about this because if you look at -- there's a</p> <p>16 section, A45, that lists really big risks. And what</p> <p>17 you're pointing out is number 2 -- that N is tiny and</p> <p>18 there -- the risk of bouncing off that a little bit is</p> <p>19 notable.</p> <p>20 DAVID: Yeah, so I just don't think anybody</p> <p>21 is going to do this. I think bravo for going through</p> <p>22 this. I think that this was a really rigorous look at</p>

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<p>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.</p>	<p>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.</p>
<p style="text-align: center;">Page 506</p> <p>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</p>	<p style="text-align: center;">Page 508</p> <p>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</p>

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<p>1 the study.</p> <p>2 DR. REX: Right --</p> <p>3 MR. HOOFTMAN: So it makes it --</p> <p>4 DR. REX: You're right. So this is powering</p> <p>5 versus actual data. So here a lot of the power</p> <p>6 questions are now gone at this point. We've invented</p> <p>7 some data. You know, we have what we have.</p> <p>8 MR. DANE: Yeah.</p> <p>9 DR. REX: Right. So I want to be sure we</p> <p>10 cover these questions, pros and cons from all</p> <p>11 perspectives. So we've got to talk about how to deal</p> <p>12 with two body sites. You know, what do you do there?</p> <p>13 Come back to concomitant therapy. Is there anything</p> <p>14 other than erta we could use? There's implicit</p> <p>15 approach to polymicrobial versus monomicrobial, just</p> <p>16 to double check. Any other thoughts on MDR</p> <p>17 pseudomonas and best available therapies? So we've</p> <p>18 kind of covered some of these, but if you're looking</p> <p>19 for a question to poke on, be sure we poke on one of</p> <p>20 these.</p> <p>21 So there was somebody holding their hand up</p> <p>22 a minute ago. Yeah, Tom?</p>	<p>1 is in whatever range is required, if you like. And on</p> <p>2 the design side, you can then ask what kind of a</p> <p>3 sample size would be needed if the true differences in</p> <p>4 a certain situation so that there's a high likelihood</p> <p>5 that that posterior probability will be sufficiently</p> <p>6 large. In other words, you can do -- you can reverse-</p> <p>7 engineer to do the design question, too.</p> <p>8 MR. DANE: Yeah, I mean, I would say on</p> <p>9 that, that's true. You still need -- a company going</p> <p>10 into a study and investing still needs to have an idea</p> <p>11 of what's going to be sufficient for approval, though.</p> <p>12 So, yeah, I agree with everything you say, but in some</p> <p>13 ways, whether it's an alpha level, whether it's a</p> <p>14 likelihood, that question still remains, is what's the</p> <p>15 acceptable regulatory risk in doing some of this in</p> <p>16 terms of incorrectly approving something.</p> <p>17 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>18 DR. REX: Yeah. Well, and I think what</p> <p>19 you're saying is that we might need to spend some time</p> <p>20 as a community getting to where we understand -- what</p> <p>21 you're talking about, I can get a feel for it from a</p> <p>22 distance, but we'd actually have to be able to</p>
<p>1 DR. LOUIS: Tom Louis. Just to comment on</p> <p>2 the previous discussion on the 95 interval, the 90</p> <p>3 interval, it becomes endless. And here's a perfect</p> <p>4 case where, let's say, with uninformative priors on</p> <p>5 the underlying parameters -- or if you have some</p> <p>6 knowledge on baseline, just put it in. Compute the</p> <p>7 posterior probability that the difference in -- the</p> <p>8 true difference in the parameters is in the range that</p> <p>9 it needs to be in. I don't know what that number will</p> <p>10 be in this case, but it's far better than, oh, what</p> <p>11 about the 90, what about the 95. Just have a direct</p> <p>12 answer to that underlying question and --</p> <p>13 DR. REX: So you're getting at the -- a true</p> <p>14 posterior probability, or in terms that I understand,</p> <p>15 the likelihood?</p> <p>16 DR. LOUIS: Well, it would be based -- is if</p> <p>17 it were uninformative and being, if you like,</p> <p>18 frequentist, it would be based on the likelihood and</p> <p>19 would ask the question directly. It would say we</p> <p>20 don't see the parameters, but we -- there is a true</p> <p>21 difference. Let's build a model that computes the</p> <p>22 posterior probability, given the data, that the truth</p>	<p>1 understand it broadly enough that even if a pair who</p> <p>2 is being shown the data is -- you're able to say in a</p> <p>3 way that actually sort of conveys the feel for the</p> <p>4 strength of the information. And so that's something</p> <p>5 to work on. It's a new form of -- you know, because</p> <p>6 we haven't often -- we have never actually publicly in</p> <p>7 these conversations done anything other than standard</p> <p>8 frequentist statistics that we all learned in -- as</p> <p>9 freshmen in college, you know, that sort of thing. So</p> <p>10 it's a well-said point.</p> <p>11 MR. DANE: John, my other point on -- just</p> <p>12 related to that was that, you know, whether we talk</p> <p>13 about alpha levels or likelihoods, that the other</p> <p>14 point is that sometimes they can be useful rather than</p> <p>15 going to bigger and bigger non-inferiority margins</p> <p>16 that people become uncomfortable with because we say,</p> <p>17 well, we can have a margin of 40 percent, for example,</p> <p>18 because it's feasible. But who's going to be happy</p> <p>19 saying, well, we could be 40 percent worse, whereas</p> <p>20 something with a tighter margin -- but you're just</p> <p>21 saying, well, we've got a big more risk of what we're</p> <p>22 doing here might be a good balance and a better</p>

<p style="text-align: right;">Page 513</p> <p>1 balance than going that way.</p> <p>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.</p> <p>14 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>15 DR. REX: Well, see, I wanted this case to 16 try to get at these debates. You're right.</p> <p>17 Okay, so Kenneth?</p> <p>18 MR. HILLIN: John, thanks.</p> <p>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</p>	<p style="text-align: right;">Page 515</p> <p>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 --</p> <p>7 DR. REX: Use the microphone.</p> <p>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 --</p> <p>22 DR. REX: Well, I want to say the approach</p>
<p style="text-align: right;">Page 514</p> <p>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.</p> <p>8 DR. REX: Okay, well, thank you. We've had 9 a good time putting it together. Lynn?</p> <p>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 --</p> <p>17 DR. REX: I think that's upside, you know. 18 I think, you know, that's helpful.</p> <p>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</p>	<p style="text-align: right;">Page 516</p> <p>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.</p> <p>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?</p> <p>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.</p> <p>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</p>

