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U.S. FOOD AND DRUG ADMINISTRATION

MONOCLONAL ANTIBODY DEVELOPMENT

10903 New Hampshire Ave.,
Silver Spring, MD 20993

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Reported by: KeVon Congo
Capital Reporting Company

<p style="text-align: right;">Page 2</p> <p style="text-align: center;">A P P E A R A N C E S</p> <p>1 Edward Cox 2 Edward Weinstein 3 Peter Potgieter 4 Wayne Danker 5 Edward Burd 6 Toni Perez 7 Kalavarti Suvarna 8 Scott Evans 9 Ann Eakin 10 Mayurika Ghosh 11 Mary Beth Dorr 12 Todd Black 13 John Rex 14 Sumati Nambiar 15 Kevin Outterson 16 Dmitri Iarikov 17 Filip Dubovsky 18 Dan Rubin 19 William Hope 20 Shampa Das 21 Tracey (Xiaohui) Wei</p>	<p style="text-align: right;">Page 4</p> <p style="text-align: center;">P R O C E E D I N G S</p> <p>1 MR. COX: All right. Welcome everybody and 2 thank you for joining us today for public workshop on 3 development of non-traditional therapies for bacterial 4 infections. And if we, you know, we think about this 5 area, we think about what's going on in the area of 6 bacterial diseases. You know we are at a time when 7 the antimicrobial resistance is getting ahead of us 8 and we need new therapies in order to be able to meet 9 patient needs. 10 We've seen an increasing interest over the 11 last several years to development of what we're 12 calling non-traditional therapies; so new types of 13 interventions that we hope will provide new therapies 14 for patients who need them; particularly, those with 15 more serious infections and infections caused by 16 resistant organisms. 17 Now folks who had been following this field 18 may recall that there was a Duke-Margolis workshop a 19 couple of months ago. That was a very helpful meeting 20 to sort of get the landscape of the different types of 21 products that are out there. And today, what we'd</p>
<p style="text-align: right;">Page 3</p> <p style="text-align: center;">A P P E A R A N C E S (Continued)</p> <p>1 Paul Ambrose 2 Helen Boucher 3 Ramya Gopinath 4 Michael Kaleko 5 Michael Bevilacqua 6 David Melnick 7 Brian Tse 8 Wes Kim 9 Vu Truong 10 Owen McMaster 11 Paul Grint 12 Jeff Wagner 13 Samareh Azeredo 14 15 16 17 18 19 20 21 22</p>	<p style="text-align: right;">Page 5</p> <p>1 like to do is continue those discussions and move 2 beyond, in essence, the inventory and sort of a first 3 blush look at the products and actually try and get 4 into some level of detail with regards to the 5 therapies, what they are, how they might be studied. 6 So you'll see we have a series of cases that 7 we'll be talking about, which we hope will prompt a 8 discussion on this very topic and we look forward to 9 hearing the groups thoughts on the different 10 development pathways. If we think about the term non- 11 traditional therapies, I just want to reflect on that 12 for just a minute. It's sort of an interesting name 13 and some might even argue it's a misnomer. I mean if 14 you think about early studies for type-specific anti- 15 pneumococcal serum and other anti-sera that were used 16 many, many years ago, maybe the smaller molecules are 17 not -- they're non-traditional. And if we go back to 18 our roots, some of the things that we're calling non- 19 traditional actually were sort of the earlier 20 therapies. 21 But I think what this reflects is that we're 22 more accustomed to the use of small molecule drugs</p>

<p style="text-align: right;">Page 6</p> <p>1 when we think about treating bacterial infections 2 clinically. And one thing that John Rex and Kevin 3 Outterson has taught me is that "It's very important 4 for us to get all on the same footing." So we'll 5 start out with a talk today from John and Kevin and 6 they'll walk through an overview of non-traditional 7 therapies and help us with some of this vocabulary 8 about these various different types of products as we 9 think through them that I think that helps us in our 10 discussions if we have a similar footing. Then we'll 11 also hear from Helen Boucher and Helen will give us a 12 clinicians' perspective. What she's seeing out in the 13 field. And that will remind us of the importance of 14 the work that we're undertaking here. And really you 15 know our real end goal here is to have new therapies 16 for patients.</p> <p>17 We will also walk through and group together 18 issues of pharm tox, (inaudible) microbiology 19 considerations that we think spans really the range of 20 the different case scenarios we present -- that we 21 will go on to present. So we try to group those 22 altogether thinking that they'll be applicable in</p>	<p style="text-align: right;">Page 8</p> <p>1 argue that a lot of what we know from the small 2 molecule antibacterial drugs and clinical trials to 3 show an effective a therapeutic is applicable, you 4 know, almost regardless of the mechanism of the 5 product. So we'll try and keep that in mind as 6 something to learn from.</p> <p>7 Obviously, there can be different 8 considerations depending upon the molecule, how it 9 acts. But there's a lot to be learned from what we've 10 done already. And then next sort of provocative 11 question. If the mechanism of action is known, should 12 we focus on mechanistic studies in patients or should 13 we be trying to show clinical benefit?</p> <p>14 So I think mechanism when understood can be a 15 very important tool and help us to understand what the 16 therapy can do, which particular types of infections 17 it may be able to treat or prevent. But as we think 18 about development and you move from the early stages 19 to the later stages, you obviously want to take an 20 advantage of your knowledge of mechanism as much as 21 possible. But ultimately what you want to do is, get 22 to the point of being able to show clinical benefit</p>
<p style="text-align: right;">Page 7</p> <p>1 general to the types of therapies we are talking 2 about.</p> <p>3 And then you'll see that we have a series of 4 cases and we'll try to make these interactive. We 5 will, to the extent possible, welcome questions from 6 the audience and from the folks at the table to try 7 and really have a rich discussion. And we know too 8 that folks are online. We're grateful for the folks 9 online that have joined in. There is an opportunity 10 to type in questions and we'll try and get to those as 11 time permits.</p> <p>12 So let me give you a few themes to think 13 about and keep in mind as we go through the workshop. 14 You know, I'll run through a couple of these and then 15 also just give you my impression. So the first theme 16 is just what we know about the clinical developments 17 of the Phase III trials for small molecule 18 antibacterial development drugs apply here or can it 19 help us. And so I'll just pause a minute and think 20 about that. If you think about what we're trying to 21 do, we're really trying to impact, you know, the 22 patient and the patients' disease process. So I would</p>	<p style="text-align: right;">Page 9</p> <p>1 for the patient. So there is this, I believe this is 2 progression over time from mechanism to clinical 3 benefit as you think about the development program.</p> <p>4 And really the question is here I think "Can 5 you demonstrate that the patient overall is better off 6 when the patient receives the therapy?" This seems 7 like really simple questions, but I think one of the 8 challenges we face here is that we're dealing with a 9 couple of different complex biologies. We're dealing 10 with the complex biology of the human then add in 11 disease, which leads to physiologic derangement, in 12 addition you've also got the bacteria present. And if 13 we think about bacteria even though they're single 14 cell organisms, they're almost like the Swiss Army 15 Knife in a single cell. Because if you think about 16 it, they have to do everything to survive and to be 17 able to do what they do just with a single cell. So 18 this really does I think underscore the importance of 19 looking at the clinical benefit of a product, you 20 know, in the patient because, you know, the 21 complexities here oftentimes will teach us new lessons 22 that we didn't anticipate and we've seen this over and</p>

<p style="text-align: right;">Page 10</p> <p>1 over with clinical trials. Things that we didn't 2 expect pop up. Sometimes we can explain them and 3 sometimes we're still left scratching our head. 4 So now moving from the philosophical mode of 5 the logistical somewhat of a transition but for lunch 6 in the back you'll see and it's all the way, so this 7 is the C and the B conference rooms, and A is a 8 different meeting beyond. But if you go beyond that 9 and over to your right, there's a window there and you 10 can check off on a paper if you'd like to get lunch 11 served from the group there can sometimes help a 12 little bit with regards to how quickly you can get 13 lunch. They ask that you get that in, if you can by 14 the break at 11:00, if you happen to be wandering out 15 there, feel free to also grab the paper and submit 16 that. The bathrooms are also just beyond and to the 17 right. Online folks I've mentioned that you can type 18 in questions and we will try and get to them as time 19 permits. 20 The meeting is being recorded. So there will 21 be a web recording available online, slides will be 22 online, and also there will be a transcript for the</p>	<p style="text-align: right;">Page 12</p> <p>1 MR. OUTTERSON: Yeah. Thank you, Ed. If you 2 notice, it's a lawyer and a doctor opening the 3 session. It almost sounds -- we should have a bad 4 joke about this job. A lawyer and a doctor walk into 5 the FDA and what do we get. John and I have been in 6 serious conversation about many of these issues for 7 the better part of a decade. And so we are 8 structuring this as a continuation of that discussion 9 hopefully something that's fruitful. 10 We've had some challenging conversations over 11 the years and we know that it'll continue to be that 12 way today with this group. But our perspective, 13 despite our academic backgrounds for both of us, is to 14 be practical. You know, we're very interested in the 15 science, we're also very interested in a practical 16 answer that helps the industry move forward. We can't 17 just wish this away. 18 We also don't think this is an FDA problem. 19 You know, it's not that they're being intransigent or 20 something. We need to pragmatically look and to find 21 a way to move forward in this space. Particularly 22 with all of the types of products, the non-traditional</p>
<p style="text-align: right;">Page 11</p> <p>1 meeting. We try to include in your packets in the 2 very back you'll see disclosures, so folks have 3 provided their work areas that may impact upon the 4 work that we're discussing today. And this is a 5 workshop and I think it's important just to remind 6 folks of that. So this is really just for the 7 purposes of discussion so that we can all learn from 8 each other and it really is not about generating 9 consensus. 10 So with that I want to thank you all for 11 joining. There've been a number of folks that have 12 worked very hard in putting this meeting together. 13 I'm very grateful for all the work that folks have 14 done. And the workshop and its value really comes 15 from everyone who is here and from all their 16 contribution, so for that I and we all are very 17 grateful. 18 I'm looking forward to the day's discussions 19 and look forward to learning from everybody. And with 20 that I'll turn the podium over to John Rex and Kevin 21 Outterson, who are going to start out with an overview 22 of non-traditional therapies. Kevin?</p>	<p style="text-align: right;">Page 13</p> <p>1 products that are coming to the market for the first 2 time moving towards clinical trials for the first 3 time, many of which are in the CARB-X portfolio. 4 So agenda for today; John and I, are going to 5 split this up and I'm going to do a little at the 6 beginning, John is going to do a lot in the middle, 7 and then you'll see me again near the end. So the 8 core problem is that in order to get, you know, 9 approval from the FDA and then also later get paid by 10 somebody who actually wants to use your drug, you have 11 to show value, you have to show distinctive value. 12 And we put it in red that this, we don't think this is 13 a regulatory issue per se. You know, this is 14 something we need to ask for any sort of product. And 15 it's just uniquely difficult sometimes, you know, to 16 show that with antibacterial products. And we're 17 having a problem in the past few years in this way. 18 For antibiotics, it's been difficult to 19 usually come up with a superiority sort of design. 20 The sort of design that you would see routinely in 21 many other drug classes. Last time the GAO looked at 22 non-inferiority designs, a lot of them were in the</p>

<p style="text-align: right;">Page 14</p> <p>1 anti-infective antibiotic space. And the reasons for 2 that are relatively straightforward and we'll talk 3 about that a little bit in the next slide. But the 4 key is that FDA could accept a non-inferiority study. 5 But what about the pairs, you know, what about the 6 hospital formulary committees, what about the, you 7 know, the folks who are making the decision on whether 8 or not, when there is a choice between an antibiotic 9 that's been generic for decades that has a cost per 10 course of treatment of \$120 versus an antibiotic which 11 is new and has a cost of 10,000 to 12,000 per course 12 of treatment. And the newer antibiotic only has a 13 non-inferiority study; how do you make that case to a 14 peer, how do you make that case to the formulary 15 committee at your hospital, Helen? 16 And so you'd expect for the bad news quote 17 here is that, you know, we need to be very clear that 18 the FDA is not the finish line. Here the finish line 19 is selling enough product so that the companies are 20 incentivized to continue to doing research and 21 development. And instead what we've seen recently is 22 companies get FDA approval and then having to let go</p>	<p style="text-align: right;">Page 16</p> <p>1 the trial more difficult, right. And as soon as you 2 know that vanco doesn't work, if you had a great 3 diagnostic to show to this patient that vanco wouldn't 4 work with what they have, you have to try something 5 else. It becomes unethical to continue. And so this 6 is why these trials it's difficult. I'm not saying 7 impossible. Some people have tried. And 8 occasionally, you know, there are superiority sort of 9 results that they can generate as well. But it's just 10 much more difficult than it is in many other drug 11 categories. 12 And when you think about just how you know 13 simple it is in other fields, I'll talk about this a 14 little bit. You know why we have so many therapies on 15 cancer in oncology, immuno-oncology and the ability 16 there for them to be the 3rd or 4th or, you know, 17 rescue treatment because they're able to identify the 18 patients and they have a little bit of time to do 19 that. And the fact that we're -- the victims, the 20 whole sector is victims of its own success and the 21 fact that most of the time the antibiotics we have 22 including the older generic ones actually work, they</p>
<p style="text-align: right;">Page 15</p> <p>1 their early development folks in order to conserve 2 cash to commercialize because they're not able to sell 3 very much. And this is not just a regulatory problem 4 is part of what we're saying. 5 So for antibiotics you know the paradox, we 6 do want them, we need these drugs, we need new drugs 7 for bad bugs and it's easy to show that in a lab 8 because in a lab you can fill a Petri dish with, you 9 know, resistant microbes and then try things to kill 10 them. Finding those patients is the more difficult 11 thing. And it's easier if you have a condition like 12 cancer where you have days or you can refer to a 13 referral center, or if it's a genetic condition that 14 you can test and know exactly what you're dealing with 15 and have some time versus a patient who is feeble and 16 to delay an hour is malpractice you know. And you're 17 going to have all sorts of other treatment. 18 And so the example we give here of limb- 19 threatening infection due to MRSA, you know, we can't 20 randomize, you know, methicillin versus the new. We 21 have to do something like vanco instead. And vanco 22 works most of the time. And so that's going to make</p>	<p style="text-align: right;">Page 17</p> <p>1 cure the patient. And when you're doing the -- when 2 the Standard of Care arm cures it's hard to improve up 3 on that, right. 4 The core here is that we're not really 5 measuring what we need in this area. The social value 6 of antibiotics is not just today's patients, although 7 Dr. Boucher will talk about today's patients. It's 8 also about, you know, tomorrow's patients and having 9 drugs available now or in the pipeline now to deal 10 with whatever comes down the pike in 5 or 10 years. 11 And it's very difficult to study the patients that 12 might emerge in 5 or 10 years today. John is 13 cackling. I think he thinks I understated that. All 14 right, I'll turn it over to John for a bit. 15 MR. REX: I was actually smiling because you 16 don't know how many hours of debate it took to 17 learning to say those words in that way about why and 18 what the problem is of why you are expected to solve 19 it anyway. 20 So I'm John Rex from F2G and Wellcome Trust. 21 Let me now talk a little bit about the question of 22 what are we, you know, talking about today. And the</p>

<p style="text-align: right;">Page 18</p> <p>1 question of what is a non-traditional has made our 2 collective heads hurt. It's been around with us for a 3 long time. I'm going to propose here an approach 4 that's perhaps a little different than has been used 5 in the past and that's to cook it down to 2 ideas. 6 It's either a non-traditional structure or it's a non- 7 traditional goal. And I like Ed's comment at the 8 beginning about "non-traditional is kind of it's 9 really what you are used to." It's a good way to say 10 that. If you look at traditional versus non- 11 traditional structures written down here, traditional 12 is a typical small molecule, you know sort of, 13 molecular weight 500 maybe up to 1,500, but it's a 14 thing you can draw a stick figure of versus a non- 15 traditional structure phage, lysins, monoclonals and 16 charcoal. But if you look in that, you know, the 17 monoclonals to antibodies, we've been using those for 18 centuries. So what's non-traditional about that? 19 Absolutely nothing whatsoever. It's a very 20 traditional product if you will. But in the current 21 context, it's a kind of a structure that we don't 22 typically think about.</p>	<p style="text-align: right;">Page 20</p> <p>1 you look mechanistically or do you look in terms of a 2 clinical benefit" and that's what this slide is about. 3 So when you're thinking about structure, the 4 development fundamentals for many of things that are 5 basically are in antimicrobials is pretty well known. 6 You know, if it does something in a way that we're 7 used to seeing a standard antimicrobial do, we have 8 pathways for that. That's the good news. Pretty well 9 developed. Now there are challenges that may come 10 from the math of small numbers. What if you want to 11 study one particular bacterium in the sea of possible 12 causes of that syndrome? That gets harder. What if 13 you want a particular just it's flat-out rare 14 Acinetobacter but you want it to be rare. Then the 15 hunt for that pathogen is hard. And ditto for rare 16 events. When you get down into small numbers, you've 17 got the problem of small numbers and I'll -- we'll 18 loop back around in a minute to diagnostics as a 19 possible aid here, but not the one you might wish for. 20 The idea of a non-traditional goal I think is 21 under explored territory. So I've already mentioned 22 the idea to consider a product or a method of use of a</p>
<p style="text-align: right;">Page 19</p> <p>1 And then there is another direction to think 2 about here, as opposed to what does it look like; it's 3 what is it you want it to do. And here the 4 traditional end is treatment or prevention of a 5 standard infection. No matter what's inside the box 6 if what it's doing is killing some bacteria in a way 7 that in theory should treat your pneumonia then that's 8 kind of on the more traditional end, even though maybe 9 the shape of it is unusual. 10 Something that we're -- I hope we are going 11 to spend some time on today is the idea of non- 12 traditional goals and what if your goal is to do 13 something that is more at a community benefit at a 14 level. So Kevin just talked about the patients of 15 tomorrow, which is all of us, you know, one day we all 16 of us are going to be -- will be pleased to not be 17 carrying some highly resistant bacteria. So what if 18 you were working on something that prevented the 19 acquisition or the development of a resistant strain, 20 or maybe there's something with your microbiome that 21 had that consequence. And I thought it was 22 interesting the way Ed asked the question here "would</p>	<p style="text-align: right;">Page 21</p> <p>1 combination or anything else you want imagine that 2 prevents resistant or prevents resist acquisition of 3 resistance. Such an end point may lack immediate 4 clinical correlate for me if I'm the one taking. Let 5 me emphasis here what I'm talking about, not talking 6 about TB where you know preventing resistance 7 developing in the course of a 6 months course of 8 therapy matters to me as an individual because if 9 resistance develops, I will fail, my therapy. 10 What about something where it's over and done 11 within a flash. With pneumonias reasonable use of 12 short-term endpoints that's because most of it is over 13 within a few days with skin infections. So it may be 14 that my infection gets treated effectively. But what 15 if I'm left, colonized with resistant strain, maybe in 16 the future I get another infection or maybe in the 17 future I hand it off to somebody else. How do I show 18 the value of that to society? Is it adequate to show 19 impact just by surveillance or do we need to prove 20 fewer resistant infections? 21 A couple of bits of language that you need to 22 be careful with today. Alternatives to antibiotics is</p>

<p style="text-align: right;">Page 22</p> <p>1 a bit of language that I try not to use very much 2 because it's such a broad term sometimes taken to be 3 the same as non-traditional, sometimes taken as a 4 superset of interesting physical devices like a super 5 smooth catheter that nothing can stick to. I mostly 6 just treat this idea as being non-traditional. 7 The phrase potentiator or enhancer is harder 8 to get away from. But the difficulty with these is 9 that -- these two words is that they tend to be 10 applied to a variety of disparate situations and I 11 generally find them too ambiguous. But if you have to 12 use them because I'll find -- I'm going to use them in 13 just a second on the slide -- you just have to 14 carefully define what it is that you're talking about, 15 just be careful that this word doesn't always mean to 16 somebody else what you think it so obviously means in 17 your head, just be careful with it. 18 There are some other potential benefits that 19 get brought up for non-traditional products that I 20 don't want to recognize now. They often have a very 21 attractive intuitive feel to them. It's narrow, which 22 is nice, less pressure on other bacteria. Its narrow</p>	<p style="text-align: right;">Page 24</p> <p>1 the one which you are going to restore the base 2 product. The base product used to work some mechanism 3 of resistance has risen and the add-on somehow undoes 4 that, undoes that I'm sorry. So the classic here 5 would be a beta-lactamase inhibitor and a beta-lactam. 6 You're restoring a previously functioning drug to 7 functionality by protecting it from beta-lactamase. 8 Category two is that of transforming. The 9 add-on enables the base to do something really new. 10 We have a lot of drugs for gram-positives where we 11 know the target is present inside gram-negatives, but 12 the drug just doesn't get there -- so if you somehow - 13 - or gets flexed out. So if you somehow cause the 14 drug to either get in or stay in, you might transform 15 a gram-negative drug with a -- sorry, gram-positive 16 drug with a gram-positive mechanism into a gram- 17 negative drug. So that would be an idea of 18 transforming an existing tool. 19 The third category is the one that 20 scientifically is the most intriguing. The first two 21 you know they're mechanistically pretty 22 straightforward and you know we have people -- we've</p>
<p style="text-align: right;">Page 23</p> <p>1 can also be a problem for development. It works via 2 the host and hence resistance can arise. It will have 3 fewer side effects. All those things might be true, 4 but you're still -- you got to prove those things and 5 through that actually just show the core value that 6 somebody should pay for. That is, it still needs to 7 do something useful and we need to be able to say "who 8 would get that benefit" and we need to be able to 9 measure that benefit. 10 So potentiators and enhancers, two words I 11 said I didn't want to talk about, but there you go, I 12 have to talk about them and that shows how hard it is 13 to get rid of these words. And a little bit about 14 diagnostics. There are a lot of products that are 15 functionally add-ons and I realized in working through 16 the slide last night that I really should've labeled 17 this about the add-ons. Where you take a base product 18 of some sort and you add something to it, and I've 19 labeled it here P for Potentiator, but E for Enhancer, 20 and A for add-on. And that add-on thing improves the 21 base product. And I think there are three useful 22 subdivisions of this strategy to recognize. First is</p>	<p style="text-align: right;">Page 25</p> <p>1 either used those in the case of restore or in the 2 case of transform they're being actively pursued. But 3 the third category is one where I've not seen as much 4 successful work. And that's the idea of an effect via 5 the host where maybe it activates the immune system or 6 it inhibits a varicose mechanism. Scientifically, 7 I've always been intrigued by this and wish to see 8 them work. They run into a problem however. 9 And these are the problems that occur when 10 you get into these categories. For many of the 11 products in this space standard tools generally seem 12 to work like BL, BLIs, we've now got several of those 13 studied and approved. But there are three specific 14 recurring issues when you're looking at the add-on 15 thing. The first is that of MIC. If the add-on 16 doesn't create a measurable MIC, you have to come up 17 with some other way to think about dose selection. 18 And I've labeled it is a problem in this, but I think 19 it's one that is more often solvable. I know Paul 20 Ambrose has had some good thoughts on this. And you 21 can probably solve it, but you still have to solve it 22 for your product in some fashion.</p>