<p style="text-align: right;">Page 517</p> <p>1 rate of treating infections.</p> <p>2 So Mike Dudley is looking at me -- what does</p> <p>3 that mean? So in -- hypothetically, I've just cut</p> <p>4 through your wall of your bowel, and I've just created</p> <p>5 an infection. Let's pretend that I create a little</p> <p>6 baby infection right at that moment.</p> <p>7 So if I then put you on an antibiotic, I'm</p> <p>8 treating this itty bitty tiny infection. Or I don't</p> <p>9 put you on an antibiotic. I'm not treating it. And</p> <p>10 post-response will control some of them. Antibiotics</p> <p>11 will control some of the others.</p> <p>12 So that's how it was computed. And it</p> <p>13 actually showed that there is a benefit of</p> <p>14 perioperative antibiotics if I'm going to transect</p> <p>15 your gut wall. I very clearly show that, which, you</p> <p>16 know, is something we want to do.</p> <p>17 And you find that there is a difference</p> <p>18 between -- and you can actually -- the math -- so go</p> <p>19 read the guide. Now that you've heard the story, go</p> <p>20 read the guidance document again. You know, I thought</p> <p>21 it was a -- not a bad approach, and it, you know --</p> <p>22 show me something better. You guys -- like, all</p>	<p style="text-align: right;">Page 519</p> <p>1 treatment or your ertapenem isn't working. And how</p> <p>2 you can send for that in a situation of HBAP/VBAP to a</p> <p>3 patient where alternative treatments, which actually</p> <p>4 are approved, are available. So for me, that is one</p> <p>5 issue.</p> <p>6 The second issue is that even you have a</p> <p>7 fantastic new drug called X-1. Actually, that doesn't</p> <p>8 come for free. There will be safety issues. And some</p> <p>9 you raised and whatever they are. So you're going to</p> <p>10 treat 75 percent of the patients in that trial</p> <p>11 empirically with a useless drug. And they're exposed</p> <p>12 to safety issues.</p> <p>13 And you know, I'm 10 years plus chief</p> <p>14 medical officer of two companies. And I -- in an</p> <p>15 internal ethical committee, we would have a huge</p> <p>16 debate whether we would expose these patients to that</p> <p>17 risk and what type of warning we would give to them</p> <p>18 and how recruitable would be the study then at the end</p> <p>19 if you display that information to the participants.</p> <p>20 And so for me, it's not only a financial feasibility</p> <p>21 or an evidence issue, it is just an ethical</p> <p>22 feasibility to get all those patients on board and</p>
<p style="text-align: right;">Page 518</p> <p>1 models are flawed. You know, if you don't like this</p> <p>2 approach, you can't just criticize. You have to</p> <p>3 solve. So you know, my hat's off for somebody for</p> <p>4 having found a path.</p> <p>5 Question?</p> <p>6 UNIDENTIFIED MALE SPEAKER: Well, I think</p> <p>7 it's great work, and all the discussion focused on</p> <p>8 regulatory aspects and on statistical aspects and on</p> <p>9 evidence. I just want to shed a little bit of light</p> <p>10 on those patients who actually do not have pseudomonas</p> <p>11 infection in that study.</p> <p>12 So first of all, in the arm -- in the</p> <p>13 experimental arm that -- actually two experimental</p> <p>14 drugs because the drugs are approved, so probably you</p> <p>15 needed the DSMB on that arm. And what happens if that</p> <p>16 ertapenem actually is inferior in the non-PS, which is</p> <p>17 75 percent of the patients --</p> <p>18 DR. REX: That's a risk.</p> <p>19 UNIDENTIFIED MALE SPEAKER: What happens to</p> <p>20 the study? You're going to stop the study not because</p> <p>21 the PS isn't working, the pseudomonas. You'll</p> <p>22 probably stop the study because your adjunctive</p>	<p style="text-align: right;">Page 520</p> <p>1 telling them what their likelihood of benefit versus</p> <p>2 their likelihood of risk is in that arm.</p> <p>3 DR. REX: Yeah. Good point, and it actually</p> <p>4 makes Jeff Loudit's (ph) comment that you ought to</p> <p>5 keep them on the study more pointed. So if you know</p> <p>6 it's not pseudomonas, you ought to just keep on</p> <p>7 running it because now you're at least getting data on</p> <p>8 how well erta works. And so I had not thought about</p> <p>9 that aspect of it, but it's a very well -- one of the</p> <p>10 risks here is that erta is not an approved drug as the</p> <p>11 combination. But you know, look -- come up with a</p> <p>12 better solution. You know, I didn't like Tigecycline,</p> <p>13 so, you know, I came down on the side of ertapenem.</p> <p>14 Jeff and then Ian.</p> <p>15 MR. LOUDIT: So Dave asked -- Dave said no</p> <p>16 one would run this study, so I'm going to put my neck</p> <p>17 out here. I would run this study, Dave, with three</p> <p>18 caveats.</p> <p>19 DR. REX: Okay.</p> <p>20 MR. LOUDIT: One, it's somebody else's</p> <p>21 money. That would be --</p> <p>22 (Laughter)</p>

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<p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>11 DR. COX: Do you want me to comment on that?</p> <p>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.</p>
<p>1 infrequently. You know, I wanted something without 2 batteries.</p> <p>3 So Ian? And then --</p> <p>4 DR. FRIEDLAND: I also wanted --</p> <p>5 DR. REX: -- Paul's wiggling his fingers, so 6 he's next.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>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 --</p> <p>6 DR. CAVALERI: Yeah.</p> <p>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?</p> <p>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.</p> <p>21 DR. REX: Okay. So let's look at these 22 questions and be sure that we've -- sorry, Paul</p>
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<p>1 Ambrose is waving his hand.</p> <p>2 Go for it, Paul. We really have plenty of</p> <p>3 time to discuss, and I don't want any idea to lie</p> <p>4 fallow.</p> <p>5 DR. AMBROSE: All right, I don't have an</p> <p>6 idea, I -- just a comment. Is there any concern that</p> <p>7 ertapenem is being picked here because -- well, it's</p> <p>8 being picked because we think its PK/PD will predict</p> <p>9 as active, right? It's got --</p> <p>10 DR. REX: Talk straight into the microphone.</p> <p>11 DR. AMBROSE: It's got no randomized</p> <p>12 clinical trial in nosocomial pneumonia. It's just</p> <p>13 being picked because the PK/PD for it -- forecasts</p> <p>14 it'll work. Is there any concern that we're comparing</p> <p>15 a new drug to something we don't really understand</p> <p>16 would work? For me, I mean, I really believe in the</p> <p>17 PK/PD as you -- I put a lot of weight in it, but it's</p> <p>18 an interesting precedent that you're setting up.</p> <p>19 DR. REX: I think that is a concern. And</p> <p>20 you know -- make another suggestion. You know, maybe</p> <p>21 as a community, we need to do an ertapenem --</p> <p>22 DR. FRIEDLAND: There actually is a clinical</p>	<p>1 DR. REX: Do you remember offhand if the</p> <p>2 mortalities were comparable in the two arms?</p> <p>3 DR. FRIEDLAND: No, I can't remember all the</p> <p>4 data. The main reason it wasn't submitted was because</p> <p>5 maybe it did too well, and at the time commercially</p> <p>6 they wanted to distinguish it from other carbapenems.</p> <p>7 They didn't want it to look as good as meropenem and</p> <p>8 ertapenem against, like, really sick patients. So it</p> <p>9 was a very strange reason why it was never actually</p> <p>10 promoted or --</p> <p>11 DR. REX: Well, it's -- so maybe there's a</p> <p>12 bit more data than we realize. And like I say, you</p> <p>13 know, the little bit I scrounged up, actually, it</p> <p>14 looks -- it looked as if it ought to work, you know.</p> <p>15 Sorry.</p> <p>16 MR. ARAKOFF: Dmitri Arakoff (ph),</p> <p>17 divisional and executive (ph) products of DE (ph).</p> <p>18 Since we have time for discussion, I'd like to address</p> <p>19 this question of immunotherapy versus dual therapy.</p> <p>20 Looking at the guidance, it seems that they deem</p> <p>21 immunotherapies acceptable as long as your drug is</p> <p>22 active against isolated pathogens. And the reason --</p>
<p>1 trial with ertapenem done in HABP and non-ventilated -</p> <p>2 - and early-onset VABP. It was just never submitted</p> <p>3 for reasons other than efficacy.</p> <p>4 DR. REX: You're kidding.</p> <p>5 DR. FRIEDLAND: But it actually was a trial.</p> <p>6 It was actually the very first trial I ever conducted</p> <p>7 in industry was a VABP -- a HABP/VABP trial with</p> <p>8 ertapenem. It is published. It was just never</p> <p>9 submitted for approval.</p> <p>10 DR. REX: Yeah.</p> <p>11 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>12 DR. REX: So I was getting comments from two</p> <p>13 directions. So you're -- actually, I think -- find</p> <p>14 those data, you know. And, sir, did you say -- how</p> <p>15 did it do? I missed that part.</p> <p>16 DR. FRIEDLAND: It was -- you know, it was</p> <p>17 done back in 2000 --</p> <p>18 DR. REX: Back in the year aught, all right.</p> <p>19 DR. FRIEDLAND: So way -- non-inferiority</p> <p>20 margins were acceptable, but it was like a 350-patient</p> <p>21 study versus pip/tazo, and it fell within the non-</p> <p>22 inferiority margin of 15 percent to 20 percent of --</p>	<p>1 we give dual therapies to -- not to prevent</p> <p>2 resistance, but to make sure that at least one drug is</p> <p>3 active --</p> <p>4 DR. REX: Is active.</p> <p>5 MR. ARAKOFF: -- meaning that if you study a</p> <p>6 drug supposedly active against resistant pathogens,</p> <p>7 maybe this criteria not applicable to your product.</p> <p>8 And it's acceptable to use a new product, at least in</p> <p>9 this active arm.</p> <p>10 DR. REX: Yeah, so -- and I think if you</p> <p>11 felt like you could do that, that would be great</p> <p>12 upside. I considered the possibility for nosocomial</p> <p>13 pneumonia of saying -- of doing it the same way I did</p> <p>14 in complicated intra-ab, which is to say Amikacin is</p> <p>15 given, but it is blinded versus placebo. So the X-1</p> <p>16 arm gets a placebo Amikacin, and the meropenem arm</p> <p>17 gets real Amikacin. And you somehow blind even doing</p> <p>18 of levels and things like that. And I think you could</p> <p>19 do that. And if you could, that would certainly help</p> <p>20 clarify the dataset.</p> <p>21 I just chose for purposes of this discussion</p> <p>22 to make us deal with the possibility that there will</p>