<p style="text-align: right;">Page 26</p> <p>1 The second one is that of the rare pathogen 2 and this is a hard numbers game and diagnostics will 3 not entirely fix this. And I will devolve to a full 4 slide of that in a moment. And the other thing that 5 happens with rare pathogens is that the need for 6 adequate empiric therapy may complicate the challenges 7 showing the effect of the new product. Here what 8 you're often looking for is the ability to provide 9 some empiric coverage for other things, while look -- 10 while your product is the only thing that treats the 11 target pathogen.</p> <p>12 So imagine a novel antipseudomonal compound. 13 The only thing it does is to treat pseudomonas, which 14 you need to wrap around it an empirical therapy that 15 has a pseudomonad sized hole in it, just have a gap, 16 just right for your product. So your product can fill 17 in that one gap and all the other things that might 18 occur in a patient can be covered by something else, 19 but here the pseudomonas is left for you and you can 20 do that for pseudomonas, you can do that for 21 Acinetobacter. It's harder to do that for E. coli or 22 Klebsiella. It's harder to do that for Staph aureus.</p>	<p style="text-align: right;">Page 28</p> <p>1 So in that 15 percent, if you're going to add 2 something on to make the standard therapy better, it's 3 got to take your mortality down from 15 percent to 10 4 percent or 5 percent. You've got a -- you've only got 5 a small zone in which to work. And unfortunately, of 6 those 15 percent who are going to die are in the 7 standard trial setting and some of them are going to 8 die anyway. They have nosocomial pneumonia for a 9 reason. It's their underlying disease. So you may 10 only have a few percent in which you can actually 11 affect an improvement and that leaves you with a hard 12 problem. I may believe you that it makes it better. 13 It's just hard to measure it because you've got so 14 little room left in the -- so little clear blue water 15 left in the clinical trial.</p> <p>16 Pathogens and Diagnostics. Unfortunately, 17 diagnostics do not have the speed and efficacy of the 18 Star Trek tricorder. I truly wish for one of those, 19 but we're not there. And it leaves you with two 20 issues. The issue number one is that diagnostics do 21 not create cases. If the bacterium is rare, it is 22 rare. So if its only present in 1 of a 100, you still</p>
<p style="text-align: right;">Page 27</p> <p>1 It's tricky to find things that have exactly the right 2 gap that they'll fit what you're doing so that you can 3 provide empirical therapy for the first few days. An 4 empirical therapy is just so often needed in this 5 space.</p> <p>6 And then finally the Augment category you're 7 going to need to show an improvement on properly dosed 8 base therapy and this can be hard to achieve. Let me 9 emphasize that. If you look at the Augment category, 10 the idea is the base product plus the new thing has to 11 improve on the base and you're going to dose the base 12 correctly. It has to be -- there is no cheating 13 allowed here because nobody wants to be in an 14 inadequate therapy arm if at all possible. You 15 actually have to give a correct dose at a correct dose 16 and then you have to improve on that. And if you 17 imagine for a moment something that has a mortality 18 outcome, you know, nosocomial pneumonia or maybe 19 you've got a 15 percent rate of mortality in the 20 clinical trial that you can do. So -- and that's with 21 the correctly dosed therapy, the 15 percent mortality 22 so further rise and 85 percent success rate.</p>	<p style="text-align: right;">Page 29</p> <p>1 have to screen 100 to define that 1 and it is just you 2 know straightforward. It took me a long time to 3 understand that idea, diagnostics don't create 4 anything, you still have to pay to look through all 5 those cases.</p> <p>6 And issue number two, Kevin alluded to this, 7 is that time is ticking and referral is really not a 8 path. In cancer and rare diseases, we don't dawdle, 9 but there is time to make a diagnosis and refer as 10 needed. You've got days or weeks to get that sorted 11 out and get somebody to the right place.</p> <p>12 With trials of anti infectives, the acute 13 illnesses so not hepatitis C, not TB, you've got to 14 treat -- you've got to enroll people at that study 15 site and put them on therapy right now. And you can't 16 really drive them -- maybe you drive them across town. 17 That's about as far as you could go in general. So 18 they have to actually present at the site that's got 19 study going on. And that just magnifies the problem 20 of finding those rare cases. And it leads you into 21 what I call the multidrug-resistant center of 22 excellence problem, which is that hospitals work hard</p>

<p style="text-align: right;">Page 30</p> <p>1 to not be the hospital that has the billboard on front 2 it says "We have the worlds most resistant bacteria 3 but don't worry, right on in and get your heart 4 transplant because we have a great trial." Now, 5 nobody wants that sign out in front of the building 6 and I used to be the hospital epidemiologist facility 7 where I worked really hard to eliminate resistant 8 bacteria and yes, we might have one or two cases. And 9 then a couple of weeks later we would have none 10 because I would have been all over whatever the 11 infection control problem was that had to led to those 12 cases. So we used to have them, but I don't have them 13 anymore. So we're trying to enroll these cases a 14 little bit like chasing the phantom menace and it just 15 we want to make them go away. 16 So non-traditional goals. Pretty much 17 everything I've been saying has been presuming a 18 standard goal of treating or preventing a standard 19 infection. And most of the examples to be discussed 20 during the workshop seem to fit here with a few twists 21 and turns. And Ed posed the thematic question of, do 22 the ideas that apply for standard development, you</p>	<p style="text-align: right;">Page 32</p> <p>1 couple of cases we're going to explore this thing. 2 And I think with that it's back to Kevin. 3 MR. OUTTERSON: So as a lawyer sometimes your 4 -- your goal is to tell clients hard news, right. And 5 not that they can't do something, but they have to do 6 it maybe a different way or that things aren't the way 7 that they're hoping. And so for CARB-X, you know, we 8 have a lot of things going and we ask, well, why are 9 we involved in this? And actually the first person 10 that I called when we thought about creating CARB-X on 11 the outside of the government was, John. And John and 12 I put together the original proposal to BARDA. And 13 this is what we're doing now. You know we've, I 14 guess, it's \$504 million now over 5 years, we're 15 focused on supporting preclinical work all the way up 16 to and including the SAD/MAD studies in Phase I for 17 the priority drug resistant bacteria. 18 We're doing that through grants, non-dilutive 19 awards to companies all around the world. We've 34 20 companies under contract as of today, dozens more in 21 process. We had over 400 applications in 2018 that 22 we're still processing at this moment.</p>
<p style="text-align: right;">Page 31</p> <p>1 know, of pneumonias, are they correct? Do they apply 2 here or is there some variation that's required? I 3 think we should listen for that theme. 4 But what if the goal is really different? 5 What if the goal is benefit not just to the patient or 6 maybe even almost no benefit to that human being, but 7 rather a benefit to the community as a whole by 8 preventing the selection for resistance or the spread 9 of resistance. 10 And you could easily imagine this on the 11 basis of a combination therapy designed right now to 12 prevent the selection of resistance. We know that if 13 I treat your nosocomial pneumonia, gram-negative 14 pneumonia, there is a small but measurable rate of at 15 the end of the treatment, the end of the successful 16 treatment of your nosocomial pneumonia. Your E. coli 17 is gone, you feel better, but you actually now have a 18 resist -- strain that is resistant to what I treated 19 you with. So you are better, the war is over, but 20 you're now carrying something that the next time would 21 be harder to treat. What's the value in that and how 22 do you measure it? And actually one, and actually</p>	<p style="text-align: right;">Page 33</p> <p>1 And in that pile includes both traditional 2 and non-traditional. We have -- probably by the end 3 of this year we'll have certainly more than a dozen 4 non-traditional products in our portfolio. Most of 5 those are non-traditional products, non-traditional 6 goals, but some have that as well. 7 And so for CARB-X the thought is that we're 8 investing in things for which the regulatory path is 9 not entirely clear. If I was a venture capitalist 10 maybe I'd be more worried about that, from a CARB-X 11 perspective we thought it would be useful to prepare 12 the ground for all the companies and for whichever 13 ones make it, you know, to FDA approval. And to begin 14 to have this conversation, not for the benefit of any 15 one company, but for the benefit of the sector. So 16 that's our interest. CARB-X is nonprofit. You know, 17 it's non-dilutive, but our goal is to try to support 18 what's happening across all of the research that's 19 happening. 20 And so this is, you know, a complex chart of 21 -- each of these dots represents a CARB-X company that 22 has been funded. And on this chart wouldn't be</p>

<p style="text-align: right;">Page 34</p> <p>1 anything that we received for an application for 2018. 2 Like I said over 400 applications we'll be announcing 3 those awards beginning later in this year. But you 4 get a sense of, you know, we have some products that 5 are a known class and a known mechanism and we rate 6 those as lower risk, but not as innovative. Some of 7 the known mechanism, but there's a new class, right, 8 so there is additional risk, because it will be the 9 first time that that class made it through. Some are 10 both a new mechanism and a new class, right. And some 11 are completely non-traditional there's never been that 12 particular type of thing approved by the FDA. 13 And the sense of this slide that you should 14 take away is that CARB-X wants to invest in things 15 across all of these ranges, you know, lower risk and 16 higher risk and that we have an interest in, in 17 supporting all of these. People ask all the time, 18 which is your favorite CARB-X company and I have four 19 daughters it's like asking me which one is my favorite 20 daughter, right. You know, we love all of our 21 companies and we want this sector to succeed. 22 So we're helping the ecosystem. We've had</p>	<p style="text-align: right;">Page 36</p> <p>1 So one of the examples John used is maybe your 2 nosocomial pneumonia was cured in you, but now you 3 carry a resistant bacteria. But move that even more 4 to a population level what if the only value for this 5 additional product or the primary value was that it 6 reduced, it bent the curve of resistance in the 7 population at large. Is that a viable product? How 8 do we measure that value? How do we, you know, put 9 that into a study that the FDA recognizes as good 10 science, right? 11 And we see some of this with the HPV, you 12 know, it's impossible or difficult to run a clinical 13 trial that would run 20 or 30 years to see really the 14 HPV developing all the way into full blown cervical 15 cancer and it wouldn't be ethical to allow that to go 16 on. And so there's intervening markers and we're also 17 able to trace now the population level impact of 18 things like the pneumococcal vaccine and the HPV 19 vaccine, you know, outside of the patients themselves 20 population level benefit. 21 And so could these be benefits value that we 22 attribute to some of these products and that gets</p>
<p style="text-align: right;">Page 35</p> <p>1 these discussions many times with the folks at the FDA 2 and one thing that we hear back from folks at FDA is, 3 "Don't give us hypotheticals. Let's talk about actual 4 companies and actual products." But we don't want to 5 wait until the company has already designed their 6 Phase II trial or is having trouble raising money for 7 the Phase II trial, because of the lack of regulatory 8 clarity. So we're trying to help that with some real- 9 life examples today and tomorrow. And to give the 10 FDA, you know, the information it needs in order to 11 write draft guidance, but also the companies to begin 12 helping them think through it. Many of the companies 13 that we deal with at CARB-X don't have a Regulatory 14 Affairs Department. They're still just serious 15 science teams, you know they're all about, you know, 16 moving the science forward. They don't want 17 necessarily to be thinking about these issues. We're 18 trying to do some of that work, you know, for this 19 sector ahead of the time. 20 And some of these thinking to explore and, 21 John has alluded to some of this population level 22 benefits, you know, what can sort of clinical benefit.</p>	<p style="text-align: right;">Page 37</p> <p>1 worked in. 2 And this is the bad new slide. You know that 3 FDA approval is no longer the finish line. It's not 4 for this sector might be for others, because it does 5 not result in sales. The adoption curves have been 6 very flat and very challenging for the developers. 7 And this is the reason why some of the developers upon 8 approval of their drug have to conserve every ounce of 9 cash, because they know that they're not going to be 10 making much cash on sales, at least in the first 11 couple of years. And so if we had a way to do what's 12 in red here to have data that was compelling, not just 13 to the FDA, but to payers so that the companies could 14 be reimbursed, you know, adequately for this 15 innovative therapy then that's going to be very 16 useful. 17 Of course, we're in the context of good 18 stewardship, which is another way of saying we're -- 19 we're not going to over market, we're not going to 20 inappropriately sell, but from a company perspective 21 this is the CDC and CMS and physicians and the entire 22 subspecialty infectious disease docs trying</p>

<p style="text-align: right;">Page 38</p> <p>1 desperately not to use your product right. It doesn't 2 happen that way in other drug categories. 3 And so many of us in the room, you know, work 4 extensively on trying to get other incentives, pull 5 incentives, market entry words for things like them in 6 order to solve for some of these problems outside of 7 the scope of today, but this is the sort of thing 8 that's required. A couple slides to kind of drive 9 this point home. 10 This is from Alan Carr, Needham and this 11 shows all of the FDA approvals for antibiotics since 12 2009. And the most successful of these would be 13 considered a very lackluster immune-oncology drug. 14 And if you drew a line across, and this is all of the 15 drugs, this isn't a cherry-picked sample, this is all 16 of them. If you drew a line across at about the \$4 17 million sales per month, you know, and drew that 18 across, I think that, you know, I don't have any data 19 from these particular companies, but it would be hard 20 to have a, you know, a sales force -- I'm looking at, 21 John and a plant that was producing the drug and doing 22 better than breaking even at \$4 million, you know, in</p>	<p style="text-align: right;">Page 40</p> <p>1 the kind of in the same range of category, one is 2 chronic, one is acute and then you see that the 3 payments at the bottom that are put in the red box. 4 So, you know, just a dramatic difference in how much 5 is being paid and dramatic difference in the market 6 capitalization. I think this is a partially -- our 7 inability collectively to articulate the value of 8 these drugs to the people who buy them. And some of 9 that is the topic of today, but like, John and I've 10 said in many sectors this is not per se a regulatory 11 problem, this is a designing a trial to demonstrate 12 value to the people that need to understand the value; 13 the FDA as well as the payers. Back to, John. 14 MR. REX: So this is the last slide. And we 15 didn't get up here to say all these difficult hard 16 things just to be obnoxious difficult curmudgeons, all 17 right. That, you know, I am as a clinician these some 18 of these tools are just a -- they feel like they ought 19 to be really helpful. You know, it feels like it's a 20 good thing to do. I want them to work. But come back 21 to Ms. Swanson the CEO of Raytheon who said, you know, 22 beg for the bad news. You really need to know what's</p>
<p style="text-align: right;">Page 39</p> <p>1 monthly sales. And so it's another way of saying that 2 only two or three drugs approved since 2009 are 3 breaking even, okay. That's a crisis, right, because 4 we're not able to demonstrate value to the people who 5 buy the drugs in order to drive the sales, dollar 6 volume not unit volume, that we need to keep this 7 sector afloat. 8 And so thinking about, you know, two 9 compounds and maybe this is an unfair comparison, but 10 they're, you know, it's similar in terms of their 11 timing. And, you know, they both had kind of markers 12 of FDA attention, right fast track, priority 13 breakthrough and on Plazomicin, QIDP and LPAD. They 14 both go after serious things, important things. These 15 aren't trivial drugs. The number of patients 16 randomized actually Achaogen had a larger trial. They 17 were able to do a superiority to the standard of care 18 versus for Plazomicin was noninferior to Meropenem. 19 It did have a superiority result against Colistin. 20 Plazomicin is life saving, not to diminish the life 21 enhancing, right, but it's lifesaving. You see the 22 other results here the number of patients, you know,</p>	<p style="text-align: right;">Page 41</p> <p>1 going on and plan for it so that, you know, tears 2 today versus tears tomorrow it's another to say it. 3 So we really have to be clear on the non-traditional 4 nature of the product and whether that's even 5 relevant; the fact that it's monoclonal is that even 6 at all relevant to your development pathway. 7 And I think that more often than when it's -- 8 if the NT (ph) component is the structure, I think 9 that more often you can use traditional tools. And 10 we're going to talk about that and see to extent to 11 which that's correct and whether there are places 12 where we need to broaden our view on that. 13 The idea of a non-traditional community- 14 oriented goal, I think is something that we're only 15 now beginning to know how to talk about. And we are 16 going to have some discussion of that. And exploring 17 and refuting and expanding these ideas is a value to 18 the whole community. And, you know, we -- you know, 19 Kevin I have both worked long and hard to make it 20 possible for companies to find money to bring products 21 forward and we are desperate just to figure out ways 22 for them to show their value in the marketplace long</p>

<p style="text-align: right;">Page 42</p> <p>1 term, because, you know, deep down, you know my, the 2 reason I stand here is that I'm an ID doc who got 3 frustrated with infections I couldn't treat and so I 4 moved into industry to see if I could do something 5 about it. Ditto Kevin's story is that he got 6 fascinated by the prom resistance many years ago and 7 patent law and those things are actually quite 8 interwoven, ask him that story if you can at the 9 break, it's a -- yes, we're both here for the same 10 reason. We see the problem of developing these 11 products and we want to solve those problems. 12 And so let's turn this over to the next 13 speaker, but that's actually the setup for today is to 14 think about how to actually make things work in a 15 pragmatic way. And I believe next up is the world 16 famous, the internationally renowned, Dr. Boucher. 17 MS. BOUCHER: Thank you very much. Let me 18 see. Thanks so much and good morning everybody. I am 19 delighted to be here and thank you so much for the 20 invitation. My disclosures are shown here, I'm really 21 non-relevant to today's discussion. I'm going try to 22 pick up on what John and Kevin talked about and</p>	<p style="text-align: right;">Page 44</p> <p>1 be some kind of reasonable reimbursement in order for 2 my hospital to take it on board and use it. 3 So I may start with an example. I have two 4 sort of potential exemplars to present for non- 5 traditional therapies and one is for external wound 6 infections. These are really common infections that 7 happen after surgery and have risk factors that we 8 know and are very well established. So being a woman, 9 being obese, diabetic, a smoker and having a 10 complicated surgery are all known risk factors for 11 these infections. 12 So the lady I'm going to tell you about is 13 lady I took care of several years ago, 50-year-old 14 lady who was obese, a smoker with poorly controlled 15 diabetes who had about a coronary bypass. And she 16 comes back 2 weeks later is in a pretty classic way 17 with high fevers and puss from her sternum, kind of 18 the worst of the worst, she has MRSA. She has the 19 usual therapy, which is an attempt to debride it with 20 antibiotics and then she goes back to the operating 21 room and has to have titanium plates placed, because 22 there was not enough substance to close up.</p>
<p style="text-align: right;">Page 43</p> <p>1 provide a little bit of clinical insight and really a 2 number of questions, because I certainly don't propose 3 to have the answers. 4 I think as we heard we heard some sort of 5 general kind of requirements for these non-traditional 6 therapies and I just thought as a clinician, well what 7 would we need? We need these medicines to work. So 8 they need to be effective and they need to be 9 acceptably safe. Do they need to be better than 10 traditional antibiotics? Do they need to be additive 11 to traditional antibiotics? I don't know and we'll 12 talk about some examples. 13 There needs to be a feasible path to both 14 double study and use these things. And I think it's 15 really important to think about how we would use the 16 stuff that we're talking about in the real world in 17 the clinic. Because changing behavior is really hard 18 thing we've learned a lot about that in stewardship, 19 but I think, you know, docs do things the way we do 20 them and so when we're thinking about a new therapy 21 it's important to think about; well, what would be, 22 what we have to do to use it? And then there needs to</p>	<p style="text-align: right;">Page 45</p> <p>1 Unfortunately that didn't work, the wound broke down 2 again, back to the operating room for more surgery. 3 Now we're, you know, month and half into this she is 4 on appropriate antibiotics with Vancomycin, still 5 doesn't work. She still draining and still has MRSA. 6 They have to go in and take out the plates and close 7 her up again, another long course of therapy that goes 8 till August. So 8 months of therapy here. And guess 9 what? That doesn't work still, she comes back in 10 again with chest pain. She has more osteomyelitis and 11 now there is bacteria in her blood. So there's no 12 doubt that we've got a failure and indeed she has 13 endocarditis. So she gets an IV and more long-term IV 14 antibiotics. Twelve more weeks of therapy we finally 15 calm her down. There is no more surgery to be done, 16 because she's had so much surgery now and the plan is 17 lifelong antibiotics. So this lady who presented in 18 2007 end up living until 2018, 11 years after surgery 19 and she actually lived reasonably well. I wish I 20 could tell you that she changed her lifestyle, she did 21 not. She smoked until her death and ended up dying 22 really of lung disease. But she lived another 11</p>

<p style="text-align: right;">Page 46</p> <p>1 years after this horrible thing.</p> <p>2 So what if we had something to impact on this</p> <p>3 kind of an infection. These are, as I pointed out,</p> <p>4 they're common, they're very morbid. This lady was at 4</p> <p>5 the -- at the extent of morbidity I would say and some</p> <p>6 are fatal. So the question is how much is it worth to</p> <p>7 prevent one of these? Certainly to this lady it would</p> <p>8 have been worth a lot. To my hospital it would have</p> <p>9 been a lot. This lady was a big user of our ICU and</p> <p>10 operating room for a year and then to society. I</p> <p>11 think those are all questions that we're grappling</p> <p>12 with.</p> <p>13 So I'm going review briefly a study that we</p> <p>14 did not many years ago that was actually a failed</p> <p>15 study that I think may be instructive. So the idea</p> <p>16 was that maybe we could vaccinate these high-risk</p> <p>17 people before cardiac surgery to prevent these</p> <p>18 infections. So Merck did a study of vaccine against</p> <p>19 Staph aureus and it was a big undertaking, a yearlong</p> <p>20 study where people were vaccinated 2 weeks before</p> <p>21 surgery. We see those patients at that time so we can</p> <p>22 vaccinate them. And then they were followed for a</p>	<p style="text-align: right;">Page 48</p> <p>1 this is an example of a study that could be done in a</p> <p>2 very high-quality way in infection where a therapy</p> <p>3 like this could make a big difference.</p> <p>4 So let's look at something else. Now let's</p> <p>5 change gears and look at C-diff, C. Difficile. So</p> <p>6 this is an infection, it has a huge burden in the</p> <p>7 United States; 500,000 infections per year. There is</p> <p>8 lots of national efforts going on to prevent and</p> <p>9 control C-diff. We have public reporting. We have</p> <p>10 pay for performance. We know that there's a high risk</p> <p>11 of recurrence up to 25 percent and we again have well</p> <p>12 described risk factors being older, comorbid</p> <p>13 illnesses, the need to continue antibiotics are all</p> <p>14 associated with recurrence.</p> <p>15 So now I'll tell you about another lady</p> <p>16 patient of mine. This is -- now 58 is a bad age by</p> <p>17 the way. These lady is about 58-year-old lady with</p> <p>18 giant cell myocarditis who had a heart transplant back</p> <p>19 in 2013 and she showed up 2 years later with</p> <p>20 refractory clustering difficile colitis in CMV. Her</p> <p>21 heart was working fine and she had had no recent</p> <p>22 rejection. So she had had a complicated course 2</p>
<p style="text-align: right;">Page 47</p> <p>1 year. And the idea was to see who -- who got an</p> <p>2 infection treated with vaccine versus placebo. We</p> <p>3 enrolled 8,000 patients in the study and found out</p> <p>4 that there was no difference in the infection. So the</p> <p>5 same number of patients who got the vaccine got</p> <p>6 placebo got infection. So that was disappointing, but</p> <p>7 what we didn't expect, to allude back to, Dr. Rex's</p> <p>8 and, Kevin's comments about we find things that we</p> <p>9 expect and things we don't expect. We found that the</p> <p>10 people who were vaccinated were actually more likely</p> <p>11 to die from their Staph aureus infection have</p> <p>12 multiorgan failures so that was completely unexpected.</p> <p>13 So maybe something was negative about the vaccine. So</p> <p>14 the conclusion was that the vaccine didn't work even</p> <p>15 though there was a robust antibody response I'm not</p> <p>16 showing you all those data and that we had this</p> <p>17 increased mortality among vaccinated individuals.</p> <p>18 So the reason I'm presenting all this to you</p> <p>19 is that this was a study that was extremely well done</p> <p>20 in a reasonable amount of time, in a population that</p> <p>21 would benefit. So it can be done and this publication</p> <p>22 was back in 2013. So we do have exam, I'm presenting</p>	<p style="text-align: right;">Page 49</p> <p>1 years ago when she presented, giant cell is a very bad</p> <p>2 disease. She was in shock. She had external wound</p> <p>3 infection with her first surgery. Her transplant</p> <p>4 itself was somewhat complicated. She had pneumonia.</p> <p>5 She had kidney failure. She had a lung rehabilitation</p> <p>6 course and some early rejection, but then she got</p> <p>7 better. And so she shows up to us back in 2013 with</p> <p>8 sort of watery diarrhea and has a diagnosis of</p> <p>9 Clostridium difficile made and this goes on and on and</p> <p>10 on. So she is in November of '13 she comes back in</p> <p>11 April of 2014 with diarrhea again. This time she has</p> <p>12 two problems Clostridium difficile as well as</p> <p>13 cytomegalovirus. We see this co-infection not</p> <p>14 infrequently in heart transplant. She had no</p> <p>15 rejection and she makes her way all the way to the</p> <p>16 summer with recurrent diarrhea. She had total of five</p> <p>17 different episodes of Clostridium difficile. And we</p> <p>18 have been talking about what to do for her. We tried</p> <p>19 Fidaxomicin, which was then a new antibiotic that she</p> <p>20 would get a little better then she'd get worse. And</p> <p>21 we started to talk about doing fecal transplant, but</p> <p>22 at that time, as it still isn't, you know, approved by</p>