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<p>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.</p> <p>8 MR. ARAKOFF: Because what would be the 9 argument to the second drug? This is my point if it's 10 -- right.</p> <p>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.</p> <p>17 Mike?</p> <p>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.</p> <p>22 DR. DUDLEY: Yeah, I'd like to go back to a</p>	<p>1 pneumonia.</p> <p>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.</p> <p>6 DR. REX: Whatever it is --</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>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.</p> <p>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.</p> <p>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</p>	<p>1 DR. REX: Right. It was all about --</p> <p>2 DR. COX: So we could say use it in 3 combination with ertapenem --</p> <p>4 DR. REX: Coming at it from more than one 5 direction.</p> <p>6 DR. COX: -- but we're really trying to 7 figure out --</p> <p>8 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>9 DR. REX: Oh, no, we're --</p> <p>10 DR. COX: Agree, yes.</p> <p>11 DR. REX: -- fully expecting E. colis and 12 Klebsiellas and other things. Absolutely.</p> <p>13 DR. COX: And that's why the ertapenem is 14 there. It's, you know -- there are other things.</p> <p>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</p>

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<p>1 and figure out -- you know, it's only active against 2 <i>pseudomonas aeruginosa</i> to try and figure out how does 3 it perform against <i>pseudomonas aeruginosa</i> because, you 4 know, in subsequent trials in patients with 5 <i>pseudomonas aeruginosa</i> this drug will be used. And 6 this is the chance to figure out whether it works or 7 not.</p> <p>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.</p> <p>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.</p> <p>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 <i>pseudomonas</i>. Your test agent -- you have pre- 22 clinical data. The only clinical data you have are in</p>	<p>1 about it. I --</p> <p>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 --</p> <p>7 DR. REX: And so that's what I'm saying --</p> <p>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.</p> <p>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</p>
<p>1 non-CF-bronchiectasis.</p> <p>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.</p> <p>10 DR. REX: Well, I think you're asking a very 11 general question. How then can I develop any novel 12 antibiotic --</p> <p>13 UNIDENTIFIED FEMALE SPEAKER: Yep.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>

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<p>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 ...</p> <p>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.</p> <p>16 At the microphone?</p> <p>17 UNIDENTIFIED MALE SPEAKER: Yeah, so just to</p>	<p>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.</p> <p>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.</p> <p>16 UNIDENTIFIED MALE SPEAKER: The reasons we</p>
<p>17 touch on a point that's already been raised but it's 18 still not clear to me, you're just ignoring the ITT 19 population it seems here. So you have subjects who 20 are potentially being treated three or four days 21 before you come back with culture positivity. And you</p> <p>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?</p> <p>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.</p> <p>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.</p> <p>16 MR. DANE: Yeah -- go ahead. Go ahead.</p> <p>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,</p>	<p>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</p> <p>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 --</p> <p>6 DR. REX: I guess if I price it high enough, 7 you'll think really hard about using it.</p> <p>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.</p> <p>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.</p> <p>18 (Off the record.)</p> <p>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</p>

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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	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
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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 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

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<p>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.</p> <p>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.</p> <p>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.</p> <p>15 CURT: Well, and that's the purpose of --</p> <p>16 DR. REX: And then that's the problem, yeah.</p> <p>17 CURT: -- is to say in advance when you're 18 going to do that so you can quantify the operating 19 characteristics.</p> <p>20 DR. REX: Okay.</p> <p>21 MR. DANE: John, it might be the role of the 22 -- what you do with this pool of combined data as</p>	<p>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.</p> <p>5 I see Ian at the mic.</p> <p>6 DR. FRIEDLAND: I have some reservation 7 about IAI as a test for activity against pseudomonas. 8 It's --</p> <p>9 DR. REX: So do I.</p> <p>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 --</p> <p>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</p>
<p>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 --</p> <p>5 DR. REX: Yeah.</p> <p>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.</p> <p>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 --</p> <p>19 MR. DANE: Yeah, and the different endpoints 20 as well that could well be here --</p> <p>21 DR. REX: All right. I recognize that. So 22 that's why I didn't really talk about any formal form</p>	<p>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.</p> <p>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.</p> <p>15 (Crosstalk)</p> <p>16 DR. REX: That -- you know, that's actually 17 -- we should minute that. That's a really important 18 observation.</p> <p>19 Was there somebody that raised their hand? 20 Todd (ph)?</p> <p>21 TODD: What about ceftaroline? I mean, it 22 does have some enterobacteriaceae activity,</p>

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1 pseudomonas --	1 DR. COX: Oh, yeah, yeah. So I think what
2 DR. REX: It does. It tips over on ESBLs.	2 we're trying to do is we're trying to figure out, you
3 So you know, may -- this might have been a place for	3 know, X-1 and its activity against pseudomonas
4 ceftaroline avibactam, which actually has never been	4 aeruginosa. So I mean -- so it would probably be
5 developed. It's a developable drug, but it's never	5 something along the lines of, you know, X-1 is active
6 been developed. So okay. So but I don't think you	6 in the treatment of or, you know, it can be used to
7 can stand ceftaroline up on its own because the ESBLs	7 treat the following infections when caused by
8 knock it over.	8 pseudomonas aeruginosa.
9 Other ideas?	9 Now, if we take, you know, one of these more
10 I mean, this for me was one of the harder	10 abbreviated pathways, it's going to have greater
11 things about it, was coming up with the fact that I	11 uncertainty around it. So I would expect, too, that
12 could only find one choice that I was comfortable	12 it would also be a reserve this use for when you don't
13 with. And I -- you know, so I did find the literature	13 have anything else, you know, available.
14 on it. And I'm just delighted here there's a study	14 And then depending upon where we end up,
15 that's not published that might be helpful.	15 because we've still got a lot more to discuss here as
16 On the panel, anybody else have comments on	16 we work down these various different tiers, the degree
17 A, questions you want to get at?	17 of sort of, you know, reservation and whether there's
18 AUDIENCE MEMBER: (inaudible - off mic).	18 any sort of formal program in place to preserve the
19 DR. REX: So in the -- so use a quinolone.	19 drug, I think you'll see that, perhaps, as we start to
20 Use moxy -- so what's the -- I don't have that in my	20 work through some of these other scenarios where
21 head -- rate of activity in moxy versus pseudomonas.	21 there's even greater uncertainty.
22 Anybody know?	22 So that's off the top of my head because we
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1 (Crosstalk)	1 haven't even worked through all these yet. But if we
2 DR. REX: Very high proportionate resistant.	2 can get to the -- you know, the information that will
3 So that might -- it's a good extra thought. But is	3 help us understand how the drug works, we'll be in a
4 moxy, you know --	4 much better position to be able to figure this all
5 AUDIENCE MEMBER: (inaudible - off mic.).	5 out. And it's very hard. I mean, you know, you can
6 DR. REX: Huh?	6 see we're all struggling with trying figure out how do
7 AUDIENCE MEMBER: (inaudible - off mic.).	7 you actually discern the -- you know, the efficacy of
8 DR. REX: But what about nosocomial	8 the drug and then gather safety information.
9 pneumonia? No.	9 DR. REX: I couldn't imagine anything less
10 (Crosstalk)	10 than the wording around use in only patients with
11 DR. REX: Yeah. So you're in the same place	11 limited treatment options and get an expert to help
12 you are with the erta, which is you've got -- I mean,	12 you do it.
13 you might know some -- this -- we can look at it. All	13 DR. COX: Yeah. Yeah, because these are --
14 right.	14 I mean, this is really, I mean --
15 UNIDENTIFIED FEMALE SPEAKER: John, my	15 DR. REX: Yeah.
16 question -- or I guess maybe it's to the regulators --	16 DR. COX: -- a very, very limited program.
17 is how do they see data from this type of scenario.	17 So it does seem like the indication would need to
18 You develop your drug. What's getting in the label?	18 have, you know, reservations and maybe even a program
19 DR. COX: It might be a little premature. I	19 around it.
20 mean, we're trying to figure out, well --	20 UNIDENTIFIED FEMALE SPEAKER: And what body
21 UNIDENTIFIED FEMALE SPEAKER: We're supposed	21 sites are you describing?
22 to go and tell this to our management.	22 DR. REX: So --

<p style="text-align: right;">Page 553</p> <p>1 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>2 DR. COX: So the question is, is what body</p> <p>3 sites are you describing. And you know, we would want</p> <p>4 data in the body sites because, you know, at least our</p> <p>5 experience has been we've showed some of these, you</p> <p>6 know, past experiences that, you know, there are drugs</p> <p>7 that don't perform well in some body sites. And</p> <p>8 sometimes -- I mean, you know, Paul went through a</p> <p>9 very nice discussion sort of helping us to understand</p> <p>10 that a little bit more. But sometimes it seems like</p> <p>11 we find that in the clinical trial.</p> <p>12 So you know, not having at least some</p> <p>13 experience to be able to have some degree of</p> <p>14 understanding about what's going on in a body site</p> <p>15 would be difficult. And you know, I would think, you</p> <p>16 know, as part of this, too, as you work towards that</p> <p>17 body site, you're going to get preclinical information</p> <p>18 that's relevant to that body site to the extent</p> <p>19 possible. Understand, you know, tissue levels,</p> <p>20 whether it be blister fluid or ELF, those sorts of</p> <p>21 things, to help you sort of as you build, you know,</p> <p>22 towards doing the clinical trial. And those would be</p>	<p style="text-align: right;">Page 555</p> <p>1 information from each of the several body sites. So</p> <p>2 you might want to do -- you know, if you're going to</p> <p>3 do two, you might shoot for, like, 50/50. Or, you</p> <p>4 know, if you think one particular site be -- might be</p> <p>5 a little more difficult, maybe you do, you know,</p> <p>6 70/30, or something like that.</p> <p>7 But you wouldn't want to end up -- and we've</p> <p>8 seen this sometimes in the past with, you know, two</p> <p>9 patients in this site, three patients in this site,</p> <p>10 you know, 100 in this other site and then, you know,</p> <p>11 expect that you have sufficient information to be able</p> <p>12 to draw conclusions about the -- what we sort of refer</p> <p>13 to the onsie-twosies in other sites where you really</p> <p>14 just don't have enough to be able to say too much of</p> <p>15 anything.</p> <p>16 So balancing it out across the sites of</p> <p>17 interest I think is a good way to think about this.</p> <p>18 Kenneth? And then we'll pop back over here.</p> <p>19 MR. HILLIN: I just wanted to make sure we</p> <p>20 did cover a topic. You specifically requested from an</p> <p>21 investor perspective. I'm not an investor. But --</p> <p>22 DR. REX: Well, then --</p>
<p style="text-align: right;">Page 554</p> <p>1 the sort of things you do anyways.</p> <p>2 DR. REX: Yeah, I should have put in a fake</p> <p>3 label. I was going to pitch for all three</p> <p>4 indications. That -- the -- that was, you know -- and</p> <p>5 in the sense that HABP and the UTI -- and the intra-ab</p> <p>6 got nice RCT data, UTI, you've only got the open</p> <p>7 label. And I was going to sort of loosely make the</p> <p>8 analogy to like (ph) the as (ph) voriconazole approval</p> <p>9 where you've got a nice big randomized trial in one</p> <p>10 disease and a related setting, related organism</p> <p>11 mucormycosis where you've got some open label data.</p> <p>12 And you sort -- you line it up with urine</p> <p>13 concentrations being really high and show that, you</p> <p>14 know, the urine also became sterile and do some stuff</p> <p>15 like that.</p> <p>16 I mean, so I was going to pitch personally</p> <p>17 for all three indications. I should have said that.</p> <p>18 DR. COX: Yeah. And usually, too, I mean,</p> <p>19 we have -- you know, had some discussions around this,</p> <p>20 too. It seems like if -- you know, if you're going to</p> <p>21 do the multi-body site approach, you don't -- you want</p> <p>22 to have some, you know, representative amount of</p>	<p style="text-align: right;">Page 556</p> <p>1 MR. HILLIN: -- I've seen you give nice</p> <p>2 talks previously to CAC (ph). And I wonder if you</p> <p>3 could comment from maybe a pharma investor perspective</p> <p>4 if you think about the cost -- and you talked about</p> <p>5 that -- and the time and then you think of the</p> <p>6 probability of technical success, both of the</p> <p>7 executing the trial -- of the trial, demonstrating</p> <p>8 what you set up to demonstrate of the regulators</p> <p>9 approving it, so both the technical and the regulatory</p> <p>10 success versus the likely commercial return, how you -</p> <p>11 - when you integrate all those things because that's</p> <p>12 what an investor thinks about. Do you think that's</p> <p>13 going to be -- what kind of scenario will that paint?</p> <p>14 DR. REX: So very briefly, I'll answer one</p> <p>15 part of it now, defer the others.</p> <p>16 So can I get a return on this product if I</p> <p>17 had it developed? I think the answer to that is yes.</p> <p>18 This meets all the criteria for a new kind of fire</p> <p>19 extinguisher for which there should be a value. And</p> <p>20 I'm going to -- if I can get it developed at a</p> <p>21 reasonable price, I get I can make a reasonable return</p> <p>22 on this one. I'd be willing to make the case.</p>

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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.	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?
8 UNIDENTIFIED MALE SPEAKER: Can I see the 9 statistics again, please, the chart?	7 So I'm going to -- let's push on because I 8 think we have covered these questions.
10 DR. REX: Oh, sorry.	9 So Scenario B, this one is chosen so the
11 UNIDENTIFIED MALE SPEAKER: So what --	10 meropenem results have -- are unchanged. What's
12 DR. REX: I keep going the wrong way. There 13 you go.	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 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,	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
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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 --	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?
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	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

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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 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 --
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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 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 --

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<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p>1 to ascribe those patients to failure. So now, this is 2 all spilling over into your other endpoints as well.</p> <p>3 So it becomes a real issue.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>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.</p> <p>7 Yes, ma'am?</p> <p>8 UNIDENTIFIED FEMALE SPEAKER: Yeah, I'm just 9 thinking about the previous comment by Tom --</p> <p>10 DR. REX: Into the microphone. Sorry.</p> <p>11 UNIDENTIFIED FEMALE SPEAKER: Sorry. Just 12 about the previous comment by Tom, yes, you -- it --</p> <p>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</p>	<p>1 Any other wisdom or -- Marco looks like he's 2 about to say something.</p> <p>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.</p> <p>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.</p> <p>20 And that's why we're open to alternative approaches.</p> <p>21 And so it's the entirety of the evidence 22 that matters. And we have to look at all aspects.</p>

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<p>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.</p> <p>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.</p> <p>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.</p> <p>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 --</p>	<p>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.</p> <p>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.</p> <p>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</p>
<p>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?</p> <p>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?</p> <p>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.</p> <p>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.</p> <p>22 So this one, the margins are the -- the</p>	<p>1 drugs are actually the same.</p> <p>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.</p> <p>8 Other insights or comments?</p> <p>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.</p> <p>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</p>