<p style="text-align: right;">Page 50</p> <p>1 the FDA there was a lot of concern about doing non-FDA 2 approved treatment. And then there was a concern in a 3 transplant patient about making her back to remik 4 (ph), because that's been seen in immuno compromised 5 people. So we hesitated to do it, but finally in 6 January of the following year we finally did it and it 7 was successful and she's been well today. So again a 8 huge amount of morbidity, but this therapy was 9 effective in this lady.</p> <p>10 So I think both of these cases teach us that, 11 you know, as we already know infections caused by 12 resistant pathogen is really bad it can happen to any 13 of us. And the traditional antibiotics, even if we 14 had all the antibiotics, we wanted it wouldn't be 15 always successful. That having these non-traditional 16 therapies is useful to our patients and to us. That 17 it's possible to study them. I think the study I 18 showed you is a study that could be done. And that 19 preventing infections is important. I think in either 20 of these cases anybody would agree if you were the 21 family member or these patients you would be happy if 22 we could have prevented that. Certainly I would be</p>	<p style="text-align: right;">Page 52</p> <p>1 certainly hope to see the CMS condition come through, 2 its still sort of pending, but the joint commission 3 has made stewardship mandatory in hospitals and long- 4 term care facilities, which is a great step forward.</p> <p>5 We also have a lot of data that stewardship 6 works, this is just one study showing the affect on 7 antibiotic resistance of having stewardship in place. 8 And then finally the reimbursement just one -- one 9 comment on that because we at IDSA have been so active 10 in this area. In principle, we hope that incentives 11 are robust, understandable and predictable to motivate 12 industry and private investors. We hope, as was 13 pointed out earlier that they target the greatest 14 areas of unmet need and that they're aligned with 15 stewardship as well as maintaining access so that all 16 of our patients could take advantage.</p> <p>17 We are grateful for all the push incentives 18 including CARB-X that we saw earlier. And then in 19 terms of pull the biggest need is in pull and things 20 like market entry rewards, per day review, tax credits 21 and others, the licensing model presented by Dr. 22 Gottlieb recently between CMS and FDA is very</p>
<p style="text-align: right;">Page 51</p> <p>1 happy if we could prevent it.</p> <p>2 Again preventing, I don't get paid 3 necessarily to prevent infections, to use expensive 4 therapies, to prevent infections in individual 5 patients, but if we could fix that I think that would 6 be very useful.</p> <p>7 So doing these trials is hard as Dr. Rex and 8 Outterson pointed out, and I think we have -- we don't 9 have a lot of templates to use certainly preventing 10 pneumonia is an area that's been studied and FMT is 11 now been studied a little bit for Clostridium 12 difficile, but we need a path and that's why we're all 13 here as, Kevin and, John pointed out.</p> <p>14 Coming back to the sort of requirements I put 15 up in quotes to begin with. The feasible path to 16 study uses is important and I think stewardship here 17 can be very helpful. Now that we have stewardship 18 programs in all U.S. hospitals, we have a mechanism by 19 which we could use these therapies in a safe and 20 ideally hopefully most effective way in hospitals. 21 And hopefully in long-term care facilities and in the 22 outpatient as well. And I'm just pointing out here we</p>	<p style="text-align: right;">Page 53</p> <p>1 interesting and we hope to learn more about that 2 shortly.</p> <p>3 So in closing, you know, in 2018 as I showed 4 in these cases, we clinicians are forced to use drugs 5 and non-traditional therapies with extremely limited 6 and often negative data. We have case reports for 7 Phage, which I'm sure we'll hear more about it and we 8 have small series for things like FMT and some 9 monoclonal antibody therapies, but we need more.</p> <p>10 The development is not going to be 11 straightforward as we heard the difficulty with non- 12 inferiority and superiority trials. And I think it's 13 likely that small clinical studies are going to be 14 needed and the best we can do and so the quality of 15 that data is very important. Clinical trial networks 16 I think are a way we could advance this ball. And 17 then maybe thinking about feasible studies focused on 18 more pragmatic endpoints things like the desirability 19 of outcome ranking or DOOR that's being developed and 20 has had some success already.</p> <p>21 And then I just wanted to say my personal 22 pitch for always thinking about looking at multiple</p>

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<p>1 body sites and infection sites and the utility of that 2 to us as clinicians as we think through this 3 complicated problem. And with that I'll just remind 4 everybody why we're all here. It's for our patients 5 and say thanks again for the invitation. 6 MR. COX: Thank you, Helen. And thank you, 7 John and Kevin too also for the talks. I think that 8 it really has helped to set the stage for the 9 discussions today. And while Owen is making his way 10 up to the podium let us go around the table too and 11 start with introductions. And if we could we'll start 12 with Ed Weinstein on my right-hand side. Ed? 13 MR. WEINSTEIN: Sure. Ed Weinstein, Clinical 14 Reviewer in the division of anti-infective products. 15 MR. POTGIETER: Peter Potgieter, President of 16 Clinical Development and Medical Affairs at Locus 17 Biosciences. 18 MR. DANKNER: Wayne Dankner, Chief Medical 19 Officer, Atox Bio. 20 MR. BURD: Edward Burd, Head of Regulatory 21 Affairs, Rebiotix. 22 MR. PEREZ: Toni Perez, Chief Medical Officer</p>	<p>1 MR. OUTTERSON: Kevin Outterson, Boston 2 University and Executive Director of CARB-X. 3 MR. IARIKOV: Dmitri Iarikov, Deputy 4 Director, Division of Anti-Infective Products, FDA. 5 MR. DUBOVSKY: Filip Dubovsky, Head of 6 Clinical Development for Infectious Disease and 7 Vaccines at MedImmune/AstraZeneca. 8 MR. RUBIN: Dan Rubin, Office of 9 Biostatistics CDER, FDA. 10 MR. HOPE: I'm William Hope from the 11 University of Liverpool. 12 MS. DAS: Shampa Das from the University of 13 Liverpool. 14 MS. WEI: Tracy Wei, Clinical Pharmacology 15 Reviewer, CDER, FDA. 16 MR. AMBROSE: Paul Ambrose, Institute for 17 Clinical Pharmacodynamics. 18 MS. BOUCHER: Helen Boucher, Tufts. 19 MS. GOPINATH: Ramya Gopinath, Clinical 20 Reviewer in the Division of Anti-Infective Products 21 CDER, FDA. 22 MR. KALEKO: Mike Kaleko, Head of Research at</p>
<p>Page 55</p> <p>1 at Combioxin. 2 MS. SUVARNA: Kalavarti Suvarna, Clinical 3 Microbiology Reviewer in the division of anti- 4 infective products CDER, FDA. 5 MR. EVANS: Scott Evans, Professor of 6 Epidemiology and Biostatistics at George Washington 7 University. 8 MS. EAKIN: Ann Eakin, Senior Scientific 9 Officer at NIAID. 10 MS. GHOSH: Mayurika Ghosh, Medical Officer 11 FDA. 12 MS. DORR: Mary Beth Dorr, Merck, Product 13 Development Team Leader for bezlotoxumab, ZINPLAVA and 14 Clinical Director. 15 MR. BLACK: Todd Black, Executive Director of 16 Antimicrobial Discovery Research at Merck. 17 MR. REX: John Rex, Chief Medical Officer, at 18 F2G Ltd. and Expert-in-Residence, Wellcome Trust. 19 MR. COX: Ed Cox, Director of the Office of 20 Antimicrobial Products, CDER, FDA. 21 MS. NAMBIAR: Sumati Nambiar, Director of the 22 Division of Anti-Infective Products, CDER, FDA.</p>	<p>Page 57</p> <p>1 Synthetic Biologics. 2 MR. MELNICK: David Melnick, Chief Medical 3 Officer at Spero Therapeutics. 4 MR. TSE: Brian Tse, I am a Project Officer 5 in Antibacterials Program at HHS/BARDA. 6 MR. LARSON: Joe Larson, Senior Vice 7 President, SMI. 8 MR. KIM: Wes Kim, Senior Officer at Pew 9 Charitable Trusts. 10 MR. TRUONG: Vu Truong, Chief Executive 11 Officer, Aridis Pharmaceuticals. 12 MR. COX: Great. Thank you. And now my 13 colleague, Owen McMaster, will talk to us some about 14 pharmacology toxicology considerations. Owen? 15 MR. MCMASTER: Good morning and welcome. My 16 name is Owen McMaster. I'm a pharmacology toxicology 17 reviewer in the division of anti-infective products at 18 FDA. And this morning I'm going to present the pharm- 19 tox perspective as we look at the development of non- 20 traditional therapies for bacterial infections. 21 The first point I would like to make is that 22 throughout this process sponsors are encouraged to</p>

<p style="text-align: right;">Page 58</p> <p>1 talk to the review teams, because this is very complex 2 development process and individual reviewers even 3 though they try as best as possible to adhere to ICH 4 guidelines et cetera, the review team for your 5 specific drugs is the best source of guidance 6 regarding the particular development product. 7 So this morning I'm going to outline the 8 traditional nonclinical safety assessments that would 9 normally occur during drug development and along the 10 way I'll point out the special considerations that 11 must be taken care of for non-traditional therapies. 12 And then my final slide will look forward to the 13 future of non-traditional therapies as we try to 14 address these issues. So nonclinical pharmacology and 15 toxicology really plays a central role in hazard 16 identification, characterization and risk assessment. 17 Pharma-Tox allows us to identify the target organs and 18 adverse events of special interest in addition to 19 determining what doses, durations, routes of 20 administration and exposures are associated with 21 specific toxicities. These all go together to inform 22 the dose selection for clinical trials.</p>	<p style="text-align: right;">Page 60</p> <p>1 Pharmacokinetic information is always useful 2 to predict margin of safety as we plan clinical trials 3 and there are -- these data are expected for 4 traditional drugs. For biotechnology derived products 5 there are no specific guidelines. For non-traditional 6 drugs we need to be quite careful, because there are 7 differences which may impact our interpretation of the 8 data. 9 For example, delays in expression of 10 pharmacodynamic effects relative to the 11 pharmacokinetic profile for example for cytokines may 12 -- affect our interpretation of the data, also 13 prolonged expression of pharmacodynamic effects 14 relative to plasma levels. And very importantly, 15 alterations in the PK profiles due to immune mediated 16 clearance mechanisms, which may affect the kinetic 17 profiles and interpretation of the toxicology data. 18 Traditional metabolism or biotransformation 19 studies are not needed for non-traditional drugs. 20 Traditionally genotoxicity studies would be conducted 21 prior to single dose clinical trials and the Ames 22 assay is one that we would need before clinical study.</p>
<p style="text-align: right;">Page 59</p> <p>1 This slide describes the regulatory 2 guidances, which form the context within which 3 nonclinical studies are conducted and the first two 4 are really the most important ones ICH M3 and which 5 describes the nonclinical safety studies for the 6 conduct of human clinical trials and marketing 7 authorization for pharmaceuticals. And ICH S6, which 8 refers to biotechnology derived products. There is a 9 reference in FDA guidance there as well and I refer 10 you to FDA.gov and ICH.org for further information 11 regarding these guidances. 12 So ICH M3 describes the studies that must be 13 conducted prior to first-in-human studies. The -- 14 they include pharmacodynamic, safety pharmacology, PK, 15 gene-tox and general toxicology studies. The first 16 two pharmacodynamic studies, which may be conducted in 17 vitro and in vivo provide us with the information 18 regarding the mechanism mode of action of the drug. 19 Safety pharmacology studies evaluate cardiovascular 20 effects, CNS effects and respiratory effects. And 21 both of these are identical for traditional and non- 22 traditional products.</p>	<p style="text-align: right;">Page 61</p> <p>1 For multiple dose trials, we would expect in vitro 2 chrome assay to be completed. For non-traditional 3 drugs genotoxicity studies may not be needed. 4 Biopharmaceuticals are not necessarily always 5 expected to direct with -- to interact directly with 6 the DNA or chromosomal material and especially for 7 dealing with large quantities of peptides or proteins 8 these may yield un-interpretable data. 9 Many biotechnology derived pharmaceuticals 10 are immunogenic, not all but many are and if such 11 antibody responses should be characterized in repeat 12 dose toxicity studies. The detection of antibodies 13 should not be the sole criterion for early termination 14 of preclinical safety study or modification of the 15 duration of the study, unless the immune response 16 neutralizes the pharmacologic and/or toxicological 17 effect. In most cases the immune response to 18 biopharmaceuticals is variable as with humans and I 19 recommend that you consult ICH S8 for further 20 information. 21 So ICH M3 decides the general studies, 22 general tox studies, which are required to support</p>

<p style="text-align: right;">Page 62</p> <p>1 early studies, early clinical trials. These are 2 usually conducted in two species and it should include 3 the most relevant species. The high dose should be 4 selected based on the maximum tolerated dose, the 5 maximum feasible dose, the saturation of exposure, the 6 limit dose or large exposure multiple depending on 7 what applies for your specific case. The duration of 8 the general tox study should be equal to or greater 9 than the duration of the proposed clinical trial.</p> <p>10 I mentioned relevant species in the previous 11 slide and by relevant species I mean species, which -- 12 within which the test material is pharmacologically 13 active based on the presence of a receptor or an 14 epitope and based on demonstrated tissue cross 15 reactivity, which would be similar to tissue -- to 16 human tissues. There are instances where there are no 17 relevant species in which case transgenic animals 18 expressing the human receptor maybe considered as well 19 as use of homologous proteins. There are however 20 cases where there are no relevant species and no 21 transgenic animals available and no homologous 22 proteins available. In these cases a limited toxicity</p>	<p style="text-align: right;">Page 64</p> <p>1 toxicological concerns for example, if the two drugs 2 have a similar target organ so that the combining of 3 the two products would be expected to produce some 4 enhanced toxicity that might be unacceptable, then we 5 would need combination studies; also if they're low 6 margins of safety or if the adverse events are 7 difficult to monitor in humans.</p> <p>8 By Stage 3 we would generally expect clinical 9 studies to be supported by a nonclinical combination 10 toxicity study if the above conditions apply. But 11 again, as I mentioned before, please consult with your 12 review team regarding the need for these studies. If 13 necessary these studies should be conducted prior to 14 clinical trials if there is a significant 15 toxicological concern, but these need to be conducted 16 only in a single relevant species for up to 90 days.</p> <p>17 It's not recommended for early stage entities 18 or for too late stage entities with adequate clinical 19 information. Also if the individual agents have been 20 studied for gene-tox, safety pharm and carci then we 21 wouldn't recommend combination gene-tox studies or 22 combination safety pharm or combination</p>
<p style="text-align: right;">Page 63</p> <p>1 study in a single species up to 14 days may provide 2 important information for off target effects.</p> <p>3 We generally expect two species, but one 4 species may suffice, if for example there is only one 5 relevant species that can be identified or if the 6 biological activity of the biopharmaceutical is well 7 understood. Also if two short-term studies have been 8 conducted and the tox profile has been shown to be 9 similar in the short-term study then a single species 10 may be used for the longer-term study.</p> <p>11 Non-clinical toxicology combination studies 12 are recommended in special circumstances in particular 13 if the individual agents are intended only for use in 14 combination. So for example, if drugs are going to be 15 co-packaged or if there is a fixed formulation also 16 for cases where there are recommendations for co-use. 17 Also if the nonclinical development programs have not 18 been completed for the individual entities, so we 19 would need co-packaging plus and the absence of a 20 complete nonclinical program to require nonclinical 21 combination studies. We also need them for two early- 22 stage studies if there are specific significant</p>	<p style="text-align: right;">Page 65</p> <p>1 carcinogenicity studies.</p> <p>2 So at the end of the pharm-tox studies we end 3 up with some very useful parameters, which may be used 4 to help guide the clinical trials that are conducted.</p> <p>5 So for example we get the no observed adverse effect 6 levels, which is the highest level of drug, which does 7 not produce adverse effects. For biologics we pay 8 more attention to the minimum anticipated biological 9 effect level. We also look at the pharmacologically 10 active dose. We will have theoretically at least 11 defined anticipated therapeutic dose range as well.</p> <p>12 And these all are considered and factored in as we 13 plan the first-in-human clinical trials.</p> <p>14 So for late Phase, as in Phase III clinical 15 trials, we need to consider the issues of reproductive 16 toxicity and carcinogenicity if the conditions apply.</p> <p>17 Reproductive toxicity studies are outlined in ICH S5 18 and these need to be conducted according to the 19 principles outlined in those documents. The 20 evaluation of toxicity to reproduction should be 21 conducted only in pharmacologically relevant species. 22 For products directed at a foreign target such as</p>

<p style="text-align: right;">Page 66</p> <p>1 bacteria and viruses, reproductive toxicity studies 2 may not be required. Again please consult with your 3 review team regarding the specifics. There may also 4 be public information based on the class of drugs that 5 you're evaluating.</p> <p>6 Carcinogenicity studies are conducted for 7 regimens, which are long term or if there is a 8 significant concern for carcinogenic risk. So for 9 example for drugs that are administered for 6 months 10 continually or repeated intermittent dosing they 11 should be conducted -- they should be supported by 12 carcinogenicity studies before the marketing of the 13 drug. If there is a significant -- I will add at this 14 point that we have under many circumstances received 15 carcinogenicity studies post marketing. If there are 16 significant concerns for risk then the -- for 17 carcinogenic risk, then the study should be conducted 18 to support the clinical trials. Please refer to ICH- 19 S1a and ICH M3 for additional information.</p> <p>20 So as we look to the future one a -- one idea 21 that's been raised by the ICH is the idea of using 22 animal models for disease in toxicology studies.</p>	<p style="text-align: right;">Page 68</p> <p>1 context of these studies. These are not very often 2 submitted to the agency so I would caution that if, if 3 tox studies are conducted in diseased animals that 4 scientific justification should be provided and that 5 concurrent control, historical control and base line 6 data be provided as there's not much experience with 7 these approaches. I also refer to ICH S6 for further 8 information.</p> <p>9 So in summary the nonclinical program for 10 non-traditional drugs should be as similar to that for 11 traditional drugs as is feasible or scientifically 12 justified. And perhaps the most important thing is 13 that sponsors should consult with the reviewing 14 division very closely in order to develop the 15 nonclinical programs. Thank you.</p> <p>16 MS. NAMBIAR: Thanks, Owen. Our next speaker 17 is Tracy Wei, is a reviewer in the Office of Clinical 18 Pharmacology and she's a member of the team that 19 provides support to the division of anti-infective 20 products. Tracy?</p> <p>21 MS. WEI: Hi. Good morning, everyone. My 22 name is, Tracey Wei. I'm a clinical pharmacology</p>
<p style="text-align: right;">Page 67</p> <p>1 Traditionally, we do toxicology studies in healthy 2 animals, which allow a very clean unconfounded view of 3 the toxic effects of the drug. I recently had one 4 drug where the disease caused certain effects and the 5 drug also caused the same effects. And we had to look 6 to the pharm-tox, which very clearly pointed out that 7 the animals, which were obviously healthy and did not 8 have this disease also had this finding and clearly 9 therefore that this was a drug effect as opposed to a 10 disease effect.</p> <p>11 The animal models may be useful in evaluating 12 new parameters. So traditional studies would allow us 13 to evaluate pharmacokinetics and pharmacology route 14 effects, the treatment regimens, durations, but there 15 are special cases where and I -- I'll refer to, Dr. 16 Boucher's example just now, where there was a case 17 where the expected treatment was not in fact to 18 improve, but actually to make worse the outcome.</p> <p>19 Animal models of disease provide an opportunity, if 20 toxicology studies are conducted in these animal 21 models, to evaluate whether or not there is any 22 undesirable promotion of disease progression in the</p>	<p style="text-align: right;">Page 69</p> <p>1 reviewer in the Office of Clinical Pharmacology in 2 CDER, FDA. So I'm going to talk about the overview 3 and the development considerations from the clinical 4 pharmacology perspective. So here's my disclaimer. 5 So the non-traditional therapy is a broad term and 6 covers a variety of products. So some products 7 exhibit direct bacteria effect and can be used as 8 monotherapies. However most of the non-traditional 9 therapy do not have the antibacterial properties that 10 enhance the efficacy of standard of care and have 11 microbials in adjunctive therapies by interacting or 12 binding to different targets.</p> <p>13 The biologic and peptide drugs such as 14 peptides, lysins, monoclonal antibodies and 15 recombinant proteins account for the majority of this 16 type of non-traditional therapy. MIC based the PK/PD 17 targets are not relevant for most of these drugs. So 18 in this presentation I will focus on biological and 19 peptide drugs used in non-traditional therapy.</p> <p>20 First, I'll talk about pharmacokinetic 21 considerations. For those non-traditional therapy 22 under the current development, linear PK has been</p>

<p style="text-align: right;">Page 70</p> <p>1 observed within the therapeutic dose range. However, 2 differences in PK behaviors were observed in infected 3 patients compared to healthy subjects. For example, 4 faster clearance and shorter half-life was observed 5 for some monoclonal antibodies in infected patients. 6 While some peptides showed us lower clearance in 7 higher exposures in infected patients than in healthy 8 subjects. In addition, PK differences may exist among 9 the sub set of patients, such as the patients with 10 different type of infections. As the big molecule 11 foreign agents, immunogenicity is observed in most 12 biologic and peptide drugs for non-traditional 13 therapy. Most exhibit low incidence of the positive 14 and high drug anti-body response. However, higher 15 positive anti-drug antibody rate was observed for some 16 lysins following systemic administration. 17 According to the FDAs guidance for 18 immunogenicity, monitoring immunogenicity should be 19 considered across the entire drug development program 20 and the neutralizing antibody assay needed to be 21 developed. It is important to understand the tissue 22 distribution of this biologic and peptide drugs</p>	<p style="text-align: right;">Page 72</p> <p>1 effect in the patients. For example, the effect on 2 the change of the cytokine levels by immunomodulators 3 following it's binding to CT28, in the impact of non- 4 traditional therapies on the anti-bacteria effect of 5 the concomitantly used antibiotics in the adjunctive 6 therapy. 7 With these PD results they can be integrated 8 with PK information and explore the clinical PK/PD 9 relationship analysis to support the dose selection. 10 So dose selection is a bigger consideration during the 11 drug development program. For most traditional -- for 12 most non-traditional therapy, dose selection needed to 13 be rely on the PK/PD approach that is not MIC based. 14 Such PK/PD data are usually first determined from the 15 in vitro or animal studies. Such pre-clinical PK/PD 16 information is useful for the Phase I or Phase II dose 17 selection. However, PK/PD results obtained from 18 patients prefer for the Phase II or Phase III dose 19 selection. 20 Phase II dose ranging studies are usually 21 conducted to facilitate dose selection, and the 22 multiple dose levels are usually tested in such</p>
<p style="text-align: right;">Page 71</p> <p>1 because multiple barriers may exist for such big 2 molecules to distribute to the site of infection. The 3 tissue sample connection for PK assessment or 4 conducting the dedicated tissue penetration study need 5 to be considered. With regard to the pharmacodynamic 6 considerations, since the MIC based PK/PD approach 7 does not apply to most of these non-traditional 8 therapies. It is important to identify and evaluate 9 the mechanism based PD biomarkers from the infected 10 patients. For some peptides with a very short PK 11 half-life accessing the long-lasting PD effect is even 12 more critical. The examples of the mechanism based PD 13 biomarker may include the characterization of the 14 binding of the antibody to antigen such as measuring 15 the antitoxin neutralizing antibody if the drug 16 targets two exotoxins or to determine the option of 17 exocytic killing effect, if the drug targets the 18 exopolysaccharide on the cell surface of the bacteria. 19 As Dr. Ed Cox mentioned earlier today, we 20 also need to understand the benefit from the mechanism 21 to the clinic. So it's also desirable to determine 22 the clinically relevant downstream pharmacological</p>	<p style="text-align: right;">Page 73</p> <p>1 studies. For combination therapy, multiple dose 2 ratios may also need to be tested. This Phase II dose 3 ranging study can then be utilized to determine the 4 mechanism base and clinically relevant PD effect from 5 the patients. Exposure response analysis is commonly 6 used clinical pharmacology tool to assist dose 7 selection. PK/PD relationship analysis, exposure 8 efficacy analysis, and the exposure safety analysis 9 are usually conducted. In some cases, drug exposure 10 at the site of infection rather than in the plasma 11 maybe more informative for the ER analysis to support 12 the dose selection. 13 Now, I'm moving to the considerations on the 14 clinical pharmacology studies. So most current non- 15 traditional therapies are still at the early 16 development stage. The clinical pharmacology studies 17 needed for each non-traditional therapy should be 18 assessed on a case-by-case basis. We also encourage 19 the sponsors to consult with the FDA at each early 20 stage. 21 Since most of non-traditional therapies are 22 used in the combination therapy or the adjunctive</p>

<p style="text-align: right;">Page 74</p> <p>1 therapy, the risk of the drug/drug interaction may 2 need to be assessed in the clinical studies. In the 3 potential of therapeutic protein drug/drug interaction 4 needed to be considered for those cytokine or cytokine 5 modulators. With regard to the PK studies in the 6 special population, hepatic impairment usually does 7 not affect the PK of monoclonal antibody, but some 8 exceptions were observed recently. Renal impairment 9 may alter the PK of therapeutic proteins with 10 molecular weight less than 69 kilodalton.</p> <p>11 It is important to assess the risk of the 12 drug on the QTC interval. Generally, monoclonal 13 antibodies are not associated with clinically 14 meaningful effect on the QTC interval. However, this 15 may not be the case for other biological and peptide 16 drugs and other assessment needed to be conducted for 17 these drugs. Depending on the specificity of each 18 drug development other clinical pharmacology studies 19 needed to be considered on a case-by-case situation. 20 For example, the lung penetration study for the 21 indication of pneumonia need to be considered. Or for 22 the Gard locally acting drug, the drug/drug</p>	<p style="text-align: right;">Page 76</p> <p>1 For most non-traditional therapy under the 2 current development, pre-clinical PK/PD data were used 3 for dose selection. So we may have the challenge to 4 translate this pre-clinical PK/PD data to human if 5 this information is not available from the patients. 6 So I just listed this several challenges but we can 7 continue to discuss these challenges or the further 8 thoughts in the next several sessions in the context 9 of the case studies. But I'll be happy to answer any 10 questions on my presentation at the end of this 11 session. Thank you for your attention.</p> <p>12 MS. NAMBIAR: Thanks, Tracy. So next speaker 13 is Kalavati Suvarna. Kala is a microbiology reviewer 14 in the division of anti-infective products.</p> <p>15 MS. SUVARNA: Good morning, I'm Kalavati 16 Suvarna, clinical microbiology reviewer in the 17 division of anti-infective products. Today, I'll go 18 over some of the microbiology considerations. Thanks. 19 So today, I'll go over some of the microbiology 20 considerations in the development of non-traditional 21 therapies for bacterial infections. In general, the 22 microbiology evaluations include mechanism of action</p>
<p style="text-align: right;">Page 75</p> <p>1 interaction study with a proton pump inhibitor or a 2 further effect study may need to be considered.</p> <p>3 So comparing to the conventional therapy with 4 small molecules, we are facing several challenges in 5 developing non-traditional therapy for bacteria 6 infection. The drug disposition of non-traditional 7 therapies may not be fully understood in the infected 8 patients. More data needed to be collected to 9 characterize the immunogenicity and understand its 10 impact on PK/PD safety and efficacy.</p> <p>11 Problems may exist to determine the drug 12 distribution to the site of infection taking account 13 the problems to access the infected tissues and the 14 questions on the representation of some surrogate 15 tissue samples. Currently, we have limited 16 experiences in understanding the drug effect of non- 17 traditional therapies to support the Phase III dose 18 selection. More work needed to be done to identify 19 the appropriate PD biomarkers and to understand the 20 clinically relevant pharmacological effect of non- 21 traditional therapies in affecting the antibacterial 22 activity of the concomitantly used antibiotics.</p>	<p style="text-align: right;">Page 77</p> <p>1 studies, evaluation of the spectrum of activity, 2 resistance development, interactions with other anti- 3 bacterial drugs, and confirmation in an in vivo animal 4 model. Coming to the mechanism of action with non- 5 traditional products, there are products where we know 6 the mechanism of action, we know the specific target 7 on which the product acts. Those include the 8 antibodies lysins, anti-microbial peptides, 9 antivirulence products and anti-resistance products, 10 even with these products you might know the target but 11 may not have a full understanding of all the upstream 12 effects.</p> <p>13 Then you have a second category where you 14 don't know the mechanism of action because it acts not 15 on the pathogen but on the host, these include the 16 immunomodulators or for lack of a better word, I've 17 used microbiota modifiers. You might be using a 18 product which inactivates the drugs or absorbs the 19 drugs, in this case you need to have a good 20 understanding of the site of action and how the drug 21 is metabolized.</p> <p>22 In case of spectrum of activity over the</p>

<p style="text-align: right;">Page 78</p> <p>1 range of non-traditional products, we have those that 2 are pathogen specific, those that are narrow spectrum 3 and those that are broad spectrum. For the pathogen 4 specific ones, it's important to understand antigen 5 variability using -- looking at large number of 6 strains from different geographical areas, looking at 7 different serotypes, ribotypes, things like that. 8 The products as mentioned before, Dr. Rex 9 mentioned, we have some products where MIC is not 10 applicable, those includes antibodies, 11 immunomodulators and biofilms here, you then have to 12 develop a different type of functional assay to show 13 spectrum of activity and these can include cell based 14 assays, opsonophagocytic killing assays, biofilm 15 eradication concentrations, and to look at maybe 16 cytokine effects and the cytokine levels. 17 In some cases the MICs may not be very 18 predictive and may need additional standardization as 19 applicable to lysins and antimicrobial peptides. Here 20 because of the rapid affect of the product, time kill 21 type of assays are more informative. And the next 22 category is the one which is very difficult to</p>	<p style="text-align: right;">Page 80</p> <p>1 have MICs usually animal models are used to show the 2 effect of the combination versus a single agent. In 3 other cases, biochemical or biophysical assays have 4 been used. However, this only shows the interactions, 5 it does not translate to what the clinical effect 6 would be. The various animal modules that have been 7 used to confirm in vivo activity, these include animal 8 modules of pneumonia endocarditis, sepsis, thigh 9 infection, catheter implants, systemic infections, 10 they've all used -- all of them always test with 11 immunocompetent and immunocompromised animals, but 12 sometimes these are not very predictive, especially 13 we've seen that with the anti-body class where you can 14 have some host specific immunevasion mechanisms or 15 virulence factors produced by the target bacteria that 16 prevent you from translating the in vivo efficacy to 17 humans. So to summarize with the challenges and I've 18 put them into three categories, one is the design and 19 interpretation. So how you design the functional 20 assay and how you characterize the activity when the 21 mechanism of action is not well understood, how would 22 you characterize the upstream effects so the --</p>
<p style="text-align: right;">Page 79</p> <p>1 interpret because there's no effect on the pathogen, 2 you're looking at other markers of, like, normal flora 3 assessments, measurements of the host immune response 4 or say, how the drug degrades in the human and how 5 that impacts the disease or how that gives you a 6 clinical benefit. 7 The next is looking at resistance 8 development. Here in the case of antibody products, 9 what you're looking at is changes in epitopes and or 10 antigenic drift. These have not been really well 11 studied for this class because some of them have been 12 developed as single dose. The other products which -- 13 where you can't use the traditional testing 14 methodologies because of its impact on growth kinetics 15 and the study design has to be modified, and then it 16 begs the question of what other methodologies can be 17 used for these products because they don't all perform 18 in the same traditional manner. 19 In terms of interactions of a traditional 20 drugs, for most products that have an MIC type of MIC 21 value, you can use the time kill assays either in 22 static or dynamic conditions. For those that don't</p>	<p style="text-align: right;">Page 81</p> <p>1 basically relates to interpretation of the functional 2 assay. A third category is when you're looking at the 3 microbiome data, how do you interpret that because 4 that's still a very exploratory analysis. 5 The next category is where there's limited 6 characterization, these include basically what would 7 be useful in the clinical studies, the potential for 8 resistant development and interactions with 9 traditional antibacterial drugs that maybe used in 10 combination or a standard of care. The third 11 challenge relates to translation of the preclinical 12 data to what would be clinically relevant, we already 13 mentioned about the lack of some predictive models for 14 antibody class, what would be the natural levels of 15 antibodies to a pathogen of interest, what would be 16 the impact of the neutralizing antibody on the 17 activity of the drug, what would be the impact of 18 heterogeneous populations or changes in the target of 19 virulence factor expressions, how do you evaluate some 20 redundant effect or functions, what is the activity of 21 the drug at the site of infection or intra cellular 22 activity. So these challenges will be discussed</p>

<p style="text-align: right;">Page 82</p> <p>1 within the context of the cases that I discussed today 2 and tomorrow during this workshop. So that's the end 3 of my talk. Thank you and if you have any questions, 4 I'd be happy to answer them.</p> <p>5 MS. NAMBIAR: Thanks, Kala. So what we'll 6 try to do in the next few minutes or so before we take 7 our first break is see if there might be any 8 clarifying questions or comments from panel members or 9 from members of the audience. Then we can check to 10 see if there might be comments online as well.</p> <p>11 MR. COX: So, I'll start out with one. And 12 this is a pharm tox question I'll ask Dr. McMaster. 13 So I'm a company and I've got a new molecule. I'm not 14 ready for an IND yet, but I've got some questions 15 about my toxicology studies. Is there a mechanism and 16 the people to contact us often about these sorts of 17 questions. And then is there something that a company 18 should do to make this most productive, if they want 19 to interact prior to the point of an IND? So I'll 20 throw that one out to you Owen and welcome your 21 comments.</p> <p>22 MR. McMASTER: Hello, thank you. So yes, we</p>	<p style="text-align: right;">Page 84</p> <p>1 and then general-tox studies, the durations of which 2 would be guided by the proposed clinical trial. So we 3 do provide a context within which companies can come 4 into the agency and seek guidance, and we encourage 5 people to do that. Thank you.</p> <p>6 MR. BLACK: So I had a question kind of 7 similar to that. So because of difference in 8 reactivity in different animal species, what 9 guidance do you give on surrogate antibodies and for 10 instance to do the tox studies relative to the actual 11 human product, and I think particularly in the context 12 where you're making half-life extending modifications 13 or other modifications that may alter that in the 14 humans?</p> <p>15 MR. McMASTER: So this is a very, very big 16 problem. And sometime, as I mentioned in my talk, 17 it's insurmountable. So sometimes there are no 18 relevant species, sometimes there are no transgenic 19 models, sometimes there's no homologous protein that 20 you can create that's going to model what you're 21 trying to look at. And in those cases, we simply 22 recommend that a short-term tox study is done because</p>
<p style="text-align: right;">Page 83</p> <p>1 do get these inquiries all the time. There is a 2 mechanism for companies that are in the middle of drug 3 development who want to make sure that they're really 4 fulfilling all these, which can become quite complex 5 guidances, and we try our best to provide a forum 6 within which they can express the problems they're 7 having and also provide guidance, guided largely by 8 the ICH, but we also have FDA guidances as well. If I 9 could be specific, can I point to my slide 6 please? 10 Because that goes through the expectations from a 11 company that's coming in with a product that has not 12 conducted any clinical trials as yet. So for a 13 company coming in, we would explain to them that we 14 expect pharmacodynamic studies and Kala just went over 15 detail of what kinds of studies we would expect. We'd 16 expect safety pharmacology studies, some PK data but 17 as I mentioned in my talk, this can be very complex 18 and so the expectations for this kind of product is 19 limited.</p> <p>20 Gene-tox studies, we absolutely would need 21 for traditional products, although again these maybe 22 complicated depending on the chemistry of the molecule</p>	<p style="text-align: right;">Page 85</p> <p>1 even these agents may have off target toxicities which 2 we will be able to evaluate in a short-term study. 3 But this is a very complex problem and sometimes 4 there's just no way to address it. And we realize and 5 sometimes if that's it then we, you know, we base this 6 on the scientifically available data and there's no 7 point wasting animals if there are -- there's no point 8 to it.</p> <p>9 MS. NAMBIAR: If I can just add to what Owen 10 said, in terms of seeking advice from the division, I 11 think we highly encourage you to reach out to us, pre- 12 IND is an appropriate way by which you can seek advice 13 from the division. We can respond in writing, we can 14 meet with you in person, we can have a call. And 15 discussions at these meetings, while a big focus is on 16 the pharm tox data package, I think, I just want to be 17 clear that we are willing to discuss the overall 18 development program. And to a point that Kevin made 19 earlier, it's much easier for us to have a discussion 20 when we actually have a product in hand rather than 21 hypotheticals.</p> <p>22 Even if you are very early in development but</p>

<p style="text-align: right;">Page 86</p> <p>1 to sort of have the long-term discussion, and some of 2 these are very challenging because we don't have a lot 3 of prior history to go by. So it might necessitate a 4 fair bit of discussion between the company and us. So 5 starting the conversation early and building upon it 6 might need more than one discussion. I think we in 7 the division are very open and welcome you reaching 8 out to us to have these conversations. So just wanted 9 to make that clear. Thanks.</p> <p>10 MR. COX: And I'll throw in one more piece 11 too and I'll look to Owen to make sure he agrees with 12 me but our experience has been too to the extent that 13 the person coming in and asking for the pre-IND 14 consultation has thought about things you know to a 15 fair degree and has put out a plan. There may still 16 be questions, they may not have all the answers that 17 can certainly help to move the discussion along and 18 get to a good answer sooner. So did I get that right, 19 Owen?</p> <p>20 MR. McMASTER: Yes, you did. Also because we 21 see so many more of these applications, we may often 22 be able to refer you to mechanisms which may be able</p>	<p style="text-align: right;">Page 88</p> <p>1 nimbly as possible and the development stream is a 2 real driver of cost and return of investment. And I'm 3 also aware of the recent experience of people in this 4 room around this but I just propose there may be an 5 alternative for us, especially if you're dealing with 6 three, four, five, different entities.</p> <p>7 And I guess the final comment is our 8 colleagues in CBER deal with this all the time. They 9 do pathogen specific multi-antigen vaccines and they 10 have a pathway which is a little bit lighter than the 11 one which some people think we need to follow.</p> <p>12 MS. SUVARNA: So along those lines I also 13 wanted to have some discussion about what additional 14 tools can be developed. Yes, so there's also one 15 thing to have some discussion about what additional 16 tools can be developed that could be used by multiple 17 companies so as to advance this field with non- 18 traditionals. You had a comment there, Vincent (ph)?</p> <p>19 MR. TRUONG: Vu Truong, Aridis, given that we 20 know the types of or the classes in non-traditional 21 anti-infective under development, does it make sense 22 for the FDA to generate a -- prepare a guidance for</p>
<p style="text-align: right;">Page 87</p> <p>1 to address your very complex issue. More questions, 2 and folks from the audience feel free too if you've 3 got a question you can come up to the microphone.</p> <p>4 MR. DUBOVSKY: I have a point, which came to 5 my mind both when we were looking at the pre-clinical 6 discussion as well as the clinical one. And for 7 pathogen specific approaches, it's pretty easy to 8 envision combination products, where you either need 9 to target different serotypes or different virulence 10 factors in your bacteria of choice. And that kind of 11 raises a conundrum for us in how we handle that and 12 how we approach it, you can do a matrix approach 13 either pre-clinically and clinically but those become 14 almost impossible to do in difficult to study 15 diseases. An alternate approach is just to take your 16 combination all the way through efficacy and examine a 17 global benefit risk ratio for eventual licensure and 18 if the sponsor makes a mistake and makes it too 19 complicated, too expensive a combination, that just 20 leaves space for competitor to come in and own that 21 space. So I make this comment in with the realization 22 that we're all trying to advance as many products as</p>	<p style="text-align: right;">Page 89</p> <p>1 the industry in terms of PK/PD studies, pharm-tox, 2 comparability studies; for example, when we switch 3 cell line (ph) and so on?</p> <p>4 MR. COX: It may. So it sounded like if I 5 understood correctly, you're talking about how the 6 product is produced, right? You're talking about 7 switching cell lines so that would be manners of 8 production or did I get that wrong?</p> <p>9 MR. TRUONG: Certainly that would be helpful 10 but also provide guidance on how many animal models 11 you need to test for, let's say, an antibody 12 development right? The relevance of some of these 13 animal models for PK/PD or toxicology is not very 14 scientifically useful or clinically predictive. And 15 so to provide guidance on how to develop license, how 16 to establish tox studies for antibodies or other 17 peptides, so on. I think that might be very useful 18 for the industry.</p> <p>19 MR. COX: Yeah. So, I mean, we do take the 20 issue of guidance and recognize it as something that's 21 very important. And in essence the workshop is in 22 that spirit to try and answer questions. And as you</p>

<p style="text-align: right;">Page 90</p> <p>1 can see there's a broad range of topics and I know 2 some of the guidances but I wouldn't claim to know 3 them all, and that's why we have a multi disciplinary 4 team that looks at things. You know with regards, you 5 know, to manners of production, and I guess really the 6 first question is, is do we have anything out there 7 that would address the questions, and if not, then 8 maybe there is a gap that would need to be filled? 9 And then you're talking about animal models and I'm 10 thinking -- I was initially thinking toxicology but 11 now you also mentioned pharmacokinetic studies. And 12 yes, I mean that may be another area. And then just 13 listening to your comment too, you also brought up the 14 topic of what's the state of the science in a 15 particular area. Because obviously it helps most to 16 write a guidance document in a setting where there is 17 at least some scientific information that allows us to 18 write something that's meaningful. If it is an area 19 where there's a need for more foundational science 20 then it may be that the foundational signs would need 21 to be done first before any of us could come up with 22 recommendation. So we appreciate your comment.</p>	<p style="text-align: right;">Page 92</p> <p>1 because what kills drugs is variability, right, in 2 biologic response? And maybe we're not doing a good 3 enough job of accounting for that. 4 MS. WEI: I have a follow-up comment 5 regarding to the discussion on the potential. Yeah, 6 so follow-up comments regarding the discussion on the 7 guidance development. I think regarding to the PK/PD 8 consideration especially using the animal model, so 9 what we should be aware that this is a non-traditional 10 therapy, it's across a very broader range of the drug, 11 like, for the some peptide, lysins, monoclonal 12 antibodies, that have very short half-life but it's 13 not like monoclonal antibody have like about three 14 weeks, even longer half-life. And their targets may 15 be very dependent on the mechanism. So it will be, 16 like, maybe some targets would be to the pathogen 17 itself or just to the host or immune system. So 18 regarding the guidance it maybe quite complex to cover 19 the current these targets. So I was thinking if we 20 have something will be very general or just very high 21 level. 22 MR. REX: So if I could pick up on the point</p>
<p style="text-align: right;">Page 91</p> <p>1 Guidance development is an area that we've been quite 2 active in and will we'll continue to be active in to 3 try to address the questions that are out there, and 4 we'll continue to find areas, and we appreciate your 5 comments because that helps us to , you know, look at 6 particular areas where there may be a need for 7 guidance or guidance may benefit drug development. So 8 we'll keep your ideas in mind and see where it falls 9 on the priorities, see where it falls in essence with 10 the state of rightness if you, with regards to the 11 foundational science that would allow us to write a 12 guidance. 13 MR. AMBROSE: Hi, I guess from our 14 perspective having worked with some non-traditional 15 things, a lot of folks they have a model that they 16 believe they're going to use to forecast what an 17 effective human dose might be. But because of that 18 model's expense or for some other reasons they study 19 one or two bacterium and everything hinges on how the 20 drug responds against those two and it may be in the 21 case where we don't have things like MICs, we need to 22 get much more comfortable with studying a lot more</p>	<p style="text-align: right;">Page 93</p> <p>1 you just made that there's a broad range here. And we 2 use the word non-traditional to mean so many things. 3 So write a guidance for non-traditionals, summarize 4 the history of the Western world, be brief. It's not 5 -- there's such a breadth here. And I am concerned 6 that we can spend all day talking in very vague terms 7 about, "Oh I want a better animal model for non- 8 traditionals" and make zero progress because we 9 haven't cooked it down to the point where the answerer 10 actually tells you what to do next. And is there a 11 better language that we could be using, I like Tracey, 12 your division on your slide of the -- you have these - 13 - some nice boxes and do we need to chop it up a 14 little bit into some agreed upon subunits and talk 15 about each one of those individually. Some of the 16 cases kind of do that but I'm not sure that we have 17 created the right conversational boxes and I am 18 reminded of conversations in the past where we would 19 spent an entire meeting arguing about what we were 20 going to talk about and only in the last 30 minutes 21 did we finally get to where we had agreed upon 22 language for that day. And the next time we start we</p>

<p style="text-align: right;">Page 94</p> <p>1 had to have the entire day again of defining what 2 we're talking about. So I really can -- is there a 3 better nomenclature for non-traditional, I have to say 4 the word but I'd like to now structure it a little 5 bit. So that's my question, what is the correct 6 structure for the conversation? What should be the 7 boxes that we're discussing? 8 MR. BLACK: Well, I think it's a critical 9 point because I guess when you segment these out, you 10 do have these direct acting types of non-traditionals 11 which I think do fall into a little bit of the 12 category of our understanding, whereas if you're 13 relying on a host response, where we know particularly 14 in these patients that almost likely have these multi- 15 drug resistant infections that can be highly variable 16 and so then how do we make sure we capture that 17 variability for bringing in antibody effects or host 18 components to the efficacy. So I do think you could 19 segment that on how much the host response is needed 20 for efficacy as opposed to how much is really directly 21 related to the activity of the entity being tested. 22 MR. DUBOVSKY: I guess another obvious box.</p>	<p style="text-align: right;">Page 96</p> <p>1 bringing in then more complexity that's where we're, I 2 think, really being challenged right now. 3 MR. KALEKO: Seems to me that, listening to 4 the discussion the description of traditional are 5 those things that can be developed through 6 predetermined algorithms. And things that are non- 7 traditional, can't. Now if you have a universe or 8 space, I should say, of traditional development, the 9 universe of non-traditional is infinite, probably even 10 bigger than the Western world. So the question is how 11 can you set up algorithms for what is an infinite 12 variety of opportunities? And I think the question 13 really boils down to how do you deal with individual 14 opportunities on a case-by-case basis without 15 algorithms? 16 MR. REX: Looking around for others with 17 wisdom on that. 18 MS. EAKIN: Well, I'll turn my mike on -- 19 MR. REX: You go for it, just speak, say it 20 clearly, here we go. 21 MS. EAKIN: Well, I'll try. So I guess one 22 observation, and I don't know if this helps with the</p>
<p style="text-align: right;">Page 95</p> <p>1 John, I guess you cover this a bit is, can you measure 2 a direct clinical benefit in a reasonable way versus 3 not? So can you actually measure what most drugs are 4 licensed upon now or are you really hoping to license 5 then something which is broader, has phenomenal public 6 health impact but may not be possible to measure the 7 clinical benefit to the individual? 8 MR. BLACK: And history of the Western world, 9 you know at a -- I'm sorry -- at a recent Vaccine 10 Congress, it's just amazing to point out that we 11 essentially have two effective biologic therapies for 12 infectious disease. We have the RSV, which is a 13 neutralizing antibody that impacted the host cell 14 interaction in infection, and then Merck had anti- 15 toxin antibodies for C. Diff. recurrence just three 16 years ago as the second biological proof for in 17 infectious therapies. So I think it does show the 18 challenge of how we're utilizing these approaches in 19 infectious diseases. It's not for lack of trying but 20 it's really something simplistic as neutralizing toxin 21 and neutralizing a virus is -- maybe a little bit more 22 straightforward and direct and as soon as we start</p>	<p style="text-align: right;">Page 97</p> <p>1 traditional and non-traditional definitions but I 2 think I certainly have used in the past a sales pitch 3 for antibiotics development that are pre-clinical non- 4 clinical models, of such high quality and so 5 predictive of clinical success that it allows, sort 6 of, the early risk assessment. So early clinical 7 development you get to Phase I, you know your safety, 8 in PK, where you can you know almost guarantee success 9 in later stage clinical development. And whether 10 that's true or not, it home could be up for debate but 11 I think we've used that. And so that to me is a 12 traditional approach for antibiotics anyway, whereas 13 some of these non-traditional approaches are waiting 14 for much deeper into clinical development where you 15 have biomarkers where maybe you don't even know what 16 the clinical indications are going to be until much, 17 much later and you see the clinical results. So that 18 puts it into a very different realm of risk, which I 19 think has some impact as well as I guess of particular 20 interest of mine is are there tools, I think you 21 mentioned that, that we could do better models so we 22 can invest in earlier to maybe help clarify that risk</p>

<p style="text-align: right;">Page 98</p> <p>1 earlier, even for these less direct acting traditional 2 approaches. 3 MR. COX: And maybe I'll throw one out too to 4 try and offer maybe a different sort of way we might 5 look at this, which is, you can look at it from the 6 standpoint of the molecule. What's the nature of the 7 molecule and how you're going to develop the molecule, 8 that may impact your tox studies and other things 9 along the way. Then as you get into later 10 development, you might look at it from the standpoint 11 of what will this molecule do for patients and, and if 12 you think about that second sort of angle of looking 13 at things, not -- so it's not just what the product is 14 but it's the other angle of what is the product going 15 to do for patients. Well, you could imagine the study 16 that Helen showed, there was a vaccine study to try 17 and reduce Staph aureus infections, and that maybe a 18 study design that could be utilized, there'd be some 19 slight differences that would be applicable to 20 different types of products. You could have a 21 vaccine, that might be one way to do it; another type 22 of product might be a monoclonal antibody, and maybe</p>	<p style="text-align: right;">Page 100</p> <p>1 studies. Can you highlight any value that you've seen 2 conducting exposure response if we have a valid 3 preclinical target? 4 MS. WEI: Yeah, because in my presentation, I 5 also mentioned that if it is also preferable that we 6 can identify the PK/PD target from the human -- from 7 the patients. So we think the -- only using the 8 preclinical PK/PD target may not be sufficient in some 9 cases. Especially, if from the animal model they use 10 some end point that it's difficult to translate to 11 human such as like the -- a survival of animal or like 12 reduction of the disease severity, sometimes it may 13 not be predictive to the human. Therefore, we prefer 14 that during the drug development in the clinical 15 stage, it is encouraged to the sponsor to collect the 16 more PK/PD data especially using the dose ranging 17 study, so you can have exposure response relationship 18 to identify the optimum dose. 19 MS. NAMBIAR: Paul, maybe you want to add to 20 that -- we will get to you in a minute. 21 MR. AMBROSE: Yeah, let me add to that, let's 22 pretend that there's a valid pre-clinical model for</p>
<p style="text-align: right;">Page 99</p> <p>1 would have an infusion of a monoclonal antibody at 2 some period of time prior to the surgery the patient 3 was going to undergo. Maybe what it would -- the 4 product that you would give would be of a Phage Lysin, 5 and you would do that. So you can start to see that 6 depending upon which angle you're looking at things 7 there may be things that are more applicable or not. 8 It's not that any one model is necessarily going to be 9 perfect but there may be a lot of foundational work 10 that can be drawn upon that teaches us important 11 lessons and that sort of guide how we look at these 12 products, and they may not be from the standpoint of 13 benefiting the patient. There may be paradigms out 14 there that are applicable. So it's just another way 15 to sort of think of things and look at this particular 16 area. 17 MS. NAMBIAR: I think we have one question on 18 line, before we go to that, I want to check if any 19 questions or comments from members of the audience. 20 No, not yet, okay. So Tracy, there's a question 21 online for you. The question is the current theme of 22 antibiotic drug development usually avoid dose finding</p>	<p style="text-align: right;">Page 101</p> <p>1 efficacy like the questioner asked. So another reason 2 to do it might be some of these compounds might have 3 target mediated drug disposition, in other words 4 binding to the target is a mechanism of clearance 5 since so, therefore, clearance can be much, much 6 faster in a patient than in a volunteer and that might 7 be a reason to conduct that study as well. 8 MS. NAMBIAR: Go ahead, thanks. 9 UNIDENTIFIED SPEAKER: I just had a question 10 targeting the pharmacokinetic tox. I was interested 11 in the reliance on PK with PD readouts in the setting 12 when there -- 13 MR. COX: We may get you to get a little 14 closer to that microphone so it picks up a little 15 better, thank you? 16 UNIDENTIFIED SPEAKER: I am sorry. So, I was 17 interested in the pharmacokinetic tox that you gave in 18 the reliance on PD biomarkers for your readout, so I'm 19 wondering in the setting, where you don't have a 20 mechanism based PD biomarker such as even blood stream 21 impacts on infections where culture clearance is your 22 readout, but maybe at the time of dosing the patients</p>