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1 some sort of an effect there.	1 .005. And then we do the Phase 3 in nosocomial	
2 So let's go on to Scenario D. So inhale,	2 pneumonia alone, so just picking one indication,	
3 exhale because now it gets awful. The culture-	3 picking the most -- the important one. And we assume	
4 positive rate is now about 5 percent, and there's	4 the things that are shown there that I won't read to	
5 absolutely nothing I can do about it. You know, I	5 you.	
6 just -- that's it.	6 And at the end of the day, I get, after	
7 So the program size explodes. At a 30	7 enrolling, 726 subjects. I have 24 and 12 on X-1 in	
8 percent margin and one-to-one, I might get down to	8 control with my target pathogen. And there are my	
9 1,276 for any one indication in order to get the same	9 made-up results. And if I want -- if I'm using a	
10 kind of crummy margins that we were getting in	10 boundary of negative 30 as my margin -- isn't that	
11 Scenario C. So you understand, that's -- that -- it	11 what I said? Where -- did I write a margin down?	
12 would take 1,300 patients to get at data as bad as	12 UNIDENTIFIED MALE SPEAKER: Thirty-five.	
13 Scenario C.	13 DR. REX: Thirty-five. Right. If I move	
14 If I bring the margin down at all, the sizes	14 one patient -- instead of it being 19 to 24, it's 18	
15 go up north of 2,000 patients. And maybe I could	15 to 24 -- I actually exceed the 35 percent non-	
16 really enrich (ph) for high-reach cases -- for high-	16 inferiority margin. Sorry I didn't write it down. So	
17 risk cases such as renal failure and more co-	17 -- and I'm not doing inferential statistics. I'm	
18 morbidities. But this, I think, is where the animal	18 signing up for no math, okay -- none. Instead, I'm	
19 rule question becomes of interest.	19 signing up for the P of .005.	
20 So Sumathi and I went back and forth on this	20 So now the discussion. Do these things	
21 a little bit. And this model doesn't exist. But	21 together create Tier C minus or D plus? Discuss.	
22 there's no reason to believe you couldn't do it, which	22 DR. TOMAYKO: John, is there any chance that	
1 is you can take a large enough mammal -- a piglet or a	Page 574	Page 576
2 rabbit -- you can put it on a ventilator and give it		1 you would be able to tell us whether or not target
3 nosocomial pneumonia. You know, I've got to assume		2 attainment was achieved?
4 that I could create something that looks a little like		3 DR. REX: Oh, well, absolutely. The desired
5 the human disease. But you know, Tom Walsh (ph) has		4 exposures were hit. And so it's like in Scenario A.
6 been doing rabbits like this for years, and they		5 You know, we hired a really good PK-ologist, and we
7 produce a very human-like pattern. I don't really		6 nailed it in our clinical program. And maybe we --
8 have reason to believe you can't do it. And then you		7 it's picking up on the idea that we actually dosed a
9 actually get into the notion of the clinical trial		8 couple of people with HABP, with VABP with single
10 being, effectively, a field trial. And you -- maybe		9 doses before we started the program just to be sure
11 you can throw in some informational (ph) control data.		10 that we were comfortable with our exposures. You
12 So here's the results. We've -- we did it.		11 know, you can do all those things. It's all right.
13 Sumathi and I got together and did a ventilated piglet		12 Absolutely, the drug -- and the drug gets
14 model somehow.		13 into the ELF, might or might not be able to do the
15 UNIDENTIFIED MALE SPEAKER: You've been		14 non-CF bronchiectasis study, depending on -- like, if
16 busy.		15 we're doing acinetobacter, I don't think I've ever
17 DR. REX: Yeah, I'll tell you what. We've		16 seen acinetobacter colonize in that. It might not be
18 been busy. It's been a -- we've had a busy month		17 a study, like, that you can do. But I can sure enough
19 since she suggested that I write this case. All		18 do an ELF.
20 right.		19 DR. TOMAYKO: But you're basically saying
21 So in the ventilated piglet model, 18 to 20		20 that all of these folks for the MIC of pseudomonas,
22 survival with X-1 and 0/10 with placebo, P equals		21 which is I think going to be something less than one,
		22 all the achieve (ph), the target exposure that they

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1 needed --	1 DAVID: But so I think what you -- yeah, I
2 DR. REX: Let's assume that.	2 think what you'd have to do -- I mean, I could go
3 DR. TOMAYKO: Okay.	3 through kind of a design that we went through thinking
4 DR. REX: Let's assume that we've got a good	4 about this particular sort of drug a while ago if this
5 exposure and that Paul Ambrose puts up one of those	5 is the right time to do that. Or I could wait until
6 plots like the other day and says, you know, it looks	6 later or not --
7 like it's in the right spot, you know. It's not a	7 DR. REX: Oh, no. There's no better time
8 guarantee, but it looks like it's in the right spot.	8 than now. So go ahead.
9 I think you must assume that.	9 DAVID: Okay. So what we were thinking
10 David (ph)?	10 about was a superiority design where you had your
11 DAVID: I just think -- I mean, again, it's	11 drug, X-1. And this would -- could either be combined
12 a huge amount of work, and you're amazing for having	12 with ertapenem or even meropenem, depending the
13 done it. But I think it shows that you can't do non-	13 sensitivity of your investigators to a new drug for a
14 inferiority for this sort of indication. The data	14 dangerous infection like pseudomonas. And I can tell
15 just become too fragile at the end of the day, and the	15 you that you do get pushback from investigators when
16 risk is too high. So I would reject the non-	16 you go out and talk to them about this in real life.
17 inferiority design for this sort of program.	17 So and you treat these patients. You try
18 DR. REX: And so let me be clear that I'm	18 and enroll patients with pseudomonas. You do all-
19 not actually going to propose a statistical	19 comers if you like. I would do all-comers. And
20 hypothesis. I'm just going to say it's a control and	20 within that population of pseudomonas -- and you have
21 it's small. And I'll bring you some external	21 to be careful about what centers you pick because if
22 controls, and I'll show you that people in the past	22 you do the trial in centers where there are very high
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1 with pseudomonas died a lot.	1 rates of carbapenem resistance, then everybody gets
2 DAVID: I think -- but again, I think if you	2 put on colistin. So you actually don't want to do
3 put in the context of a different design approach,	3 your trial there.
4 then it gets a lot easier in a way -- in some ways.	4 You want to do your trial where you have UDR
5 DR. REX: What is that design?	5 rates of carbapenem resistance, which is on the order
6 DAVID: A superiority approach using	6 of 15 to 20 percent kind of globally, and their
7 external controls and other controls, again, not	7 physicians are still using carbapenem mostly to treat
8 necessarily powered at P .05.	8 pseudomonas aeruginosa infections.
9 DR. REX: Well, let me be sure I've heard	9 So you then look -- so you treat everybody
10 what you said because you said use the external	10 with your drug plus ertapenem or your drug plus
11 control to show superiority. So I can do that right	11 carbapenem. But you specifically look from among that
12 now because I can tell you that, in the historical	12 group --
13 data, people with untreated nosocomial pneumonia or	13 DR. REX: This is open label --
14 incorrectly treated nosocomial pneumonia have a all-	14 DAVID: It's open label, yeah.
15 cause survival of about 30 to 40 percent.	15 DR. REX: This is open label, one arm.
16 DAVID: Yeah. So --	16 DAVID: Yeah, it's one label, one arm and
17 DR. REX: So I -- so it's -- so that's	17 historically controlled. And I'm going to get to this
18 buried down deep in here. And I bet I could do that	18 controls because you have to do a lot of work on the
19 with contemporaneous controls.	19 controls up front to make this all work. And I
20 DAVID: Right.	20 actually don't know the numbers because nobody's ever
21 DR. REX: I bet I could that with some --	21 done the work that I'm -- that I have in mind.
22 like, the Di Carlo data --	22 But you treat everybody up front with this

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<p>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.</p> <p>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.</p> <p>15 And then what you have to do --</p> <p>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.</p> <p>19 DAVID: Yeah.</p> <p>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</p>	<p>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.</p> <p>6 DAVID: Right.</p> <p>7 DR. REX: So --</p> <p>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.</p> <p>12 DR. REX: Okay.</p> <p>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.</p>
<p>1 response rate in the carbapenem resistance subset --</p> <p>2 DAVID: Yes.</p> <p>3 DR. REX: -- of that group.</p> <p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>6 DR. REX: So Ian Friedland, where are you? 7 You're summoned to the microphone.</p> <p>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 --</p> <p>16 DAVID: No.</p> <p>17 DR. REX: No? Sorry. One -- no, it's the 18 rate of dual resistance --</p> <p>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 --</p>

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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 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 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: 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.