<p style="text-align: right;">Page 102</p> <p>1 aren't bacteremic anymore but we know that you need 2 prolonged therapy even in post clearance of culture. 3 How you look at things like dose finding or even 4 efficacy readout in absence of PD biomarkers? 5 MS. WEI: So, yeah -- so you mentioned that 6 maybe in your case, there's the lack of mechanism 7 based PD bio marker, but I think in the other point 8 maybe you can use some microbiological endpoint, so 9 that maybe -- also be -- can be categorized to be as 10 the -- one of the clinical endpoint. So, we just want 11 to have something to link of your -- the mechanism of 12 the working of the drug to the clinical end points. 13 So especially in the early drug development stage, in 14 the Phase II then the patients -- the sample size is 15 not big enough to interpret a clinical outcome. So 16 some of those endpoint like microbiology reading or 17 some sort of (ph) endpoint may help you just to 18 confirm the -- like proof concept the drug or to give 19 you some hint for the dose selection. Hope I answered 20 your question. 21 MS. NAMBIAR: Didn't -- sorry, looks like 22 you've follow-up come?</p>	<p style="text-align: right;">Page 104</p> <p>1 you, we'll see you back in 15 minutes. 2 (Recess) 3 MS. GHOSH: Good morning, my name is Mayurica 4 Ghosh, and I'm a medical officer in the division of 5 anti infective products. I'm going to discuss today a 6 hypothetical case of a monoclonal antibody for 7 prevention of a bacterial disease. It's an injectable 8 humanized immunoglobulin the IGG-1 capa. It has an 9 exogenous target, it binds specifically to the alpha 10 toxin of Staphylococcus Aureus blocking alpha toxin 11 pore formation in the target cell membranes and that's 12 protecting the cell from lysis. It is of narrow 13 spectrum and it has no activity against other 14 pathogens, it is being developed for the prevention of 15 Ventilator Associated Bacterial Pneumonia by 16 Staphylococcus Aureus. In terms of the non-clinical 17 studies, in a murine model of Pneumonia, prophylaxis 18 with a murined version of the product reduced disease 19 severity with an EC90 of 200 micrograms per 20 milliliters. 21 A two week repeat dose toxicology study in 22 rats showed no evidence of toxicity. However, a six</p>
<p style="text-align: right;">Page 103</p> <p>1 UNIDENTIFIED SPEAKER: Yeah. Well, I think 2 the challenge is for something like bloodstream 3 infection, where at the time of dosing in a trial a 4 patient may no longer be bacteremic, but it's 5 challenging in those situations where there is no PD 6 biomarker and even pre-clinically for dose selection, 7 where -- for example, if you have intracellular target 8 you can't measure activity at your site of drug 9 activity. 10 MS. WEI: So in that situation, where we -- 11 yeah, we welcome the case by case discussion to reach 12 out to the FDA to our group. We can just look at each 13 specific case and then to see how the PK/PD approach 14 or if that there is a lack of the data as I mentioned 15 as in one of the challenge, how do we solve that. But 16 we welcome more of this case discussion at the early 17 stage. 18 MS. NAMBIAR: So, if there are no more 19 questions or comments, we'll take our first break. 20 We'll reconvene at 11:15 a.m. And just a reminder 21 that if you're interested in getting lunch, I think 22 you have time now to sign up at the booth. So thank</p>	<p style="text-align: right;">Page 105</p> <p>1 week repeat dose toxicology study in monkeys showed 2 evidence of immune complex arthritis. A tissue cross 3 reactivity study was negative, it crossed the 4 placenta, hence, reproductive toxicology studies were 5 performed, and a single dose pharmacokinetic study in 6 monkey showed positive anti drug antibodies. 7 A Phase I first in human study was completed. 8 The terminal half life was 90 to 110 days. The serum 9 concentrations maintained above the PK target for 30 10 days. In terms of clinical immunogenicity, 5 percent 11 of the subjects tested positive for anti drug antibody 12 during the study and 35 percent developed infusion 13 reactions. A Phase II dose ranging study in 14 ventilated subjects colonized with Staphylococcus 15 Aureus in their lower respiratory tract was completed. 16 The primary efficacy endpoint here was incidence of 17 Staph Aureus Pneumonia during the 30 days post dosing. 18 A PK analysis showed a half life of 40 days, 19 lower than healthy subjects as the clearance was 20 higher in patients. And a dose of 4,000 milligram 21 achieved the PK target, which was the same 22 concentration of 200 micrograms per milliliter.</p>

<p style="text-align: right;">Page 106</p> <p>1 Antibody concentration in tracheal aspirates was 2 measured. Adverse re events of urticaria and rash 3 were noted and there was one case of laryngeal edema, 4 which was thought possibly secondary to a 5 hypersensitivity reaction. A Phase III randomized 6 double blinded placebo-controlled superiority trial 7 with a sample size of 582 subjects in ventilated 8 subjects colonized with Staph aureus in the lower 9 respiratory tract was completed. The inclusion 10 criteria were tracheal or bronchial sample positive 11 for Staph aureus PCR within 36 hours prior to 12 randomization and no diagnosis of new onset pneumonia 13 within 72 hours prior to randomization. The primary 14 efficacy end point here was incidence of Staph aureus 15 pneumonia during the 30 days post dosing. This was 16 based on clinical signs and symptoms and microbiologic 17 cure.</p> <p>18 Culture: The secondary efficacy endpoint was 19 all-cause mortality at day 28. Safety was assessed by 20 adverse event monitoring through 30 days, 90 days, and 21 190 days post dose. The incidence of pneumonia in the 22 treatment group was 23.4 percent compared to 29.9</p>	<p style="text-align: right;">Page 108</p> <p>1 proceed, our webinar participants kindly asked us to 2 speak up a little bit because they have problems 3 hearing us. Thank you.</p> <p>4 MS. DORR: Well, first, I'd like to thank the 5 FDA for inviting my colleague Todd Black and I to come 6 and provide our perspective on drug development of 7 monoclonal antibodies for infectious disease therapy. 8 So our experience is based upon the development of 9 basil toxin MAb, a monoclonal antibody for prevention 10 of C. Difficile infection recurrence. So it's a 11 little bit different than this case in that this case 12 is for primary prevention of a disease, where we 13 studied prevention of a recurrence. So our drug is 14 given as adjunctive treatment to antibiotic therapy.</p> <p>15 So, we Merck end licensed this product after 16 Phase II. Phase II was robust proof of concept it was 17 a combination product that was studied in Phase II 18 based upon two toxins known to be virulent factors for 19 C. Difficile infection, largely based upon animal 20 models. And so, the first thing I want to say is that 21 development of monoclonal antibodies for infectious 22 disease targets is complicated, and we encountered</p>
<p style="text-align: right;">Page 107</p> <p>1 percent in the placebo. The difference in rate was 2 6.5 percent with a 95 percent confidence interval of 3 negative 0.7 percent to 13.7 percent, and a two-sided 4 P value of 0.08. Forty five deaths occurred in the 5 treatment arm versus 35 deaths in the placebo arm at 6 day 28.</p> <p>7 Some of the questions which can be discussed 8 later this morning would be, how would you address the 9 challenges of designing such a prevention trial 10 including the need for a large sample size, 11 identification of the at-risk subjects, challenges 12 with the diagnosis of pneumonia itself, and 13 confounding of safety assessments by underlying co- 14 morbidities. What other study designs and indications 15 would you suggest for this or a similar product? 16 Thank you for your attention.</p> <p>17 MR. IARIKOV: And now Mary Beth Dorr from 18 Merck and she's a Clinical Director, I would remind 19 you, of clinical research in infectious diseases, 20 would provide industry perspective. And then Dr. 21 Ghosh will provide FDA perspective on the subject of 22 monoclonal antibody development. And before we</p>	<p style="text-align: right;">Page 109</p> <p>1 many challenges through the development. We were 2 fortunate that at the end of the day we had -- we 3 achieved regulatory success but as people have 4 mentioned and if you noted our drugs in Plava (ph) was 5 on a slide that was shown earlier, that doesn't 6 translate necessarily into marketing success. But -- 7 so that others can learn from our experience, we offer 8 some comments for your consideration.</p> <p>9 So first is what is the appropriate target? 10 For us, you know toxins for C. Diff, toxins make sense 11 because they are the virulence factor but which toxin? 12 And if you are looking at a bacterium that have more 13 than one virulence factor, you need to consider that. 14 And then, if you are going to look at multiple 15 virulence factors it's important early on to 16 understand the relative contribution of each one of 17 the antibodies because as many of you are familiar 18 with our situation, we moved forward with a 19 combination based upon Phase II-B, but the FDA, in 20 their wisdom, required that we also study each 21 antibody separately, and at the end of the day, we 22 found that only one of those antibodies was</p>

<p style="text-align: right;">Page 110</p> <p>1 contributing to the efficacy of the product. 2 And so, that was a very costly lesson to 3 learn, very late in development. Our development 4 program was 2,800 patients that was our target. We 5 ended up being able to drop the single antibody arm 6 after an interim analysis, so at the end of the day we 7 enrolled 2,650 patients, very large clinical 8 development program for monoclonal antibody. 9 So, again that goes back to the idea of 10 animal models, so is the animal model reflective of 11 the clinical situation? Nobody knew what the relative 12 contribution of each toxin was in the human, it was 13 these monoclonal antibody studies, that we conducted, 14 that found that toxin B was the relevant virulence 15 factor in humans. 16 The other question is, can animal models help 17 inform potential furmutter (ph) genecity. So you know 18 what is the right animal model to study that? And 19 then for prevention studies, if you're trying to 20 prevent a disease, even like for us, it was secondary 21 prevention but if you're trying to prevent something, 22 you need to enroll patients who are at high risk. In</p>	<p style="text-align: right;">Page 112</p> <p>1 their stool because C. Diff. sporelates and PCR picks 2 up the spores as well. So patients can be decolonized 3 and their diarrhea could be due to the taco they ate 4 the day before. 5 So that brings us to the definition of the 6 end point really should include the physician's 7 decision to treat the infection, because the symptoms 8 could be due to something else and if that was ruled 9 out then it should not be attributed to as -- to the 10 specific disease that you're studying. But, when 11 you're talking about an infection where you treat 12 empirically before you have your microbiologic results 13 that can get a little complicated. 14 So another thing that was brought up is the 15 difference in PK between healthy's and patients. So, 16 what we found with our monoclonal antibody, which is 17 something that's known for monoclonal antibodies in 18 general, is that there was a correlation with serum 19 albumin. So if the patient had low serum albumin 20 their clearance was higher. And so, how do you adjust 21 for that if you have a narrow therapeutic index 22 monoclonal antibody? We were fortunate in that we</p>
<p style="text-align: right;">Page 111</p> <p>1 our situation, we were fortunate in that 75 percent of 2 our population had at least one risk factor for C. 3 Difficile recurrence, but if you don't enroll enough 4 patients with risk factors then you're going to dilute 5 your true effect size. And so that's really important 6 to understand what the risk factors are before you 7 embark upon a large Phase III clinical development 8 program. 9 So also the definition of the end point is 10 really important. If you've got a soft end point it's 11 going to be more difficult for you to show a 12 difference. What we found is that we used an 13 algorithmic approach based upon a patient's symptoms 14 and also microbiologic. So we didn't ask the 15 investigator what they thought, so we called some 16 patients failures, who weren't even treated for their 17 infection because they had a single day of diarrhea 18 and they had a positive PCR test. 19 So then that brings us to the PCR test. The 20 PCR test can detect patients who are colonized but 21 that doesn't necessarily mean, at least in the 22 situation for C. Diff. that the patient has toxin in</p>	<p style="text-align: right;">Page 113</p> <p>1 feel that we were significantly overdosing the 2 patients, so that that didn't impact our efficacy, but 3 if you've got a monoclonal where, you know, this 4 example is 4 grams, that's a lot of monoclonal 5 antibody. The cost of goods for 4 grams is quite 6 high, so you really want to make sure you've got your 7 dose right and you don't want to under dose. So it's 8 important to understand the impact, for example, of 9 co-morbidities on the PK before you embark upon your 10 Phase III trial. 11 We also saw that sample size is important, so 12 if your sample size is too small and you've designed a 13 superiority trial, you can fail even if you've shown a 14 difference that's clinically meaningful. So it's 15 really important to consider what things are going to 16 impact your endpoints and to, you know, is there a 17 valuable population as opposed to the mITT population, 18 what things are going to impact that? So for many of 19 these anti-bacterial trials, you've got patients with 20 co-infections, you know, you've got patients getting 21 antibiotics that could target the same bacteria for 22 other infections, and then how do you handle that</p>

<p style="text-align: right;">Page 114</p> <p>1 patient's data? You really wouldn't want to include 2 that patient, because it's confounded. So you need to 3 consider those things as you design your endpoints. 4 And then the other thing is the fact that 5 serious infections occur in patients with co- 6 morbidities who are at high risk for adverse outcomes, 7 that aren't related to the infection, leads to 8 multiple early discontinuations. And how do you count 9 those early discontinuations in your endpoint 10 estimation? It doesn't seem fair to the product to 11 count them as -- to impute those as failures. So you 12 need to have some way of adjusting for those early 13 dropouts. And in part, you need to over enroll to 14 account for that. 15 And then in terms of safety, fortunately, if 16 your target is a protein that isn't found in the human 17 body then there is less potential for off target 18 effects. So that is one advantage of studying 19 monoclonal antibodies. But as has been mentioned, you 20 do need to be concerned about anti drug antibodies 21 being formed. So it's really important early on to 22 understand the potential for anti drug antibodies and</p>	<p style="text-align: right;">Page 116</p> <p>1 versus in the comparator arm, you know, 15 percent 2 then it could just be by chance that the rate was 3 lower in that comparator arm. But if you don't have 4 any idea, you know, what the rate is in the general 5 population it's really hard to be able to understand 6 if it's the drug that caused it or if it's just by 7 chance. So that's my comments, thank you. 8 MR. IARIKOV: And now, Dr. Ghosh. 9 MS. GHOSH: Thank you for your comments, Mary 10 Beth. I will make some general comments in this 11 context and I share similar concerns as reflected in 12 Mary Beth's comments. In terms of trial design, if a 13 product is being developed for -- as an adjunctive 14 treatment of standard of care anti-bacterials, then 15 generally need to demonstrate superiority over 16 standard of care and placebo. In terms of sample size 17 for diseases with low incidence, a large sample size 18 will be necessary to show the treatment effect of the 19 product for prevention of disease. A small reduction 20 in the incidence of the disease could have an impact 21 on the sample size and the potential for benefit of 22 the treatment is also a critical factor. In terms of</p>
<p style="text-align: right;">Page 115</p> <p>1 what can cause those. So this example here was 2 humanized versus a fully human that could have 3 potentially caused this. Formulation is important too 4 because a propensity to cause aggregates can increase 5 the chance for acute hypersensitivity reactions. And 6 also if you're going to give a single dose for an 7 acute infection versus you're going to give multiple 8 doses for, you know, long-term prevention, multiple 9 dose will increase the risk of immunogenicity, so you 10 need to take all that into consideration. 11 Then the other question that came up was 12 about imbalances in adverse effects that you see -- a 13 serious adverse effect in this situation mortality, 14 there was an imbalance that was seen. So these 15 patients are really sick, how do you know that it 16 wasn't just by chance versus something that was caused 17 by the therapeutic? And you know, one way to look at 18 this is if you have information based upon large 19 database trials of how many -- what is the incidence 20 in that population. If you can get that information, 21 so if you know that the death rate is 20 percent and 22 you know, you found 20 percent in the intervention arm</p>	<p style="text-align: right;">Page 117</p> <p>1 selection of endpoint, for treatment trials choosing 2 an endpoint which has a large treatment effect would 3 provide the strongest evidence of efficacy, but just 4 as Mary Beth said, clearly defining the disease itself 5 would also help in selection of the endpoint. If the 6 product is being developed for a reduction in 7 recurrence of the disease, one needs to consider not 8 only the reduction of recurrence of the disease as a 9 primary endpoint, but also the cure of the initial 10 index infection. As we have seen with basil toxin 11 MAb, (ph) an imbalance in the initial cure rate could 12 result in the treatment groups being not comparable 13 and then the effect of the study drug on the 14 recurrence of -- reduction in recurrence of infection 15 would be difficult to interpret. One option could be 16 potentially treating the index infection and then 17 randomizing, so the cure of the initial episode could 18 be with a different product. 19 One other scenario that comes up is, let's 20 say, an antibody targets a specific pathogen like 21 Staph aureus, with reduction in incidence of Staph 22 aureus pneumonia. However, the subject then develops</p>

<p style="text-align: right;">Page 118</p> <p>1 Pseudomonas aeruginosa pneumonia, then consideration 2 should be given as to how to address this problem and 3 how to address this analysis. What would be 4 clinically relevant would be if the subject is alive 5 and free of pneumonia overall. 6 In terms of VAP prevention trials, sometimes 7 it's difficult for diagnostic confirmation of the 8 disease, for example, if a sputum culture is positive 9 for a pathogen in the absence of clinical signs and 10 symptoms, it may just reflect a prior colonization of 11 the disease and in this situation clearly defining the 12 infection would help. 13 In terms of safety, sometimes assessing off 14 target actions of the product could be difficult when 15 there is a high mortality due to the disease itself 16 and a separating out of the treatment effect in such 17 situations is also challenging. One should also 18 consider what would be the size of the safety database 19 in such prevention trials when you're using the 20 product to, let's say, treat a large population of 21 uninfected population and would that tip the risk 22 benefit ratio?</p>	<p style="text-align: right;">Page 120</p> <p>1 less toxicity of the combination as compared to the 2 individual components, and that's all I have. 3 MR. IARIKOV: Thank you very much, it was 4 very informative, and now we open the floor to 5 discussion. But before we proceed, we have a question 6 from our web audience that very relevant to our 7 current session, so I'm going to read it and I will 8 ask, actually my co-chair, to address it. 9 The question is MedImmune. If we are 10 targeting several virulence factors with the 11 combination monoclonal antibodies, how do we overcome 12 regulatory challenge to this several single mono 13 therapy arms versus a multi combination arm in a first 14 in human study? 15 MR. DUBOVSKY: Right, so I think we just two 16 sentences ago heard opinion about combination 17 approaches and how -- and there are reasons to rip 18 them apart and test each individually. But I think we 19 need to weigh this against what's actually practical. 20 So, if you're doing a study to prevent C. diff that's 21 one population. If you're doing it to prevent VAP 22 that's completely different and I would propose that</p>
<p style="text-align: right;">Page 119</p> <p>1 In terms of adjunctive treatment, like Mary 2 Beth said, when monoclonal antibodies can be 3 administered, let's say, with standard of care; pre- 4 clinical animal efficacy studies could be considered. 5 However, as mentioned in Doctor Suvarna's talk earlier 6 this morning, these models may not be predictive of 7 human efficacy. 8 Lastly, a combination of antibody cocktails; 9 when an antibody is being developed as a combination 10 of antibody cocktails, one has to show the 11 contribution of each component. And a study with a 12 factorial design may be helpful in such situations to 13 assess the contribution of the component, and 14 sometimes in vitro and animal studies may be helpful. 15 However, we have seen in the case of basil toxin MAb 16 (ph), the animal studies predicted that the 17 combination to Antitoxin-A and Antitoxin-B may be 18 beneficial. However, as the clinical development 19 program progressed and Mary Beth can chime in, the -- 20 showed that be basil toxin MAb (ph) was, if more 21 effective. Sometimes the studies with the factorial 22 design can also inform -- the -- more that there is</p>	<p style="text-align: right;">Page 121</p> <p>1 if you're going with a combination of four -- three, 2 four, five monoclonals it's not feasible to do five 3 arm study to look at clinical endpoint in this 4 indication. And that's why earlier I proposed that 5 perhaps a complete different approach would be 6 required, one that would push the risk into different 7 directions than it is now and perhaps to push the risk 8 more into the sponsor side, where they would take the 9 risk of being accountable for the product in general 10 benefit risk. But they would also take an additional 11 risk, a more nimble product could take them over in 12 the marketplace. 13 MR. PEREZ: As soon as I got the case and 14 when I review all the safety profile, the clinical and 15 non-clinical and the clinical results, being honest 16 with you all I was asking myself, does it make sense 17 to keep developing this drug based on these results 18 enable us to know what is the opinion of the audience 19 because if we were in some of these meetings in a 20 company these results at least for my taste not really 21 worrisome. I've never seen a monoclonal with this 22 preclinical safety profile, I've never seen a</p>

<p style="text-align: right;">Page 122</p> <p>1 monoclonal in clinical with this clinical profile that 2 is just an question. 3 MR. COX: I might make a comment on the 4 combination issue. So yeah, we do see combinations of 5 drugs whether they be small molecules or whether they 6 be monoclonal antibodies and, you know, in this 7 instance, you know, folks of Merck have described the 8 factorial design that they used to help them sort of 9 dissect this. There are various different ways that 10 we look at combinations -- combination products and 11 the type of information that we get to justify, you 12 know, that the product has more than one component. 13 You know in some instances you don't do monotherapy 14 studies, you don't do a factorial clinical trial 15 because of concerns that if you went in with one agent 16 you would lead to resistance that would lose the one 17 agent that you got and then you ended up with so -- 18 and then there's also a difference of if all of the 19 components of the drug are targeting, you know, the 20 same organism as compared to having multiple different 21 components that are each targeting different 22 organisms. So there's a lot of different questions</p>	<p style="text-align: right;">Page 124</p> <p>1 Are they produced in the same sorts of magnitudes in 2 the two different species? 3 MR. BLACK: The standard diagnostics for 4 toxin do measure toxin levels as Mary Beth said, that 5 was kind of our early assay. So you know, Toxin A is 6 certainly produced in the situation. We could have 7 looked at strain epidemiology if you had trusted that 8 because you will almost always see Toxin B or A and B 9 coproduced but you, I think, on very rare occasions 10 might see an A only strain from a clinical lysis. So 11 that was very rare and so there seemed to be some 12 implications there that B might be the appropriate 13 toxin in that. So yeah, we do think that, you know, 14 toxin is produced it's not that it wasn't present. 15 Now, in terms of translatability of animal 16 study, so after we had licensed in the product we did 17 support a study at Tufts with (Inaudible) during the 18 gnotobiotic piglet model and that model actually did 19 recapitulate the human data both with the monoclonal 20 or with polyclonal antibodies that neutralizing Toxin 21 A had no effect in his model, either only Toxin B 22 seemed to be impactful in that. So if we have the</p>
<p style="text-align: right;">Page 123</p> <p>1 here and I think, you know, the bottom line is, is 2 that we do look at it from the standpoint of, how do 3 you justify each of the components, what's the role 4 for each of the components, and how can you show that? 5 The answer is not always a factorial clinical 6 trial design, it is sometimes. In other instances 7 there may be other information based on the science 8 that helps up to understand the role for each of the 9 components within an overall combination product. 10 MR. AMBROSE: So, maybe it's to Mary or the 11 antibody experts around the table, but is the failure 12 of -- you know you predicted in the preclinical model 13 that antibody or Toxin A was a potential target for 14 your drug. Is there a way to know before you move 15 into man or propose to move into man how much of that 16 toxin is produced in the rabbit or grasshopper, 17 whatever your model is relative to what's produced in 18 a person. So is it a chance that yeah, it was 19 produced, that toxin was produced in your preclinical 20 species whatever that was but it wasn't produced in 21 people and that's why the FDA found that, that toxin 22 was important. So it's not just as a toxin, right?</p>	<p style="text-align: right;">Page 125</p> <p>1 foresight to know that, that was going to be the 2 translatable model we might have been able to 3 preclinically make that prediction. But years of, you 4 know, of lore was that we had both toxins to address. 5 MR. COX: I think one of the fascinating 6 things is that -- I mean how much we learned from 7 that, when it really did call into question some of 8 what we had thought we knew before. 9 MR. BLACK: Well, I mean the fascinating 10 thing is I think people are still having difficulty 11 accepting that Toxin A isn't doing anything and, you 12 know, we can't definitely argue that it's still isn't, 13 that something else clinically happened but, you know, 14 this was the first clinical result and I think it 15 addresses kind of what Ann's saying too that we have 16 so much comfort in the way that we do small molecule 17 development and how translatable and predictable and, 18 you know, probably people like William and Paul have 19 modified these but we have a lot of confidence if we 20 know the drug is there that we're going to have an 21 effect. But with these new therapies, our animal 22 models, you know, just may not be telling us what we</p>