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<p>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.</p> <p>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?</p> <p>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.</p>	<p>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 --</p> <p>4 DR. TOMAYKO: Well --</p> <p>5 DR. COX: -- within your institution. Is 6 that --</p> <p>7 DR. TOMAYKO: I think you're getting to the 8 point. I'm not arguing that.</p> <p>9 DR. COX: Yeah, I'm not being --</p> <p>10 DR. TOMAYKO: Let me tell you --</p> <p>11 DR. COX: I'm just trying to figure it out.</p> <p>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</p>
<p>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.</p> <p>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.</p> <p>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.</p> <p>18 DR. COX: And I'm not being critical. I'm 19 just trying to understand a little bit more.</p> <p>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</p>	<p>1 like.</p> <p>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.</p> <p>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.</p> <p>22 So I mean, I'm trying to figure out if you</p>

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<p>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?</p> <p>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.</p> <p>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.</p>	<p>1 DR. COX: Do tell.</p> <p>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.</p> <p>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.</p> <p>21 And then you know, it's also -- and I was 22 thinking about this a little bit. I was sort of</p>
<p>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.</p> <p>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.</p> <p>16 DR. TOMAYKO: No --</p> <p>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.</p> <p>20 DR. TOMAYKO: No, this is important, too, 21 because you just gave me a great idea for a field 22 study.</p>	<p>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.</p> <p>13 So I'm just trying to think through it.</p> <p>14 DR. DUDLEY: Yeah. Mike Dudley. The 15 medicine's coming out.</p> <p>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.</p> <p>22 So I -- where I thought David was going to</p>
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<p>1 go and which I think was on the superiority side is --</p> <p>2 is that you may -- what we may want to be thinking</p> <p>3 about, in fact, the multi-drug-resistant situation</p> <p>4 here, not for inferential testing and -- but perhaps</p> <p>5 for trying to see signals of superiority because if</p> <p>6 the drug has a big enough treatment effect, that's</p> <p>7 probably the population where you're going to be</p> <p>8 seeing that.</p> <p>9 So I never thought I'd see myself arguing</p> <p>10 for a superiority, but I do think that if the</p> <p>11 properties that were described in the case, that of</p> <p>12 being able to go where you think the biggest treatment</p> <p>13 effect may be.</p> <p>14 And then thirdly, I was thinking about the</p> <p>15 population. And you know, the anti-PCRV (ph) antibody</p> <p>16 work that's been done with pseudomonas, the trials</p> <p>17 that were done in 40 hospitals in France enrolled 30</p> <p>18 patients with pseudomonas infections in nine months.</p> <p>19 And so perhaps maybe specifying a patient population</p> <p>20 that's particularly high risk, which they identified</p> <p>21 as having tracheal bronchitis, might be a population</p> <p>22 where we could go and see that treatment effect.</p>	<p>1 known infections because this dataset is small. And</p> <p>2 that's something that our community looks at when we</p> <p>3 decide to bring these drugs in.</p> <p>4 And then perhaps -- the next place I could</p> <p>5 see early use would be in -- if, God forbid, there was</p> <p>6 an ICU kind of problem where we had a particularly</p> <p>7 nasty organism that we knew about that was</p> <p>8 circulating, you know, that that would be another</p> <p>9 place where -- thank Heavens I haven't had to do that</p> <p>10 -- but we -- where you could envision tapping into</p> <p>11 something like this.</p> <p>12 But we'd want to see more clinical data,</p> <p>13 whether that's Phase 4 -- you know, however we got it</p> <p>14 before we moved on. And I think that's largely what's</p> <p>15 happening, at least in our hands and in those around</p> <p>16 the country with the two new agents, even though</p> <p>17 they're kind of relatives of drugs we know well with</p> <p>18 the ceftolozane/tazo and the ceftazidime/avibactam.</p> <p>19 You know, we're using them in individual cases with</p> <p>20 the best susceptibility testing we can get and getting</p> <p>21 experience with them before we think about broader use</p> <p>22 -- in stewardship programs, you know, in a very kind</p>
<p>1 But I vote for the animal rule.</p> <p>2 DR. COX: You know, I would vote against it.</p> <p>3 DR. REX: Sorry. So sort of Helen and then</p> <p>4 David. Sorry. We're going to go back and forth.</p> <p>5 DR. BOUCHER: Okay. So I would just say as</p> <p>6 much as I agree with a lot of what John said, from a</p> <p>7 clinical perspective, especially in Scenario D, I</p> <p>8 think that the way the drug would be used would be in</p> <p>9 those settings like my first patient that we talked</p> <p>10 about where we know that we've got nothing else to</p> <p>11 offer, or we know that --</p> <p>12 DR. REX: Okay. But you're talking about</p> <p>13 your first patient from your presentation --</p> <p>14 DR. BOUCHER: From my presentation.</p> <p>15 DR. REX: -- from this morning.</p> <p>16 DR. BOUCHER: The lady with the MDR</p> <p>17 Klebsiella that was resistant to everything except</p> <p>18 colistin, including the two new agents, where this</p> <p>19 drug might offer something that's potentially</p> <p>20 tolerable to this woman for whom colistin really</p> <p>21 wasn't an option and that, through our stewardship</p> <p>22 program, we would gain some experience in people with</p>	<p>1 of -- in a way that probably our sponsor colleagues</p> <p>2 don't like to hear. But that is what's happening, I</p> <p>3 would say.</p> <p>4 So I think the answer to your question on</p> <p>5 the prior example maybe is a little more difficult.</p> <p>6 But I find it hard to imagine in 2016 with the way</p> <p>7 things are working where I work that we would be able</p> <p>8 to think about using this stuff empirically at this</p> <p>9 point.</p> <p>10 DR. COX: So that's helpful, Helen. So that</p> <p>11 sounds like situations where culture results tell you</p> <p>12 that you essentially don't have options or in the</p> <p>13 setting of ICU outbreaks with the particularly</p> <p>14 problematic organisms circulate around where you have</p> <p>15 a resistance profile that tells you you don't have</p> <p>16 other options or you have very, very, very few what --</p> <p>17 other options.</p> <p>18 Okay. Thank you.</p> <p>19 DR. REX: We need to talk about the</p> <p>20 economics of that at some point.</p> <p>21 So David?</p> <p>22 DAVID: Yeah, I was just going to Ed's</p>

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<p>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.</p> <p>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.</p> <p>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.</p> <p>19 DR. REX: Right (ph), go ahead, please. And 20 introduce yourself.</p> <p>21 MR. WARREN: So Travis Warren (ph) from the 22 U.S. Army.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>21 DR. NAMBIAR: Yeah, I thank you for your 22 comment. And that's what's probably (ph) was the last</p>
<p>1 Could you go back to the previous slide from 2 this one? It's the one where you introduced the 3 animal model.</p> <p>4 DR. REX: I think it's this one.</p> <p>5 MR. WARREN: Next one.</p> <p>6 DR. REX: Yeah. Well, so I've got some 7 made-up data with the animal model here.</p> <p>8 MR. WARREN: Okay. So well -- so it was --</p> <p>9 DR. REX: And so -- and by the way, this is 10 --</p> <p>11 MR. WARREN: There was the one --</p> <p>12 DR. REX: -- kind of like the animal model -</p> <p>13 -</p> <p>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 --</p> <p>19 DR. REX: Oops.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>20 DR. REX: And Lu to -- so Ed -- Lu and then 21 Ed.</p> <p>22 DR. BORIO: And I know you asked the</p>

<p style="text-align: right;">Page 605</p> <p>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?</p> <p>9 DR. NAMBIAR: It will -- so I think the 10 approval for levofloxacin was levofloxacin versus 11 placebo.</p> <p>12 DR. REX: So was the answer that you 13 typically do it this way?</p> <p>14 DR. NAMBIAR: Yeah.</p> <p>15 DR. REX: Right, since this is the model you 16 made up. So I was --</p> <p>17 DR. NAMBIAR: Like --</p> <p>18 DR. REX: -- hoping it was --</p> <p>19 DR. NAMBIAR: -- in humans.</p> <p>20 DR. REX: -- correct.</p> <p>21 DR. NAMBIAR: This is not good, you know.</p> <p>22 DR. REX: Well, and the -- and you know, it</p>	<p style="text-align: right;">Page 607</p> <p>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 --</p> <p>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.</p>
<p style="text-align: right;">Page 606</p> <p>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.</p> <p>4 DR. NAMBIAR: Yeah. I think maybe off by a 5 couple of numbers, but it was --</p> <p>6 DR. REX: Or less. Right.</p> <p>7 Ed?</p> <p>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.</p> <p>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,</p>	<p style="text-align: right;">Page 608</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>

<p style="text-align: right;">Page 609</p> <p>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.</p> <p>6 UNIDENTIFIED MALE SPEAKER: Is that a 7 combination product of two --</p> <p>8 DR. REX: Well --</p> <p>9 UNIDENTIFIED MALE SPEAKER: -- of different 10 types --</p> <p>11 DR. REX: It's --</p> <p>12 UNIDENTIFIED MALE SPEAKER: I mean, what --</p> <p>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.</p> <p>22 But to have the staff to make -- to have the</p>	<p style="text-align: right;">Page 611</p> <p>1 base exist so that Helen can do her experiment? I 2 mean, I -- ouch. I just want to observe that.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>22 So now we're down to can't do it, can never</p>
<p style="text-align: right;">Page 610</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>21 So let's pretend 500 courses a year. What 22 do I have to charge for each course to have the warm</p>	<p style="text-align: right;">Page 612</p> <p>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.</p> <p>4 So discuss. I told you the cases were going 5 to get harder. Everybody take a deep breath.</p> <p>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.</p> <p>16 Otherwise, it's just all getting mixed up in noise.</p> <p>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.</p> <p>22 So I'm not sure I've given any answers there</p>

<p style="text-align: right;">Page 613</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p style="text-align: right;">Page 615</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>21 And I think the last time we did something 22 like that was for isavuconazole, which is approved for</p>
<p style="text-align: right;">Page 614</p> <p>1 Marco's smiling at me fixedly. And Ed and 2 Sumathi are in deep debate.</p> <p>3 So opine on agents approved based solely on 4 external controls.</p> <p>5 DR. COX: So yeah, we were talking about 6 something else.</p> <p>7 (Laughter)</p> <p>8 DR. NAMBIAR: Well, I can reveal what that 9 is, is I was asked to find another job.</p> <p>10 (Laughter)</p> <p>11 DR. REX: Well, at least we all share the 12 pain here. That's the good thing.</p> <p>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.</p>	<p style="text-align: right;">Page 616</p> <p>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 from 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.</p> <p>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.</p> <p>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,</p>

<p style="text-align: right;">Page 617</p> <p>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.</p>	<p style="text-align: right;">Page 619</p> <p>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,</p>
<p style="text-align: right;">Page 618</p> <p>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</p>	<p style="text-align: right;">Page 620</p> <p>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</p>

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<p>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.</p> <p>7 DR. COX: Right. You know, thanks, Aaron.</p> <p>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.</p> <p>19 So it is possible that if you had a clinical 20 trial network this would -- you know, where you've go 21 a protocol that's stable, you're at similar or the 22 same institutions over time, it might give you some</p>	<p>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.</p> <p>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</p>
<p>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.</p> <p>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.</p> <p>15 DR. REX: Lynn?</p> <p>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.</p>	<p>1 just I've got something else I'm going to add in.</p> <p>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.</p> <p>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 --</p> <p>19 DR. REX: Oh, sorry. But wait. I'm sorry.</p> <p>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</p>

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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 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 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 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.

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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.	1 examples from yesterday I thought were particularly 2 striking and really underscored the importance of 3 doing that.
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 --	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. COX: Okay.	10 DR. REX: Mike?
11 UNIDENTIFIED MALE SPEAKER: -- killing of 12 cells.	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.
13 DR. COX: Okay. So you're picking the 14 target from other drugs, yeah.	21 So it -- maybe you could talk a little bit 22 about dose response control, where there we're not
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.	
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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.	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?
6 DR. COX: Yeah.	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.
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 --	9 DR. COX: Do you want to do this one, John?
12 DR. COX: Right.	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
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.	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.
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	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

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1 bit.	1 different way? Because yesterday, Paul presented a
2 So I think what you're -- what you want to	2 number of examples. And I think some of them were
3 do is you want to be -- there's going to be	3 related to pseudomonas -- the doripenem (ph) data, the
4 variability. So what the dose response curve	4 Ceftobiprole data, maybe some Tigecycline data. And
5 essentially does is it spreads your exposure response	5 if you do a pharmacometric analysis and you see that
6 out over a greater period -- a greater number of	6 when you achieve exposure, if you have those failures
7 exposures. Obviously, you could have somebody in the	7 already and you could make an argument that those
8 high-dose arm be among those patients that had	8 failures are dose-related, well, it just basically
9 actually the lowest exposures because of variability.	9 says I didn't have an antibiotic here.
10 So I think the dose response is, more or	10 So you can get a pretty good estimate of
11 less, just sort of spread the field. You'd obviously	11 what it's like not to treat one of these patients. I
12 not be wanting to choose the lowest dose that would be	12 mean, is that not correct, Paul? I mean, do you --
13 getting you 90 percent of your patients having a sub-	13 DR. AMBROSE: Yeah, I think what you're --
14 therapeutic exposure --	14 what you may be referring to is when you model the
15 DR. REX: No, I just said that I --	15 exposure response and you can basically use the
16 MIKE: -- but it would be --	16 intercept of the no exposure as kind of your
17 DR. REX: -- would not be willing to sign on	17 equivalent placebo by extrapolating back to that.
18 to the one -- to even the one mg per kg having a low	18 That then allows you to estimate the magnitude of the
19 target attainment because that sets me up for public	19 treatment effect.
20 shaming. You know, I --	20 UNIDENTIFIED MALE SPEAKER: And between what
21 MIKE: Well, I --	21 Paul -- I guess I'm taking it one step further. He
22 DR. REX: -- I'm just not willing to do	22 showed it -- made the point in a number of different
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1 that.	1 programs. And FDA probably has a number of different
2 MIKE: I don't think it has to be -- you	2 databases where maybe we could even fortify that
3 know, again, I don't think it has to be, you know, low	3 learning. And that could be useful information, and
4 target attainment. As I've -- as we've talked about	4 it may be better than an external control.
5 before, we always -- we pot our doses up to get 100	5 UNIDENTIFIED MALE SPEAKER Yeah. Well, I
6 percent target --	6 think you use -- you may be able to use the intercept
7 DR. REX: Right.	7 if you're doing that intercept pharmacometric method
8 MIKE: -- attainment. So --	8 to be able to compare that to the external control
9 DR. REX: But then you're --	9 data just to sort of see where you are in terms of
10 MIKE: So I think you could --	10 your treatment effect.
11 DR. REX: -- Paul and -- but Paul -- what	11 DR. REX: Ed. Sorry. We kind have been
12 Paul said was that I'm picking them both to be	12 going around.
13 efficacious. I mean, I -- it's -- you're asking for	13 DR. COX: Yeah. So I think our experience
14 both sides of this simultaneously.	14 has been, you know, similar to the debate that you and
15 MIKE: But again, the objective of trying to	15 John were having, which is, you know, most folks going
16 get, you know, information about safety as well as	16 into the serious infection, you know, the dose that
17 efficacy in that population having dose response or	17 they pick is going to be one that's going to be
18 exposure response as the ultimate analysis plan, that	18 ideally on the flat part of the curve. So I think
19 would do that compared to a simultaneous external	19 that's one part of it. I understand you're asking
20 control group. What are the thinking about dose	20 about a second part.
21 response or exposure responses in control?	21 So the -- you know, the idea of doing a
22 DR. TOMAYKO: Mike, can I just ask a	22 second dose, I mean, and most -- it seems like most