<p style="text-align: right;">Page 126</p> <p>1 want to know.</p> <p>2 We know in vaccine's side, we know, you know,</p> <p>3 we say mice lie, you know, monkeys fib and humans tell</p> <p>4 the truth. So as you're trying to sort these out it</p> <p>5 is very difficult to get, you know, high confidence in</p> <p>6 the translatability until you start to get some</p> <p>7 clinical experience that replicates what you're</p> <p>8 observing in these models.</p> <p>9 MR. REX: I just -- I want to -- go ahead.</p> <p>10 MR. KALEKO: Actually just to confound --</p> <p>11 confound things further. If I remember the 1980s</p> <p>12 mouse data, all the data with pure toxin was very</p> <p>13 different than those with knockout bacteria, but</p> <p>14 that's not my question. And I may have missed it, I'm</p> <p>15 sorry, I was more concerned with getting my lunch, I</p> <p>16 apologize. But why is this Staph protocol designed as</p> <p>17 a prophylactic protocol as opposed to a therapeutic</p> <p>18 one, where you know that certain strains tend to cause</p> <p>19 certain diseases. Maybe you have a strain that causes</p> <p>20 endocarditis. Why not take endocarditis patients</p> <p>21 treat them then you'll also have time to do your</p> <p>22 diagnostic and you could stop the antibody if it turns</p>	<p style="text-align: right;">Page 128</p> <p>1 it seems like the ability to tap into what's now</p> <p>2 called big data and start looking at incidents of</p> <p>3 disease, what are some that are going to be the</p> <p>4 confounding factors to do the natural history is going</p> <p>5 to better set the company that may be developing a</p> <p>6 product such as this or other products in a state</p> <p>7 where they actually can make the best decision of</p> <p>8 whether it's even worthwhile to pursue a prevention</p> <p>9 study in this type of a setting.</p> <p>10 MR. DUBOVSKY: So, in this particular case</p> <p>11 the attack rate and the placebo rate was quite high,</p> <p>12 right? I mean we could all hope to be doing studies</p> <p>13 in this kind of situation where it could be easily</p> <p>14 powered, our colleagues from (Inaudible) were facing a</p> <p>15 different situation completely. So when you think</p> <p>16 about prevention and the size of this H (ph) database</p> <p>17 I think you need to think a little bit more granularly</p> <p>18 and what's the attack rate. How much were you able to</p> <p>19 enrich the population before you did this study and</p> <p>20 that should perhaps inform the size of this H database</p> <p>21 and not strictly whether your prevention versus</p> <p>22 treatment.</p>
<p style="text-align: right;">Page 127</p> <p>1 out to not be useful; seems to me that would be an</p> <p>2 easier trial design. Am I missing something?</p> <p>3 MS. NAMBIAR: No, this is really just meant</p> <p>4 to be an example for us to have a discussion around</p> <p>5 how one might develop a product for prevention of</p> <p>6 disease. You are right just if, you know, this</p> <p>7 antibody could potentially have been used for the</p> <p>8 treatment of Staph aureus pneumonia.</p> <p>9 MR. KALEKO: Okay.</p> <p>10 MS. NAMBIAR: This is really just meant to be</p> <p>11 a hypothetical case. To stir a discussion and raise</p> <p>12 some of the points that one would encounter when you</p> <p>13 develop a product for prevention, that's the intent</p> <p>14 here.</p> <p>15 MR. KALEKO: Okay. My apologies.</p> <p>16 MS. NAMBIAR: No problem. Just to clarify.</p> <p>17 MR. DUBOVSKY: So --</p> <p>18 MR. DANKER: I think the discussion points of</p> <p>19 the questions are all the ones that normally would</p> <p>20 come up in trying to think about a prevention study</p> <p>21 such as this but what seems to have been missing is</p> <p>22 how do you get the data to make these decisions? And</p>	<p style="text-align: right;">Page 129</p> <p>1 MR. HOPE: So some of us in the room grew up</p> <p>2 in the anti-fungal era when there were no animal</p> <p>3 models or experimental models and it took a large</p> <p>4 amount of funding from NIH to make new experimental</p> <p>5 models especially even basic mold infections and that</p> <p>6 unlocked a huge amount of ability to make new anti-</p> <p>7 fungal agents. So my question is strategically -- so</p> <p>8 I've heard continuously that there's a failure of</p> <p>9 translatable experimental models but what's the</p> <p>10 community's, I guess, strategy given that there were a</p> <p>11 whole lots of dots up in the right hand side of the</p> <p>12 CARB-X compound library about who's going to fund all</p> <p>13 of those experimental models so we could get better</p> <p>14 predictability for disease because it seems that's</p> <p>15 difficult just to put that onus on to sponsor alone.</p> <p>16 MR. REX: So if you pick up that question and</p> <p>17 come back to the story that we heard a minute ago</p> <p>18 about the Merck compound where presumably Toxin A does</p> <p>19 something in some models, right? And is it the case</p> <p>20 that in general neutralizing Toxin A in human beings</p> <p>21 isn't necessary, is it hurtful? And before you jump</p> <p>22 into that, the next place I'm going with it is, what</p>

<p style="text-align: right;">Page 130</p> <p>1 if the products that have gotten registered was 2 Antitoxin A plus Antitoxin B and we kind of left 3 somewhat undefined the question of which one mattered 4 the most. And I know it sounds unscientific not to 5 know okay, because I am here -- I'm extending a little 6 bit of Filip's question. What if there were five 7 toxins that you were interested in neutralizing? And 8 you had -- you can put in five monoclonals and so -- 9 and I can't swear to you that neutralizing Toxin 3 is 10 all that important but I've chosen to stick it in and 11 I do the study with my mixture of my five monoclonals 12 and it does something that seems to be broadly useful 13 to the human beings who get it but you can't swear 14 that neutralizing 3 mattered. Do I care? 15 MS. DORR: So very good question. So Merck 16 actually had proposed to just develop the combination 17 and the only reason why we didn't was because the FDA 18 insisted. So again, you know, congratulations to the 19 FDA for having a very precise crystal ball. But 20 you're right, I think that was our argument. So what, 21 you know, if the combination is safe and effective 22 what does it matter. I mean in the end it was a</p>	<p style="text-align: right;">Page 132</p> <p>1 each arm. So you couldn't -- there was no difference 2 between the two. But you could say well, it was a 3 really small study, it's inconclusive, maybe it was 4 just by chance. But it was enough for Merck to feel 5 that A alone -- the A lone antibody would not work but 6 we had no information about the B alone antibody. So 7 in our first study we included each one of the 8 antibodies alone, a combination and then placebo and 9 everyone got standard of care antibiotic, so nobody 10 got only placebo. Everybody got standard of care plus 11 one of these four treatments. And then we had an 12 interim analysis after 40 percent of the patients were 13 enrolled. 14 What we saw at the time of the interim 15 analysis is that the combination separated from 16 placebo. The B antibody separated from placebo. The 17 A alone did not separate at all, and not only that 18 there were more SAEs than deaths in the A alone arm. 19 Now again, these are really sick people. Is that due 20 to chance or is it due to, you know, what you 21 suggested, John, is that perhaps giving A alone 22 actually without also neutralizing B is a problem. We</p>
<p style="text-align: right;">Page 131</p> <p>1 benefit to us because monoclonal antibodies are very 2 expensive so our cost of goods is half but I mean you 3 -- one can't necessarily argue against what you're 4 suggesting. If you show the combination is safe that 5 would be my feeling but, you know, our situation -- 6 we're glad that we have that information. So, it's a 7 balance. 8 MR. IARIKOV: If you don't mind me please. 9 Was Toxin A arm performing worse in the Phase II 10 study? 11 MS. DORR: So -- no. So in Phase -- so there 12 were two phase, two studies. 13 MR. IARIKOV: Right. 14 MS. DORR: One was only Toxin A antibody. 15 And that study was stopped early because animal 16 studies showed that you needed to neutralize both 17 toxins. So then the companies that we end licensed 18 the monoclonal antibody firm decided to do the 19 combination and the Phase II-B study was only with a 20 combination. They never did anything with Toxin B 21 antibody alone, so they only had a very small study 22 with Toxin A alone and there were five recurrences in</p>	<p style="text-align: right;">Page 133</p> <p>1 don't know, we may never know the answer to that 2 question. 3 MR. REX: So just to be clear the combination 4 if A is toxic then A plus B should -- might also be 5 toxic. But you are then saying if you compared A plus 6 B to B alone there wasn't a corresponding shift. 7 MS. DORR: No, no. So, if you look at B 8 alone plus A plus B there was no difference in safety. 9 And so -- so, you know, we have spoken with people who 10 do preclinical research specifically on the roles of 11 the toxin and their concern is, if you only neutralize 12 A it could be helping B to be more virulent. So there 13 is some kind of interplay. 14 MR. DUBOVSKY: I'd like to pick up on a 15 thread that we heard both from the FDA as well as from 16 Merck and that's about endpoints and how to deal with 17 them. And I'd like to bring it back to the case we 18 talked about because in this case there was a clinical 19 case definition, which didn't meet significance but it 20 depends a lot on how you count that. We also saw 21 there was, in this case there were a large number of 22 deaths. And back to the point on how do you deal with</p>

<p style="text-align: right;">Page 134</p> <p>1 those because it's essentially missing data. It's 2 missing data if they die before you reached the 3 window, it's missing data if you don't get a 4 bacteriological diagnosis, or even if you get an 5 alternative pathogen, but you can't be sure that Staph 6 wasn't in the case.</p> <p>7 So one option is to dump them all as failures 8 and though obviously decrease your point estimate of 9 efficacy. The other option is to examine them, a, 10 either through sensitivity analysis or as a safety 11 finding and the let the global benefit risk drive 12 whether it's a real product or not. So I'd be curious 13 to see if people have opinions on this and I have to 14 say from a product development perspective when you 15 count those as failures -- and these drugs shouldn't 16 impact death directly and they shouldn't impact other 17 pathogens. So the assumption is that these would fall 18 out equally in the placebo and the active group and 19 therefore just dilute your effect and that has real 20 implications for the value ascribed to the product 21 both from the payer as well as the practitioner's 22 perspective and its ultimate use.</p>	<p style="text-align: right;">Page 136</p> <p>1 concept where you match on whether they had VAP and 2 then you match whether they had death and then you 3 basically form some kind of statistical analysis based 4 upon the matching and see how that pans out.</p> <p>5 And then obviously the other thing that would 6 be a concern in this particular scenario was we saw 7 the data from the Merck vaccine trial for Staph aureus 8 and we saw more deaths in those individuals who 9 eventually got the vaccine and had Staph, we don't 10 know why. But now you have a monoclonal antibody 11 that's directed against some virulence factor in Staph 12 and interestingly there's more deaths in the arm who 13 had gotten the monoclonal antibody.</p> <p>14 MR. DUBOVSKY: I guess I wasn't suggesting we 15 ignore the data. I just think that looking at it as a 16 safety finding may be one, an alternate approach. And 17 if you do count this as failures do you actually get a 18 label claim that you stop all-cause pneumonia or all- 19 cause mortality as part of it? Seems like a pretty 20 broad claim.</p> <p>21 MR. COX: So let me throw some numbers out to 22 this because I think, you know, these are good</p>
<p style="text-align: right;">Page 135</p> <p>1 MR. DANKER: There's the other problem of the 2 fact that in the United States there's a whole 3 aversion to calling anybody as having VAP because it 4 impacts negatively upon your CMS standing and so they 5 called them VAEs, did a VAP study this was a real 6 issue in the US. So less of an issue in Europe, they 7 don't seem to have as a big a deal about it but in the 8 US people avoided calling things VAPs.</p> <p>9 So number one that starts to -- automatically 10 start to impact your endpoint, it then would be useful 11 to have an adjudication panel that could look at all 12 the events, not just the ones that are called VAP but 13 then -- and then this way it relieves the hospital of 14 calling something VAP and they're not caught up in it.</p> <p>15 But the deaths are also, I think, an 16 important issue of how you look at the deaths, you 17 know. The FDA for years moved away from attributable 18 mortality because attribution is sort of like beauty 19 is in the eye of the beholder and it gets very 20 complicated to try to sort those out. I'm not sure 21 what you do with the deaths unless you make it a 22 composite endpoint or you do what this winner take all</p>	<p style="text-align: right;">Page 137</p> <p>1 questions. And the other -- so if we think about the 2 pathophysiology of you know nosocomial pneumonia, 3 you've got something somewhere in your mouth and 4 you're fearing something and then you're aspirating 5 and that stuff is getting down there. What's in your 6 mouth, what is in your pharynx maybe influenced by 7 whatever treatment or preventative that you're getting 8 because if it's only active against one or a couple of 9 bacteria those may disappear and then there's always 10 this question of replacement colonization. So let me 11 throw out one for you there -- and this scenario is 12 not unfamiliar I'll say. So the test drug is active 13 against Staph aureus so it's one of the examples that 14 we saw. The rate of Staph aureus pneumonia in the 15 test drug arm is 20 percent. The rate of Staph aureus 16 pneumonia in the placebo arm is 25 percent. We'd just 17 assume this is statistically significant; we won't 18 bother getting too hung up on the numbers. But then 19 if we look at all-cause pneumonia the test drug is 40 20 percent and the placebo arm is 30 percent. So, I'll 21 give you those numbers again. So test drug Staph 22 aureus pneumonia 20 percent, all-cause pneumonia 40</p>

<p style="text-align: right;">Page 138</p> <p>1 percent, and then placebo Staph aureus pneumonia 25 2 percent, all-cause pneumonia is 30 percent. And 3 obviously I've picked these numbers for the purposes 4 of discussion and I've made this a difficult case. I 5 mean if the all-cause pneumonia was, you know, I mean 6 you'd hope to see some decrement but -- so, you know, 7 this is the question I'm trying to get -- 8 MR. REX: It was protective against Staph 9 aureus -- 10 MR. COX: Oh, so there was something going on 11 with shifting the flora and you can always make an 12 explanation of you shifted the flora to something 13 that's more likely to cause pneumonia when aspirated. 14 So the Staph aureus is still a problem but whatever 15 replaced it is in fact, you know, a lower innoculum 16 when it gets down into the lung it's more likely to 17 cause pneumonia. That's the post-hoc explanation. 18 So what do people think about that? So this 19 therapeutic only goes after Staph aureus, what's the 20 right endpoint? Is it the Staph aureus pneumonia? Is 21 it the all-cause pneumonia? Should we be looking at 22 both? What do we do with that?</p>	<p style="text-align: right;">Page 140</p> <p>1 a sense because, you know, what you've just argued is 2 the monoclonal prevented pneumonia, the Staph aureus, 3 it did that part of the box. But as a consequence of 4 that there was an off target toxicity, which was that 5 the elimination of the Staph aureus from your trachea 6 caused E. coli to overgrow -- I am making all this up 7 -- E. coli to overgrow, which caused you to get more 8 E. coli pneumonia. So you're right, it did stop the 9 Staph aureus but it triggered an off target 10 consequence. And, you know, I think we do pay 11 attention to those, and so -- and argue that this, you 12 know, that in fact this product reduces Staph aureus 13 but increases something else and it's not a use so I 14 wouldn't want that personally. 15 So, I mean that is a very interesting way to 16 describe the importance of measuring this. But what 17 if -- we've drift a little way from the question of 18 the combination bit and I do -- I wish I had a better 19 understanding of that, you know, this idea of what if 20 there were multiple components in there and you didn't 21 care what each one of them did so much as the product 22 as a whole. And Ed made the comment that in fact</p>
<p style="text-align: right;">Page 139</p> <p>1 MR. REX: Well, you don't want to take away 2 from the fact that the drug or the monoclonal did the 3 job it was supposed to do. So this gets into this 4 concept of process versus outcomes. I mean you look 5 at just pure outcomes, you can basically throw the 6 baby out with the bathwater sometimes. So I would say 7 if I were that company I would hook up with somebody 8 that had monoclonal against the other pathogens so 9 that I can get the all-cause mortality lower but the 10 drug did what it was supposed to do. The issue is if 11 it's causing replacement pathogens that may be an 12 issue that has to be looked at more from a, I guess, a 13 societal perspective and are you causing more serious 14 pneumonias than you had before. 15 MR. COX: But could you argue too from a 16 patient perspective, not even a societal perspective. 17 The patient essential is not better off in this 18 instance because you're getting 40 percent of patient 19 getting pneumonia with the test and 30 percent with 20 the placebo. 21 MR. REX: So effectively what you got I'm 22 call it for a second an off-target toxicity. Yeah, in</p>	<p style="text-align: right;">Page 141</p> <p>1 that's what polyclonal is. It's -- when we don't 2 insist on the polyclonal, what if I invented rather 3 than a single monoclonal to Filip's five toxins I have 4 a polyclonal. Do I have to study each of the 5 components of the polyclonal, which I don't -- maybe I 6 have to purify them out as antibodies against the 7 individual antigens and re-administer them as a 8 combination or separate components. You know it's 9 interesting that we choose to study the individual 10 components because we can, but do we have to? 11 MR. OUTTERSON: John, before we let Ed answer 12 that I want to pile on just a little bit, okay? And 13 because I was thinking about microbiome, I mean what 14 is the unit of analysis for the monoclonal antibody? 15 We understand what the unit of analysis is. But if 16 you have, you know FMT you know, how many species are 17 in that? You know do we extend this analysis in the 18 microbiome and what is the unit? Is it every species, 19 is it, you know, you can go on forever, right? And 20 so, you know, this question of combination becomes 21 more acute in the next case, is that where we're about 22 to go to?</p>

<p style="text-align: right;">Page 142</p> <p>1 MR. REX: And there is no one single answer 2 to the combination question. And, you know, the 3 combination rule talks about, you know, you can use a 4 variety of different ways to try to understand the 5 contribution of each of the components within the 6 combination product. So it really becomes, I think, a 7 scientific question and yes, issues of feasibility 8 come in there too. There are certain things that are 9 doable and other things that are not. And yeah, as 10 the number of components starts to increase it becomes 11 exceedingly difficult and the question is are they 12 even separable or, you know, are they yeah, depending 13 upon how they're made and such so, you know, it would 14 be -- I mean there's no way that I can answer the 15 question as to what the one answer is as to how you 16 address the combination, you know, the combination 17 rule but I can tell you that, you know, when you're 18 thinking about it you got to think about, you know, 19 how can you demonstrate the component and each 20 component is adding something, what are the various 21 different ways to do that, you know, thinking of 22 preclinical and clinical and all the way through.</p>	<p style="text-align: right;">Page 144</p> <p>1 MS. BOUCHER: Thanks. I just wanted to come 2 back to the endpoint discussion and see if we could 3 push out a little further. So, from what a patient 4 wants I think and from the discussion earlier this 5 morning of getting to products that people want to pay 6 for, thinking about maybe more of a continuum of 7 priorities. You know everybody wants to survive. You 8 want to survive without an infection. You want to 9 survive without an infection and toxicity, and this 10 kind of gets to DOOR. And, you know, just want to tip 11 it over to Scott to talk a little bit because I think 12 as we think about these products that kind of an 13 assessment is even more important because you're 14 talking about in large part adding two drugs that 15 we're already giving patients who are very complicated 16 in the hospital getting a lot of therapies and having 17 a value around that just seems even more important. 18 So I just want to raise that and see if maybe we can 19 hear more from Scott. 20 MR. EVANS: In statistics we have a saying 21 that there are lies, damned lies, and antibiotics. I 22 think one of the issues is you mentioned this issue</p>
<p style="text-align: right;">Page 143</p> <p>1 And, you know, how much data we need really becomes a 2 scientific question which depends a little bit on what 3 we understand from the pathophysiology of the disease. 4 So if that is something that you're thinking about 5 doing come in and visit us. You know the anti- 6 infective division, that's certainly a question that 7 we're more than happy to entertain and recognize that 8 it is an important part of product development. 9 And I think -- Kevin I think your question is 10 sort of falling in the same sort of area, you know. 11 You're putting out the example where, you know, maybe 12 there's many, many different components and the 13 question is how do you try and figure out that you 14 need each of these many different components. And I 15 think again, you know, that's something -- yeah, we 16 probably, you know, work to try and figure out what 17 the answer is to that question, when somebody's got 18 such a development program and come up with something 19 that is scientifically doable that, you know, helps to 20 address this question about the role of each of the 21 various different, you know, parts of what's in an 22 overall mixture of stuff.</p>	<p style="text-align: right;">Page 145</p> <p>1 around death for example, is a missing data problem, 2 but it's not really a missing data problem. We know 3 exactly what happened to the patient, it's not 4 missing. We know their outcome. It's a competing 5 risk problem. And so one possibility in going back to 6 this example, what could be done. What happened in 7 this example study was that, you know, we did a 8 primary -- there was a primary analysis on Staph 9 aureus pneumonia, seemed to a trend going in one 10 direction but wasn't significant. There was some 11 trend in mortality although again not a big enough 12 sample size to really distinguish very much. But one 13 way you can think about this is instead of using the 14 patients in the trial to analyze the outcomes, you use 15 the outcomes in the trial to analyze what happened to 16 the patient and by doing that you eliminate your 17 competing risk problem that you just brought up. 18 So what you have is a scenario of a drug that 19 appears to have some effect on preventing Staph aureus 20 pneumonia, it may even have some -- but it wasn't 21 significant. But if I just look at Staph aureus 22 pneumonia by itself, I don't recognize that some of</p>

<p style="text-align: right;">Page 146</p> <p>1 that prevention is actually of mortality. I don't 2 pick up this sort of this extra signal that I'm 3 getting in mortality. And by looking at mortality by 4 itself I am unable to pick up the signal that I get by 5 preventing Staph aureus pneumonia particularly in 6 those that survived.</p> <p>7 So suppose, in this particular trial that I 8 create an outcome, let's consider three levels, 9 ordinal levels. The most desirable level is the 10 patient survives and they avoid Staph aureus 11 pneumonia, or any pneumonia, even all-cause.</p> <p>12 Second, the bottom category is the patient 13 dies, in the middle, so the most desirable category 14 survival without any pneumonia, least desirable the 15 patient dies. But then there's this middle category 16 where the patient survives but gets pneumonia, has a 17 pneumonia diagnosis. So with placebo the patients are 18 going to fall into these three categories wherever 19 they happen to fall and you had a certain percentage 20 that died, you had a certain percentage that got 21 pneumonia. And what's you're hoping for is that with 22 preventative treatment that you can get patients to</p>	<p style="text-align: right;">Page 148</p> <p>1 duration of hospitalization, the shorter the duration 2 the better off I am. But the patient, the faster the 3 patient dies, the shorter the duration. So when you 4 give me any summary statistic of duration of 5 hospitalization, I don't even know how to understand 6 it. But if you tell me whether the patient survived 7 or not, now I understand but we keep separating them.</p> <p>8 Or even if I analyze efficacy in ITT 9 population safety, and some safety population, you say 10 well, I do some benefit risk and put them together. I 11 don't even know how to interpret it. I'm analyzing 12 different outcomes in different populations. How do I 13 even generalize what's happening? Somehow I have to 14 sort this out in a more comprehensive way. So you may 15 be able to improve on your sensitivity issue in terms 16 of sample size problems by thinking about these finer 17 gradations which are also a more complete 18 characterization of what's happening to the patient 19 than trying to think about how to chop it up into 20 different pieces.</p> <p>21 And the last sort of thing I would say about, 22 you know, this particular example is a prevention</p>
<p style="text-align: right;">Page 147</p> <p>1 migrate to more desirable categories, this notion of 2 desirability.</p> <p>3 And because you've got finer gradations of 4 these outcomes your sample size problem and your 5 significance problem is going to begin to diminish. 6 You're picking up signals, gradations of outcomes. 7 And if you think about what this was, the purpose of 8 thinking of things this way is actually much more 9 pragmatic. You know we created this DOOR outcome and 10 many people use it to think about this sort of sample 11 size problem that you get perhaps more sensitivity in 12 the outcome. And that can be true in some cases, and 13 in this particular case may indeed be true.</p> <p>14 But the real reason that DOOR was created had 15 a much more pragmatic purpose that this is the outcome 16 that the patient experiences. You're using the 17 outcomes again to analyze what happens to the patient 18 rather than the other way around. And this is 19 important because if you analyze each endpoint by 20 itself you can get very distorted -- you have this 21 distortion problem, you know, maybe I am measuring 22 duration of hospitalization. And I think that</p>	<p style="text-align: right;">Page 149</p> <p>1 trial. And so the other thing you may even have to 2 think about factoring in is you've got 70 percent of 3 the patients in this particular trial that never get 4 the infection even without any preventative treatment. 5 So you're going to have to treat a lot of patients, a 6 fair number of patients in order to prevent a few, few 7 events.</p> <p>8 So with preventative treatment the toxicities 9 have to be either one, very rare or two, very 10 manageable. So whether you're able to manage or 11 resolve any sort of adverse events is really the key 12 about whether you're going to be able to think about 13 whether this is going to be a reasonable thing to 14 apply. So, I'll stop there. Thanks.</p> <p>15 MR. MELNICK: So Scott, you beat me -- you 16 beat me to the punch here. You know the hypothetical 17 case addresses preventative therapy. One wonders 18 whether the endpoint, you know, the sort of ordinal 19 endpoint that you're describing would work better in a 20 setting where we were looking at adjunctive therapy 21 for established infection. You know on the face of it 22 you think; well, it's very difficult to show</p>

<p style="text-align: right;">Page 150</p> <p>1 superiority versus antibiotics that work pretty well.</p> <p>2 On the other hand if you use the appropriate endpoint</p> <p>3 could we in treatment of established infection show,</p> <p>4 you know, an adjunctive effect from the antibiotic</p> <p>5 plus antibody.</p> <p>6 MR. DUBOVSKY: I guess I'd like to maybe</p> <p>7 shift the discussion a bit and that's to alternate</p> <p>8 endpoints completely, nontraditional endpoints. So</p> <p>9 with a monoclonal antibody you could well anticipate</p> <p>10 maybe having data or even a label claim around</p> <p>11 preservation of microbiome, perhaps about doing</p> <p>12 resistance versus nonresistant organisms, perhaps</p> <p>13 something around AMR in general, or use of antibiotic</p> <p>14 which you could possibly measure but maybe not in a</p> <p>15 sick ICU setting. The question is more global and</p> <p>16 we're going to get this in some of the discussions</p> <p>17 later, in the next day and a half. Is there actually</p> <p>18 a way to capture that because I think that has true</p> <p>19 societal value and one that at least from a sponsor's</p> <p>20 perspective could be useful in helping the medicine we</p> <p>21 use. I mean how do you get label claim for microbiome</p> <p>22 preservation?</p>	<p style="text-align: right;">Page 152</p> <p>1 you show it? And if there is something that can be</p> <p>2 given that will reduce the rate of development of</p> <p>3 resistance and rate of resistant infections that</p> <p>4 patients experience, and then showing that in a</p> <p>5 clinical trial I think is really the answer to the</p> <p>6 question about how you would, you know, essentially</p> <p>7 show that the product does such a thing. What gets to</p> <p>8 be a little bit tougher is if you're just showing an</p> <p>9 alteration in the bacteria that you culture from</p> <p>10 somebody's GI tract, there become, I think,</p> <p>11 significant questions about, you know, what's the</p> <p>12 right mix, what does this mean, is this going to</p> <p>13 persist, is this is going to go way on its own a day</p> <p>14 or two later anyways and the patient will experience</p> <p>15 no clinical consequences? So, you know, oftentimes</p> <p>16 the way I think about this is, is to think about, you</p> <p>17 know, if you had a person how would you explain to</p> <p>18 them in lay person languages what benefit you've</p> <p>19 conveyed to them. And if you can do that you can say,</p> <p>20 you know, Mr. Jones, if I give you this therapy you're</p> <p>21 less likely to get a pneumonia that's caused by</p> <p>22 resistant organism. I think Mr. Jones can understand</p>
<p style="text-align: right;">Page 151</p> <p>1 MR. COX: Would anyone else like to answer</p> <p>2 that one? So Filip, I think what you're talking about</p> <p>3 is do you want something in the label that talks about</p> <p>4 the patient's microbiome?</p> <p>5 MR. DUBOVSKY: Or the greater public health</p> <p>6 societal benefits we think the nontraditional</p> <p>7 antibacterials bring to the hospital setting.</p> <p>8 MR. COX: And so, what is that benefit and</p> <p>9 how is it shown?</p> <p>10 MR. DUBOVSKY: Well, that's the question,</p> <p>11 isn't it? So you know, maybe the microbiome is more -</p> <p>12 - it's a harder task. Perhaps something around does</p> <p>13 not promote antimicrobial resistance and that could be</p> <p>14 one just based on the mechanism of action of the drug.</p> <p>15 MR. COX: Right.</p> <p>16 MR. DUBOVSKY: Or perhaps it's something even</p> <p>17 softer, but one which I think as a society we all</p> <p>18 crave and would be useful in the greater public health</p> <p>19 perspective.</p> <p>20 MR. COX: Right. So -- I mean, you know, if</p> <p>21 there is a benefit, then the question, I think, is</p> <p>22 more -- it's more how do you demonstrate it? How do</p>	<p style="text-align: right;">Page 153</p> <p>1 that. If you say Mr. Smith, I'm going to alter the</p> <p>2 distribution of the different bacteria that are in</p> <p>3 your GI tract. If I were Mr. Smith I'd say, so?</p> <p>4 What's that going to do for me as patient? So I think</p> <p>5 a lot of this comes back to what is the clinical</p> <p>6 benefit. And for some of these scenarios it can be</p> <p>7 quite challenging to actually design a study. If the</p> <p>8 effect size is small, if the event that you're trying</p> <p>9 to capture occurs only rarely, then that is, you know,</p> <p>10 unfortunately a difficult trial to do even though the</p> <p>11 product may have that mechanism, and that's one of the</p> <p>12 -- you know, we didn't create that challenge, that's</p> <p>13 actually the biology of the disease that we're</p> <p>14 learning and understanding and that's what makes it</p> <p>15 difficult. But I'll stop there and welcome comments</p> <p>16 from other folks on that very topic or things that are</p> <p>17 related.</p> <p>18 MR. BLACK: So maybe, if I can look at it a</p> <p>19 little bit different way. So, Helen commented how</p> <p>20 important prevention is and I think we see that over</p> <p>21 and over again. If you can prevent the infection, you</p> <p>22 know, that is really the best outcome for that</p>

<p style="text-align: right;">Page 154</p> <p>1 patient. So we have a situation where they're using, 2 you know, a diagnostic for colonization and I was just 3 looking at guidelines and we have guidelines for 4 empiric use but none of these have incorporated PCR 5 tests or colonization tests into risk factors for 6 potential to progress to pneumonia in these ventilated 7 patients. So I guess does this approach kind of lower 8 our hurdle for a therapeutic intervention at something 9 as, you know, maybe benign as colonization because we 10 think we could prevent that progression, whereas we 11 certainly are trying to discourage utilization of 12 antibiotics in that type of situations to prevent 13 resistance development. So is it through, you know, 14 preventing use of treating an infection because we 15 actually are intervening earlier with a therapeutic, 16 which should not be driving drug resistance, is that 17 the type of benefit that we could, you know, really 18 enumerate? 19 MR. COX: So what you're describing sounds 20 enumerable, but if the antibiotic usage is appropriate 21 and what patients need, it seems that the reason that 22 they would not get them was because they did not have</p>	<p style="text-align: right;">Page 156</p> <p>1 MR. DUBOVSKY: And they ask about the 2 prophylactic study because I do think this gives you 3 an opportunity to show superiority towards no 4 treatment or placebo in this case as opposed to a 5 treatment regimen, do we have the confidence that this 6 would be a monotherapy or you do have to show actually 7 benefit above standard of care which I think that is 8 then a superiority design, that's going to be very 9 challenging. 10 MR. COX: So that one is a little more 11 complicated. 12 MR. DUBOVSKY: Right. 13 MR. COX: Because if you're adding in 14 additional therapy, but showing no added benefit for 15 that additional therapy because you're arguing that 16 you can't show it above the standard of care, then I 17 think there are some primary questions about what the 18 role of that therapy is. Unless what you're talking 19 about is, you know, there is some noninferiority 20 margin that you can develop for what the standard of 21 care is and you're trying to replace that and show 22 that the effect size of this new thing, you know,</p>
<p style="text-align: right;">Page 155</p> <p>1 an infection. So it sounds like at the core of your 2 argument is a reduction in clinical infections -- 3 MR. DUBOVSKY: I think at the core what is 4 the value of that diagnostic for risk factor for 5 progression to ventilated pneumonia, I guess. And at 6 this point we don't think that colonization is 7 sufficient to prescribe antibiotics. But if that 8 patient population is in fact at a higher risk to 9 progression, do they still benefit, then if you could 10 prevent that with a nonantibiotic therapeutic. 11 MR. COX: So I think I'm understanding what 12 you're saying, which is you're trying to identify a 13 higher-risk patient population and going with some 14 nonantibacterial agent and show a reduction in 15 infection. And that sounds like a very doable trial. 16 With the one caveat being that the size of the trial 17 will be somewhat dependent upon how high risky this -- 18 how high the risk is for this patient population to 19 progress to the disease. In this case I think it was 20 pneumonia, yeah. But that sounds like a doable trial 21 and one that would show clinical benefit to patients. 22</p>	<p style="text-align: right;">Page 157</p> <p>1 absent the standard of care in the one arm is 2 essentially coming out the same as the people who get 3 the standard of care. That's just the way I'm 4 thinking if I'm understanding your question correctly. 5 MR. REX: Kevin and I had a jovial debate 6 about this one day. When I -- we're talking about the 7 spread, and I proposed I'm going to register sterile 8 water as my add-on, sterile water plus antibiotic is 9 not inferior to antibiotic but being hydrated is good. 10 So it's -- I think that, you know, when we started to 11 think about it that way, you know, this notion that 12 there might be some secondary benefit being hydrated 13 by the sterile water is a good thing. But it is not 14 enough really to compel me to buy that at an 15 interesting rate of return. 16 MR. IARIKOV: We're approaching lunch time 17 which is sacred since -- and we have one question from 18 our web audience, I'm not sure who is going to address 19 it, maybe -- we'll see it, maybe Collins. For the 20 staph or this antibody example, will you look to see 21 how much of the toxin is neutralized from patient 22 samples? Is it better to select patients based on</p>

<p style="text-align: right;">Page 158</p> <p>1 toxin detection rather than staph aureus colonization 2 status? And -- 3 MR. DUBOVSKY: I'm not sure it would be 4 practical to select on a serum biomarker versus 5 dominic (ph) PCR at with the current tests that are 6 available. 7 MR. IARIKOV: Right, because antibody might 8 reflect prior colonization infection and that would be 9 very hard to put the patient at risk for development 10 of infection based on serological markers, right? 11 MR. DUBOVSKY: I would think. 12 MR. IARIKOV: All right. And after we dealt 13 with such a difficult question I think it's time to 14 summarize our session. 15 MR. DUBOVSKY: Are they -- right. So we, 16 just at a high level we talked a lot about 17 combinations which vaguely surprised me since this 18 case does not contain any combinations. But I think 19 we got some pretty decent guidance about the 20 flexibility of approach depending on what the specific 21 product is. There was also lot of discussion about 22 the endpoints with some cautionary tales about using</p>	<p style="text-align: right;">Page 160</p> <p>1 imbalances. And yeah, I think it covers. All right, 2 so we're adjourned for lunch. And from 12:35 exactly 3 to 1:35, we'll have a hour. And we'll open our next 4 session with public comments at 1:35 sharp. 5 (Recess) 6 MS. NAMBIAR: Speaker at the public comments 7 is Dr. Grint from AmpliPhi Biosciences. 8 MR. GRINT: Thank you very much. Good 9 afternoon, everybody. My name is Paul Grint. I'm CEO 10 of AmpliPhi Biosciences. We're a company focused on 11 bacteriophage development based in San Diego. Very 12 much enjoyed this morning's discussions. It's been 13 very, very interesting. But I'm going to just have a 14 couple of slides in a few minutes to add a slightly 15 different layer of complexity, I think above and 16 beyond what we've already talked about this morning as 17 we consider natural bacteriophage development. 18 So by background I'm actually an infectious 19 disease physician, but have been in the industry a 20 very long time, privileged to have worked on a number 21 of products in antibacterial, antifungal, antiviral 22 space. But I've now been involved for last 3 years</p>
<p style="text-align: right;">Page 159</p> <p>1 PCR that can lead to false positive endpoints and 2 having to deal with comorbidities and -- either 3 compounding or missing data for that endpoint. 4 I guess we also had some discussion about how 5 PKP can be different in patient populations with whom 6 we are -- healthy normal volunteers to your sick 7 populations. Then we did talk about the utility of 8 animal models and the trickiness of them being 9 actually relevant and not knowing that until you do 10 the experiment in people to validate them. And I 11 guess, yes, I think those were the major themes I 12 captured. 13 MR. IARIKOV: Right, and I don't have much to 14 add. I think we talked about the importance of -- 15 also talked about the importance of sample size. We 16 talked about the importance of the sample size and the 17 study that dovetails with the importance of 18 appropriate endpoints and maybe to all enrolled 19 subjects and account for early discontinuations which 20 could be critical in these trials and the importance 21 about natural history data to inform us on the trial 22 designs and help maybe to interpret data mortality</p>	<p style="text-align: right;">Page 161</p> <p>1 with bacteriophage development which I must say 2 certainly has been a real education for me. 3 So just to remind you, bacteriophages were 4 actually discovered just over a 100 years ago. So 5 we've known about them for a long time. But it's 6 really only more recently that we've really tried to 7 develop them as proper therapeutics. Having said 8 that, many people were really not aware that they were 9 actually sold as therapeutic products back in the 10 1930s by some of the larger pharmaceutical companies 11 both in Europe and the U.S. at that time but really 12 disappeared from the scene as antibiotics became -- 13 penicillin in particular became more broadly available 14 in the 1940s. 15 So just quickly about bacteriophage biology, 16 if you're not aware of it. Of course this is a 17 natural virus, the so-called predator of a bacteria. 18 It infects the bacteria. We're talking about lytic 19 bacteriophage here now. Infects the bacteria, binds 20 to a very, very specific binding site on that 21 bacteria, so phages are very specific, which is good 22 news in some ways. But obviously a challenge when it</p>

<p style="text-align: right;">Page 162</p> <p>1 comes to drug development. Obviously DNA is injected, 2 there is replication that goes on and the 3 bacteriophage lysis the bacterial, releases progeny 4 virus that go on to infect other bacteria in the 5 vicinity. So that's a bit of basic history, so a 6 basic lifecycle.</p> <p>7 So if you think about it, these are very, 8 very interesting organisms. So the question is how do 9 we harness them and use them as potential 10 therapeutics. So our approach has been to build 11 bacteriophage libraries, screen these and select a 12 limited number of products that actually have broad 13 spectrum across the specific bacteria strain that 14 we're interested in. And currently we actually have a 15 staph aureus product and pseudomonas product, a 16 pseudomonas aeruginosa product in the clinic soon be 17 entering Phase II clinical trials. But what I wanted 18 to do today was just to highlight some of the 19 difficulties or differences that we think about and 20 face when it comes to administering, in essence a live 21 virus which when it gets to where you want it to get 22 to, which is a pathogenic bacteria will in fact</p>	<p style="text-align: right;">Page 164</p> <p>1 said, serum concentration really is not relevant in 2 terms of predicting what we're doing. So I'm not 3 going to go in too much the detail, but I'm trying to 4 give you some ideas.</p> <p>5 And preclinical toxicity, so studies in 6 unaffected animals may obviously show you some 7 toxicity of the manufactured product, but obviously 8 don't really reflect phage exposure locally in a given 9 organ or tissue that happens in an infected animal.</p> <p>10 So I just very simply put a table together 11 again just to drill into a bit more detail to 12 highlight some of the differences and maybe just to 13 help you understand some of the things we think about 14 every day as we take what is known about the 15 bacteriophage science and we try and translate that 16 obviously into the clinical setting.</p> <p>17 Sensitivity testing. Yes absolutely, you can 18 test the sensitivity to bacteriophages and we do that. 19 And clearly that's -- we do that on the samples before 20 we treat patients and then subsequently as patients 21 are going through patient treatment. But it's not 22 what we used to, it's more molecule antibiotics being</p>
<p style="text-align: right;">Page 163</p> <p>1 replicate, create more of itself, obviously locally in 2 that environment. But once that infection is cleared 3 it is then naturally cleared by the body.</p> <p>4 So we had an interesting discussion this 5 morning, obviously, you know, talking about potential 6 dose selection for antibodies. So think about a dose 7 selection for a bacteriophage. This is not very easy 8 as you can think about it because clearly the dose you 9 administer doesn't necessarily affect the dose or 10 concentration of bacteriophage you're going to end up 11 with at the site of infection.</p> <p>12 Persistence in unaffected animals really is 13 unrelated to what you see in infected animals. And we 14 have done bacteriophage kinetics in humans, limited 15 amount of work, but if you inject these IV and that's 16 how we generally treat, within an hour or 90 minutes 17 they're actually cleared from the bloodstream. So it 18 doesn't really tell you very much. But clearly that's 19 as much information we have.</p> <p>20 Moving on to PKPD. So obviously as long as 21 sufficient dose is reached at the site, then we -- and 22 replication is initiated, then obviously as I just</p>	<p style="text-align: right;">Page 165</p> <p>1 MIC based. So we're still really trying to understand 2 what that means, you know, what does an intermediate 3 sensitivity look like for bacteriophage.</p> <p>4 PKPD models. Again, we've done some work in 5 the space. We'll continue to do some. But the real 6 question is how relevant are these given some of the 7 bacteriophage biology that I just briefly discussed. 8 That's a very, very interesting question.</p> <p>9 Proof of concept animal models. Yes, we have 10 conducted some of these in some of the classic models, 11 let's say, of, you know, pseudomonas pneumonia or 12 other ones we can demonstrate that bacteriophage 13 dosing is similar to -- has similar effects to in 14 terms of efficacy to some antibiotics. But again how 15 far do we take this. We had this interesting 16 discussion this morning that really one needs to get 17 into the clinic, I think, to understand more before 18 you can really understand how useful some of these 19 translational models are and do they really translate.</p> <p>20 So our idea is move forward to the clinic as 21 much as we can and then try and take that information 22</p>

<p style="text-align: right;">Page 166</p> <p>1 back and refine the models by the predictors of what 2 we might see clinically. 3 Toxicology. Again we've done limited work. 4 But the question is when you think about a lot of the 5 conventional toxicology that's required, the small 6 molecules, how much of that is really relevant for 7 what we're trying to do. And again, we're trying to 8 work that out as we go along. 9 And finally, clinical experience. You know, 10 many, many tens of thousands of patients have been 11 treated with bacteriophages over the decades. That 12 information is really very sparse and not very helpful 13 as one thinks about a more conventional sort of 14 regulatory package. You may have seen that there are 15 now a growing number of case reports that are coming 16 out on an individual patient basis. We're actually 17 publishing some of these right now ourselves. 18 We've been working very closely with CDER on 19 the expanded -- single patient expanded access program 20 under the emergency INDs where we have been able to 21 treat quite a number of folks now at a limited number 22 of institutions in the U.S. and in Australia and</p>	<p style="text-align: right;">Page 168</p> <p>1 following on to Paul's stimulating presentation to 2 Tunable Target Degradation where we can tag any 3 bacterial gene of interest and whether that's 4 nonessential or essential and then selectively degrade 5 the protein product of that gene. A very powerful 6 tool for target identification, target validation, 7 pathway elucidation. 8 Anti-persister where we use artificial 9 intelligence to elucidate bacterial physiology in 10 order to develop potentiators of existing antibiotics. 11 We've tackled the aminoglycosides first, we have 12 potentiators of both tobramycin and amikacin in 13 development, but we've extended that now to 14 fluoroquinolones as well. And then we acquired the 15 LPA platform, seem down at around 6:00 p.m. here, as 16 initially a payload for engineered phage. However the 17 profile that's emerging with these LPAs as standalone 18 therapeutics is very exciting. This is our portfolio. 19 Generally speaking, a mixture of both in-licensed and 20 in-house developed products. 21 With respect to LPAs, as you all know, some 22 of today's most successful antibiotics are peptides.</p>
<p style="text-align: right;">Page 167</p> <p>1 capturing that data. And that's useful and it helps 2 guide perhaps narrowing some degrees of dose selection 3 and duration of therapy and the types of patients that 4 we may treat in the future. 5 But really for us to really understand the 6 potential of bacteriophage therapeutics, we do need to 7 move forward into randomized clinical trials. And we 8 are heading towards that in the early part of next 9 year and I really look forward to try to being able to 10 investigate bacteriophage therapeutics as an adjunct 11 to antibiotics in some of the real multi-drug 12 resistant infection settings. So thank you for your 13 attention. 14 MS. NAMBIAR: Thank you, Dr. Grint. Our next 15 speaker is Dr. Wagner from EnBiotix. 16 MR. WAGNER: Good afternoon, everyone. So 17 EnBiotix is an engineered antibiotics company founded 18 on the synthetic biology and artificial intelligence 19 platforms of the Collins Laboratory at MIT. Jim 20 Collins is a noted researcher in this area and has 21 licensed to us a number of exciting platforms shown 22 here, ranging from engineered bacteriophage just</p>	<p style="text-align: right;">Page 169</p> <p>1 We acquired this actually from a laboratory in Germany 2 that had been funded by both Boehringer Ingelheim 3 Venture and Novartis Ventures. So far the profile is 4 very unique, very novel mechanism of action, very good 5 potency, broad spectrum gram-positive, gram-negative 6 activity. Very low mammalian cell toxicity as well. 7 And we've demonstrated this both in vitro and in 8 several animal models so far. 9 You see here that the difference between 10 these LPAs and traditional antimicrobial peptides is, 11 as you know, the previous generations of these types 12 of molecules have shown high mammalian cell tox 13 because they have been primarily membrane disruptors. 14 And that's the mechanism by which they call -- cause 15 cell lysis. In our case we're actually targeting the 16 ribosome. I will get into that in a moment. 17 The two classes of these that we're 18 developing, they're both insect-derived, one from the 19 honeybee, another from the milkweed bug. We have 20 extensively derivatized them from the starting 21 peptides, not only to be more proline rich which 22 confers some of this antiribosomal activity, but there</p>

<p style="text-align: right;">Page 170</p> <p>1 is a number of other properties that we've been able 2 to design into the molecules as well. 3 There are specific transporters in the inner 4 membrane that are very, very redundant for both 5 classes of LPAs that we are developing. We've done 6 some fairly extensive resistance development studies 7 that show that the redundancy here is thought to 8 confer a strong resistance to resistance development, 9 so we're quite encouraged by that so far. 10 There is a few mechanisms of action that are 11 involved in terms of being antiribosomal. First with 12 respect to the Apidaecin class. We have two that 13 we're investing, one is ribosome subunit assembly. 14 Thus far by a unknown mechanism of ribosomal assembly 15 inhibition we are investigating that. We're still -- 16 it's too early to publish on that yet. 17 The other mechanism which we have published 18 on, not shown here, is whereby release factors in the 19 ribosome are inhibited which then prevent the 20 elongated peptide from the ribosome from being 21 released. 22</p>	<p style="text-align: right;">Page 172</p> <p>1 agents that are out there obviously because these are 2 peptides molar comparability in terms of MICs does 3 amount to a slightly higher dose, but still something 4 that is administrable. With that, happy to take any 5 questions if that's allowed. If not, thank you. 6 MS. NAMBIAR: Thank you very much. So our 7 next speaker is Dr. Lajaunias from Combioxin. 8 MS. AZEREDO: Thank you for the opportunity 9 to say a few words about our efforts to move forward 10 with a nontraditional agent named CAL02. Combioxin is 11 a very small Swiss company and we develop liposomes as 12 anti-infectives. Since 1995 more than 10 liposomal 13 formulations have been approved for human use. All of 14 them have been used as vehicles for an active drug. 15 None of them have been described with a 16 pharmacological activity of their own. These are 17 biologically neutral compounds. 18 And we've been working on liposomes in a very 19 novel manner. We engineered specific mixture of anti- 20 liposomes that can mimic cell lipid microdomains used 21 as docking stations by numerous bacterial toxins. 22 Preclinical studies have shown that when given the</p>
<p style="text-align: right;">Page 171</p> <p>1 In the Oncocin class we actually blocked the 2 entire exit tunnel of the intact ribosome. This is 3 actually we think quite significant for a number of 4 reasons. We think that the mechanism by this blockage 5 is really steric hindrance along the entire exit 6 tunnel. And because it overlaps several known binding 7 sites to other antibiotics, again resistance 8 development is very slow. 9 We have good in vivo efficacy thus far for 10 both the Oncocins and the Apidaecins. Here is an IP 11 model on the left and showing both very good survival 12 data in E. coli and Kpn. Thigh Burden Model for both 13 Oncocins and Apidaecins. Here showing Oncocins with a 14 4 logger, so a reduction in CFU recovery in Thigh 15 Infection Model. Apidaecin, similar types of 16 reductions and similar types of survival curves in the 17 IP model as well. 18 We are continuing to derivatize both classes 19 in order to expand spectrum to both gram-positives and 20 gram-negatives. That's shown on the bottom 21 particularly. Potency is quite good, especially when 22 viewed from a molar level. Very comparable to other</p>	<p style="text-align: right;">Page 173</p> <p>1 choice to target cells or these anti-liposomes, toxins 2 fully bound to CAL02 irreversibly. So the mode of 3 action of CAL02 is to act as a winning decoy in order 4 to entrap and neutralize a large panel of toxins. 5 Here the liposomes are the active agent. 6 As you all know, toxins are bacteria's most 7 deadly weapons. They play a key role in a number of 8 components of severity that may lead to long-term or 9 even fatal complications. CAL02's activity is 10 complementary to that of antibiotics which effectively 11 kill the bacteria, but fail to neutralize these toxic 12 missiles. It is however independent from antibiotic's 13 MIC or class. 14 It has a unique broad-spectrum activity 15 against both gram-positive and gram-negative bacteria 16 including some escape pathogens regardless of the 17 resistance profile, and it does not prompt any 18 resistance on its own. And because it entraps these 19 toxic components that play an important and upstream 20 role CAL02 is expected to have a wide therapeutic 21 impact including an organ dysfunction or inflammation. 22</p>