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<p>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.</p> <p>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 --</p> <p>10 I mean, you've got, essentially, a superiority design 11 where you've shown a clear effect.</p> <p>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.</p> <p>17 So is that -- that's part one of your 18 question, I think, right?</p> <p>19 UNIDENTIFIED MALE SPEAKER: I think that's 20 right. I mean, I think that what Paul's data showed 21 vividly there --</p> <p>22 DR. COX: Yeah.</p>	<p>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?</p> <p>5 UNIDENTIFIED MALE SPEAKER: Yeah, I think I 6 --</p> <p>7 DR. COX: Okay.</p> <p>8 UNIDENTIFIED MALE SPEAKER: But I think it's 9 more of --</p> <p>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.</p> <p>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 --</p> <p>16 UNIDENTIFIED MALE SPEAKER: Yeah.</p> <p>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</p>
<p>1 UNIDENTIFIED MALE SPEAKER: -- in the best 2 laid plans --</p> <p>3 DR. COX: Right.</p> <p>4 UNIDENTIFIED MALE SPEAKER: -- there are 5 still going to be patients who have low exposures 6 and/or higher (inaudible - off mic) ranges.</p> <p>7 DR. COX: Right.</p> <p>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.</p> <p>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.</p> <p>21 Is that fair? Have I answered your 22 question? Or was there another part to it? I</p>	<p>1 clearly get concentrations where we need it. So --</p> <p>2 DR. COX: Right.</p> <p>3 UNIDENTIFIED MALE SPEAKER: -- there's 4 always limitations that you're always going to have on 5 these things.</p> <p>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?</p> <p>12 DR. COX: Right. So --</p> <p>13 UNIDENTIFIED MALE SPEAKER: And so --</p> <p>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.</p> <p>17 UNIDENTIFIED MALE SPEAKER: Yeah. I --</p> <p>18 DR. COX: Okay.</p> <p>19 UNIDENTIFIED MALE SPEAKER: I would say that 20 we would pick doses that --</p> <p>21 DR. COX: Yeah.</p> <p>22 UNIDENTIFIED MALE SPEAKER: -- are above,</p>

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<p>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 --</p> <p>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.</p> <p>19 So I -- good. So we're -- so --</p> <p>20 DR. COX: Maybe just one last quick comment 21 and then I'll stop.</p> <p>22 It's just the issue of -- I mean, if you</p>	<p>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?</p> <p>5 UNIDENTIFIED MALE SPEAKER: Yeah, 6 biologically.</p> <p>7 DR. COX: Yeah, yeah, yeah.</p> <p>8 DR. REX: Because the exposure is --</p> <p>9 DR. COX: Yeah, and you say there's no data 10 for that.</p> <p>11 UNIDENTIFIED MALE SPEAKER: Not really --</p> <p>12 DR. COX: Okay.</p> <p>13 UNIDENTIFIED MALE SPEAKER: But --</p> <p>14 DR. REX: Yes, ma'am?</p> <p>15 DR. COX: All right. So a topic for a 16 longer discussion.</p> <p>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.</p> <p>21 So yes, ma'am? On to you.</p> <p>22 UNIDENTIFIED FEMALE SPEAKER: Okay. So the</p>
<p>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.</p> <p>10 And that's the difficult question.</p> <p>11 DR. REX: The exposure --</p> <p>12 DR. COX: So the de-convolution is very 13 difficult.</p> <p>14 DR. REX: So we're going to move on.</p> <p>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 --</p> <p>19 DR. COX: So you -- so --</p> <p>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.</p>	<p>Page 642</p> <p>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.</p> <p>9 DR. REX: Right.</p> <p>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.</p> <p>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.</p> <p>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</p>

<p style="text-align: right;">Page 645</p> <p>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.</p> <p>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.</p> <p>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</p>	<p style="text-align: right;">Page 647</p> <p>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 things 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.</p> <p>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.</p> <p>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.</p> <p>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</p>
<p style="text-align: right;">Page 646</p> <p>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.</p> <p>7 So I would advocate the registry element if 8 Helen thinks that's viable.</p> <p>9 DR. REX: A long-term registry after the 10 fashion of Fungiscope. Okay.</p> <p>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.</p> <p>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.</p> <p>21 But in discussions both in the fungal space 22 and the antibiotic space, there's been a lot of, I</p>	<p style="text-align: right;">Page 648</p> <p>1 data of carbapenem resistance in Europe.</p> <p>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.</p> <p>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.</p> <p>22 MR. DANE: Yeah, it might help you</p>

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<p>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.</p> <p>6 DR. REX: Kenneth?</p> <p>7 Sorry. Did you have a follow-up? No, you 8 didn't. Okay.</p> <p>9 Kenneth?</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>7 DR. REX: So both Ed and Marco should 8 comment.</p> <p>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.</p> <p>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.</p>
<p>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.</p> <p>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.</p> <p>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</p>	<p>1 You want to amend your question, I see.</p> <p>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.</p> <p>8 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>9 DR. COX: Which is? We'll give Marco a 10 chance to talk in just a minute.</p> <p>11 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>12 DR. COX: Sorry?</p> <p>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 -</p> <p>17 DR. COX: Most tests of cures are a clinical 18 response. The patient's better.</p> <p>19 AUDIENCE MEMBER: (inaudible - off mic).</p> <p>20 DR. COX: It's a clinical response. Yeah, 21 yeah. Okay.</p> <p>22 So just to clarify that issue, so usually,</p>

<p style="text-align: right;">Page 653</p> <p>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</p>	<p style="text-align: right;">Page 655</p> <p>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</p>
<p style="text-align: right;">Page 654</p> <p>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</p>	<p style="text-align: right;">Page 656</p> <p>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</p>

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<p>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.</p> <p>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 receptor (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,</p>	<p>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</p>
<p>1 which essentially is the (inaudible) nosocomial 2 pneumonia study.</p> <p>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 then supplement it after authorization 10 (ph) with other data that could bring us to a full 11 understanding of the benefit risk.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>

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<p>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</p>	<p>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</p>
<p>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</p>	<p>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.</p>

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<p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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</p>
<p>1 an appropriate agent for being out there, so.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>21 The second thing I've learned is that 22 everything is going to be based on having fabulous</p>	<p>1 data.</p> <p>2 Number five is we need to validate 3 ertapenem. Somebody needs to help me figure out how 4 to do that.</p> <p>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.</p> <p>11 So those are my six quick observations from 12 today.</p> <p>13 So again, thanks to all of you for your 14 participation.</p> <p>15 Ed?</p> <p>16 DR. COX: Thanks, John.</p> <p>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</p>

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<p>1 given what we know about microbes and their ability to 2 evade our therapeutics. So many thanks.</p> <p>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.</p> <p>7 In particular, I want to thank Sonita (ph), 8 too, who also helped us tremendously with our workshop 9 and getting it together.</p> <p>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.</p> <p>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.</p> <p>22 We're all working through this, you know, at</p>	<p>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?</p> <p>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.</p> <p>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.</p> <p>22 So I want to thank everybody. And we will</p>
<p>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.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>19 And with that, any final words, John? Or -- 20 all right.</p> <p>21 We will close the meeting. And thank you. 22 And we wish you all safe travels back to home and look</p>

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1 forward to seeing everybody again sometime soon.	1 CERTIFICATE OF TRANSCRIBER
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