<p style="text-align: right;">Page 174</p> <p>1 Preclinical studies were carried out against 2 a number of toxins and bacterial strains. Toxins 3 neutralized by CAL02 include pneumolysin or 4 streptolysin, alpha-hemolysin or PVL. And in vivo 5 studies were performed with a view to translating at 6 best the clinical situation. So pneumonia and 7 bacteremia models CAL02 are systematically used hours 8 after an infectious challenge. And in some cases 9 hours after the start of antibiotics. And infections 10 were caused by strep pneumoniae or pseudomonas or 11 staph aureus including some MRSA strains such as 12 USA300. 13 And overall, results highlighted that adding 14 CAL02 to antibiotics improved outcome. I'm not giving 15 much details about the preclinical studies, but we 16 also observed that CAL02 alone as a monotherapy could 17 provide full protection. We met -- we had a 18 scientific advice with the U.K. agency to discuss the 19 preclinical package and a first-in-human trial 20 directly in patients and we used the VHP to launch the 21 trail in France and Belgium. And this first-in-human 22 trial was recently completed.</p>	<p style="text-align: right;">Page 176</p> <p>1 The severity of the 19 patients that were 2 finally recruited was as expected by the protocol. 3 More than half of the patients were in septic shock at 4 baseline and more than 40 percent under invasive 5 mechanical ventilation. Overall, placebo patients 6 were less severe than those randomized to the CAL02 7 treatment arms with a mean APACHE II of 17.4, for 8 example, as compared to 25.3 or 22.1 in the CAL02 9 treatment arms. 10 And also all bacteremic patients were in the 11 CAL02 treatment arms. The primary objective was 12 safety and tolerability. All AEs were in line with 13 the profile of the study population. There was no 14 concern raised regarding safety. And regarding 15 exploratory efficacy, there was one death in each arm 16 and all surviving patients were cured at TOC. 17 However, at early TOC on day 8 which was set 1 to 2 18 weeks earlier than TOC, more patients in the CAL02 19 high dose arm were cured, 56 percent versus 20 in the 20 placebo arm, and this translated into a shorter time 21 to cure. This arm also presented a shorter duration 22 of invasive mechanical ventilation.</p>
<p style="text-align: right;">Page 175</p> <p>1 It was a randomized double-blind placebo 2 controlled study that was composed of three arms, 3 CAL02 -- namely CAL02 low dose, high dose or placebo 4 in addition to standard of care. And the primary 5 objective was of course safety and tolerability. Now 6 for this first assessment in human we decided to focus 7 on a specific population, severe pneumococcal 8 community-acquired pneumonia for a number of reasons. 9 Importantly, it still addresses a huge medical need 10 since considerable percentage of patients still 11 developed complications, need to be admitted to the 12 ICU where they spent about 2 weeks and where mortality 13 rates still surpasses 30 percent despite best 14 available care. 15 CAL02 was administered intravenously twice 16 within 24 hours and after first group of patients were 17 treated with either CAL02 low dose or placebo and IDMC 18 reviewed safety, dose was escalated to the high dose 19 and this IDMC reviewed safety once again after first 20 group of patient was treated with CAL02 high dose or 21 placebo to allow continuation. 22</p>	<p style="text-align: right;">Page 177</p> <p>1 Now for both the CAL02 low dose and CAL02 2 high dose arm we observed faster improvements of organ 3 dysfunction with a 50 percent decrease in the SOFA 4 score by day 5 versus 12.5 in the placebo arm. We 5 observed a protection and full stabilization of the 6 hemodynamic parameters versus no improvement or even 7 worsening for some placebo patients and a faster 8 normalization in inflammatory biomarkers. 9 So all this is in line with the mechanism of 10 action of CAL02 and was translated in a shorter ICU 11 stay, length of stay of 5 days for the CAL02 high dose 12 arm versus 12 for the placebo arm. By the way, this 13 length of stay for the placebo arm is in line with 14 that described for patients under standard of care in 15 similar populations in recent trials. 16 So overall, no parameter got worse with CAL02 17 high dose enough to plan another larger trial. And 18 our priority now is to meet with the FDA and help 19 authorities to discuss the next step. 20 We are here with a broad-spectrum agent, 21 quite different from other antitoxins in development. 22 It has the potential to be used on top of any</p>

<p style="text-align: right;">Page 178</p> <p>1 antibiotic standard of care treatment to improve 2 standard of care for severely infected patients. We 3 will have to show superiority, we need to decide on 4 the study populations and the endpoints. And we 5 certainly want to address the full potential of CAL02 6 and expand to other pathogens including MDR strains. 7 Thank you.</p> <p>8 MS. NAMBIAR: Thank you and our next speaker 9 is Dr. Mannino from Matinas BioPharma.</p> <p>10 MR. MANNINO: Thank you very much for giving 11 me the opportunity to speak to you today. What I'd 12 like to do is to tell you about a process that we 13 have, a little lipid nanocrystal that allows us to 14 take traditional pharmaceuticals, antimicrobials and 15 deliver them by a very nontraditional process.</p> <p>16 This is just a way of pointing out that along 17 with the physiology that bacteria change enzymes, ways 18 of rejecting drugs from the cell, a lot of microbial 19 pathogens find a way to get into the cell and to take 20 over the animal cell physiology, for example 21 preventing destruction by macrophage. And they use 22 the interior of the cell in two ways; one to grow and</p>	<p style="text-align: right;">Page 180</p> <p>1 there is enough calcium and enough is only about 0.5 2 millimolar, this crystal with the drug on the inside 3 can be boiled in detergent and it won't open. 4 That provides high stability in two ways. 5 Number one, because this is an anhydrous process 6 unlike a liposome or a lipid nanoparticle, which has a 7 fluid bilayer and some sort of water associated with 8 this. As this crystal forms, it ejects the water. So 9 it's an anhydrous process, so it eliminates hydrolysis 10 and the material on the inside is not susceptible to 11 oxidation. So we stabilize it on the shelf, that's 12 number one.</p> <p>13 But number two, because physiological calcium 14 on the outside of cells is between about 1.5 and 4 15 millimolar, when you introduce these particles into an 16 animal, either through IV, IM, or through oral or 17 intranasal delivery because there is enough calcium in 18 gastrointestinal secretions for example, the crystal 19 does not open. 20 These crystals then enter the 21 gastrointestinal tract and the pharmacokinetics 22 suggest that it goes across the GI tracts through the</p>
<p style="text-align: right;">Page 179</p> <p>1 multiply, but the other way to avoid the ability of 2 very potent antimicrobial drugs such as 3 aminoglycosides, for example, to get through the 4 membrane and attack them. So they hide from the drug 5 there.</p> <p>6 What I'd like to show you today is a little 7 lipid nanocrystal that we are using which enables us 8 to deliver very, very safely and in a very targeted 9 fashion the antimicrobial drugs into the interior of 10 the cell. This lipid crystal is formed simply and we 11 have this now at GMP scale so we're making 100 liter 12 batches of this. So it's a little nanocrystal which 13 forms from the addition of calcium, and this is very 14 unique to calcium to a lipid cell made of 15 phosphatidylserine.</p> <p>16 So the process is you take your liposome, you 17 add your API to it, you drip in calcium and the 18 liposome changes. It goes from a fluid structure, 19 sort of like water changing to ice. The lipid 20 structure of the bilayer turns into a crystal and it 21 rolls up. So the process you see here is the little 22 nanocrystal, multilayered, highly stable. As long as</p>	<p style="text-align: right;">Page 181</p> <p>1 lymphatics at which point you still have the drug in 2 the crystal. And I think this is a very unique 3 phenomenon because we are hiding the drug from the 4 body and you'll see the toxicity effects. The 5 reduction of toxicity is a consequence of this.</p> <p>6 So we've shown it reduces environmental 7 attack and it reduces attack by the body. So now, how 8 does this crystal with the drug inside actually 9 deliver anything that can have an effect? Well, it 10 turns out this calcium and the lipid we're using is a 11 negatively charged lipid called phosphatidylserine. 12 This is a process that is used for example for the 13 secretion of neurotransmitters and synapses or the 14 secretion of adrenaline in the adrenal cortex.</p> <p>15 The calcium channel opens the intracellular 16 calcium is about 1,000 to 10,000 times lower than 17 extracellular and that's to prevent membrane fusion on 18 the inside of the cell which would destroy the 19 integrity of the cell. So what happens is if you want 20 the release of adrenaline, the body sends a signal to 21 the plasma membrane, the calcium channel opens, 22 calcium goes in, binds negatively charged lipid and it</p>

<p style="text-align: right;">Page 182</p> <p>1 makes membrane fusion, and the adrenaline is released. 2 This natural membrane fusion process, it has 3 no positively charged lipids, it has no proteins. So 4 we reduce toxicity, we reduce inflammation, we reduce 5 any immune response to these crystals and you can see 6 here in the picture we have a fluorescent dye in the 7 little aggregative crystals interacting with 8 spleenocytes and you can see how the fusion of the 9 crystal membrane, because this is an intermediated 10 membrane fusion with the target cell now allows the 11 delivery of the drug into the cell. So it's naturally 12 taken up by cells, it is taken up by activated cells 13 such as activated macrophage neutrophils. We've also 14 delivered it to virally infected cells. 15 In healthy animals you see very little 16 targeted distribution. In infected animals you see 17 highly targeted to the site of infection and you also 18 see very, very low blood levels. I'll show you some 19 of the tox studies that we've got. So we're 20 fundamentally changing the pharmacokinetic dogma. 21 We're saying that we get very low blood levels, which 22 gives us low toxicity and very high targeting to the</p>	<p style="text-align: right;">Page 184</p> <p>1 candidiasis. Because they were treated with azoles 2 for long periods of time, they're azole resistant. 3 Amphotericin, you know, has been around for a 4 long time. If you give any of the IV formulations, 5 more than 2 or 3 weeks you begin to kill the kidneys. 6 The literature tells you that giving a human being 7 more than 3 grams of Amphotericin in your life will 8 cause kidney damage. You can see the patients that we 9 have here, we've had two of our patients on the drug 10 for over 545 days at the same doses. The clinical 11 symptoms have been reduced. The study protocol is 50 12 percent. Most of these women now are living 13 clinically free of the disease and there are no kidney 14 problems, and they've all signed up to maintain a 15 longer term on the protocol because if they come off 16 the drug because they don't have an immune system, the 17 Candidiasis comes back. 18 I'm going to show you some data that we're 19 doing. Dr. Peter Williamson at the NIH with his mouse 20 model of cryptococcal meningoencephalitis. And I 21 don't have any of the efficacy data but Dr. Williamson 22 has shown that the oral Amphotericin in this model is</p>
<p style="text-align: right;">Page 183</p> <p>1 target tissue and very good efficacy. 2 So I just gave you some examples of the three 3 of the drugs that we are using. Our lead product is 4 Amphotericin B. We are in Phase II clinical trial, 5 I'll show you some data of that, at the NIH Clinical 6 Center right now. But you can see in animal studies 7 it's worked against Candida, Aspergillus, Cryptococcus 8 which are both intracellular and extracellular, but 9 it's worked against Leishmaniasis in an in vitro 10 model, which is just intracellular. 11 The Amikacin data, and I'll show you one 12 slide of that, against mycobacteria, we have that in 13 Phase I and for Francisella we've show in an in vitro 14 model. And with Atovaquone, we've shown that in an 15 animal model of Pneumocystis that again we have very 16 low blood levels, we have oral delivery, we have 17 systemic bioavailability and high efficacy. So let me 18 show you three examples. 19 This is a study being run at the clinical 20 center at the NIH by Dr. Alexander Freeman, the 21 patients are born with immunodeficiency diseases which 22 make them highly susceptible to mucocutaneous</p>	<p style="text-align: right;">Page 185</p> <p>1 as effective as injectable Fungizone. But what he 2 wanted to do is see actually can you give this crystal 3 orally and have it appear in the brain, going across 4 the blood-brain barrier. 5 And so we gave him rhodamine-labeled 6 Amphotericin crystal that he gave in his mouse model 7 and you can see the top two panels that we were not 8 treated, so there's no rhodamine in the brain. In the 9 bottom one, they're infected with crypto, but they 10 were not given any drug, but in the third panel down 11 you can see in the infected treated animal there are 12 high levels of the Amphotericin rhodamine particle in 13 the brain at the site right by where the crypto -- the 14 yeast is. 15 Finally, with Amikacin, this is a cystic 16 fibrosis mouse model that we are in collaboration with 17 Dr. Diane Ordway of Colorado State. And in cystic 18 fibrosis you have two levels of barrier to get through 19 to treat mycobacterium. One is the intense mucus that 20 you have in the lung which prevents material from 21 getting down into the lung and then the second one is 22 again the cell membrane. How do you get a highly</p>

<p style="text-align: right;">Page 186</p> <p>1 charged water-soluble aminoglycoside like Amphotericin 2 into these sites? 3 Our hypothesis for how these lipid 4 nanocrystals target and deliver suggested that rather 5 than trying to get through the mucus into the infected 6 tissue we would give this orally and macrophage which 7 originate in the bone marrow as monocytes, as they 8 evolve. That the macrophage which are activated 9 because of inflammation would pick up the crystals, 10 the Amikacin would be released as the macrophage 11 travel into the infected lung. And you can see here 12 that we have very strong efficacy in all lung, spleen 13 and liver. And Dr. Ordway did the Pathology and you 14 can see both in the low dose and the high dose of the 15 Amikacin and the lipid crystal the lesions in the lung 16 are essentially gone after long-term treatment. 17 So basically what we say we have is a very 18 nontraditional way of being able to deliver highly 19 potent and well-understood antimicrobials. We can 20 increase the oral bioavailability of injectable drugs. 21 Both Amphotericin and Amikacin are only available by 22 injection at this point. We use a natural targeting</p>	<p style="text-align: right;">Page 188</p> <p>1 me speak today. 2 MS. NAMBIAR: Thank you, Dr. Mannino. 3 Our last speaker in this session is Dr. 4 Leininger from Aridis Pharmaceuticals. 5 MS. LEININGER: Good afternoon, I'm Lizzy 6 Leininger with Aridis Pharmaceuticals. 7 Like to talk a little bit about the products 8 we are developing at Aridis Pharmaceuticals and some 9 of the challenges that we are facing. We actually 10 have a repertoire of like three or more antibodies, 11 antibacterial human monoclonal antibodies that are 12 under clinical development for acute pneumonia. 13 I'll talk about AR-301 which is against staph 14 aureus alpha-toxin, AR-105 which is against 15 Pseudomonas aeruginosa alginate, and AR-105 which is 16 against Pseudomonas aeruginosa LPS. So all of these 17 are targeted against the bacteria. These are fully 18 human monoclonal antibodies that have been made by 19 Ardis' proprietary technology where we are able to 20 make them from the B-cell repertoire of convalescent 21 patients. They're fully human to start with. 22 We are in different phases of development</p>
<p style="text-align: right;">Page 187</p> <p>1 to get the drug to the site of the infection or the 2 inflammation. We have very low blood levels, which is 3 a wonderful blessing because we have very low 4 toxicity, but it's kind of a curse when you're trying 5 to figure out how do you bring a drug forward when the 6 plasma PK does not tell you anything about the 7 efficacy, okay. 8 This material right now we are making again 9 routinely 100 liter batch, the particle size is highly 10 reproducible. The encapsulation of the drug is highly 11 reproducible and it's made from a soybean lipid. So 12 the matrix again is simply soybean, phosphatidylserine 13 and calcium, very safe, very nontoxic. Because there 14 is no water in it you can either save it and deliver 15 it as a crystal suspension or you can spray dry it, 16 laphalyze (ph) it, we've done all of those things and 17 it works. 18 Again we're in human clinical trials and for 19 those of you who are interested also in the nucleic 20 acid polymer world, we're using this now to try to 21 achieve intracellular delivery of nucleic acid 22 polymers as well. So thank you very much for letting</p>	<p style="text-align: right;">Page 189</p> <p>1 ready for Phase III with our Pseudomonas aeruginosa 2 antibody and going on we are in Phase II with AR-105. 3 We are looking at these antibodies as adjunctive 4 treatment with -- to standard of care of antibiotics. 5 And the reason we're looking at it as an adjunctive 6 therapy is really to avoid commercialization risks 7 that were discussed earlier today, which is associated 8 also with the prevention in the low attack rate and 9 we're looking at a preventive mode. So we are in the 10 therapeutic mode here. 11 We are also looking at clinical superiority, 12 since we're in an adjunctive therapy to standard of 13 care and we are looking at superiority based on 14 clinical cure, which I'll talk a little bit more about 15 that. And we are in VAP patients, so in ventilator- 16 associated pneumonia and hospitalized patients. 17 So I'd like to discuss just a little bit, 18 present some of the development challenges that we 19 have been facing, developing these therapeutic 20 monoclonal antibodies. And as we had discussed this 21 morning and it was presented, of course we are facing 22 challenges with the study design. And this is really</p>

<p style="text-align: right;">Page 190</p> <p>1 based on the patient population that we are dealing 2 with. 3 Here we are hospitalized patients that are 4 ventilated, so that whole setting is a little 5 complicated. We are also looking at pathogen-specific 6 infections in these patients in addition to other 7 associated infections that they may have. And we are 8 also giving it as an adjunct therapy to the standard 9 of care of antibiotics. So just standardizing 10 standard of care is another challenge itself in these 11 trial designs. 12 So in addition to the trial design setting 13 itself, we are challenged with the definition of our 14 clinical endpoint. We've been challenged all cause 15 mortality as a clinical primary endpoint and we have 16 also brought into the discussion and have agreement 17 with the agencies to use clinical cure as a primary 18 endpoint. 19 The problem with clinical cure as your 20 primary endpoint that's not a standard definition, so 21 we have been negotiating the clinical cure definition 22 based on clinical meaningful parameters and also</p>	<p style="text-align: right;">Page 192</p> <p>1 indication that we're dealing with. 2 We also have challenges in our development 3 program with the CMC area. I'm not going to go into 4 detail. These are monoclonal antibodies that as we 5 start early on in development and then move forward 6 there's always going to be optimization to outline 7 changes, manufacturing changes, so we have to deal 8 with those comparability issues independent of 9 treating antibacterials. 10 And finally, I'd like to talk a little bit 11 about the challenges and the need for effective 12 communication with the FDA and with regulatory 13 agencies in general. As I mentioned, not only are we 14 in these new therapy approaches for bacterial 15 therapies, infections, we're also in orphan drug 16 setting and we're also in unmet medical need. So 17 there is an urgency to get these products out there 18 and to demonstrate they are effective and safe and get 19 them out there to the population. 20 And having an effective way of communicating 21 with the agency is really critical. And we believe 22 that we want to pave the path together because we</p>
<p style="text-align: right;">Page 191</p> <p>1 parameters that are measurable. So we have been in 2 consultation with FDA, with the EMA, with key opinion 3 leaders to come up with a consensus on our definition 4 of clinical cure for this specific setting of our 5 pathogen-specific pneumonia in the VAP population. 6 In addition, we have also -- have challenges 7 along the size of the safety database and trying to 8 understand what is the minimum safety base that would 9 be required to be able to bring this product to the 10 market. In many of our discussions, the database 11 suggested has been larger than maybe what required to 12 demonstrate efficacy and based on that this is a 13 limited population. 14 So in addition to having hospitalized VAP 15 patient in a ICU setting, we are also dealing with 16 these are unmet medical needs and we're dealing with 17 in some of our indications with orphan drugs, so 18 there's a very limited population. And so trying to 19 define what that minimum safety database is, sometimes 20 the magic number of 300 shows up. But we would like 21 to challenge and understand more based on the product 22 safety profile and the patient population and the</p>	<p style="text-align: right;">Page 193</p> <p>1 don't have that regulatory precedence of other 2 therapeutic products to understand what needs to be 3 done and what's required. We are paving a new path 4 here and we really want to partner with the regulatory 5 agencies in doing so. 6 There is a big need for the timing of these 7 communications and we are very thankful that we have 8 very good relationship with the agency in 9 communication and their doors have been open to us 10 with all the standard PDUFA meeting settings and we 11 have set fast track designation et cetera. But 12 sometimes I like to challenge a little bit more what 13 is the optimal timing besides the PDUFA standard 14 meeting and questions. 15 If we have additional pre-IND meetings or 16 questions or during the IND review or prior, post IND 17 meeting, pre IND meeting and before filing your IND 18 mechanisms to communicate in an efficient manner. And 19 I asked the agency what are the best mechanisms to do 20 that for us to provide them adequate information and 21 get a speedier feedback. 22 Normally we get 4 to 6 weeks when we have</p>

<p style="text-align: right;">Page 194</p> <p>1 submissions and request for consult offline from the 2 PDUFA meetings. And then finally we're also in a 3 global development, so in order -- we're looking for 4 mechanisms. And one of our challenges is to expedite 5 how we get global consensus, because we're going to 6 the FDA, we're going to the EMA, we're with key 7 opinion leaders to really understand the practice of 8 medicine and how to expedite our drug development for 9 these novel therapies.</p> <p>10 I would like to encourage to have additional 11 workshops like these and maybe even more focus, like 12 clinical cure definitions where we can bring all those 13 key opinions leaders and experts in a room and define 14 these kind of endpoints that are critical in these 15 novel therapies. And maybe I'd like to propose if 16 there was a mechanism with the agency just to have 17 brief pause with them. You know we're using e-mails 18 and everything and we have our conference calls with, 19 again, preset conference with PDUFA meetings, but is 20 there a mechanism to have "informal" communications 21 orally with the agency in addition to written? Thank 22 you.</p>	<p style="text-align: right;">Page 196</p> <p>1 emphasis of this case is on the outcome that can be 2 evaluated if such a product were to be developed, 3 where clinical benefit can be demonstrated in a 4 patient who is receiving such treatment. And Dr. 5 Kaleko from Synthetic Biologics will give his 6 perspective on the case, and followed by some comments 7 from Ramya on the case.</p> <p>8 The second case will be presented by Dr. Rex. 9 This case, the attempt is to highlight a different 10 aspect on the effect on gut microbiota where a 11 hypothetical case of a drug that reduces the 12 prevalence of MBL producing organisms in the gut of an 13 individual who has received this drug will be 14 discussed. The intent in presenting this case is 15 really to have a discussion about the scientific 16 challenges that one might encounter in developing such 17 a product where the benefit to the patient might be 18 difficult to demonstrate. However, there is a 19 potential for such a product to have an impact on the 20 community. And so we have sort of two slightly 21 different cases. We're discussing very similar 22 effects on the gut.</p>
<p style="text-align: right;">Page 195</p> <p>1 MS. NAMBIAR: Thank you, Dr. Leininger. 2 Should we take a couple of minutes break -- 3 So Kevin's recommendation is that we all take 4 a 1-minute stretch break. I think it looks like post 5 lunch people are tired and -- 6 MR. OUTTERSON: One minute. 7 MS. NAMBIAR: One minute. 8 (Recess) 9 MS. NAMBIAR: So let's move into session 3 10 that Kevin and I will be co-chairing. So this is a 11 little different from the previous session. This is a 12 two-part session. We will have two case studies. A 13 panel discussion after the first case study. We'll 14 take a short break and then discuss the next case and 15 have a final discussion for that case as well.</p> <p>16 So just to give you a little bit of 17 background about the intent of this session. The 18 first case will be presented by Ramya Gopinath, who is 19 a Medical Officer in the Division of Anti-infective 20 Products. Ramya will discuss a hypothetical case of a 21 drug that minimizes the effect on the gut microbiota 22 following exposure to antibacterial drugs. The</p>	<p style="text-align: right;">Page 197</p> <p>1 So with that Ramya, we'll have you present 2 the first case. Thank you. 3 MS. GOPINATH: Good afternoon everyone. 4 Seems very appropriate to be talking about the gut 5 microbiome as our own gut microbiomes are digesting 6 lunch. So I'll start by presenting the first case 7 study. So this is drug Z2 for prevention of C. 8 difficile infection by minimizing disruption of the 9 gut microbiome.</p> <p>10 So to begin with just let's consider the 11 principles of therapy here. Antibacterial use 12 disrupts the gut microbiome, reduces alpha diversity 13 and is known to reduce colonization resistance of two 14 antibacterial resistant bacteria. The extent of 15 disruption is dependent on the concentrations of 16 antibacterial drugs achieved in the gut, the degree of 17 local inactivation of these drugs, and the duration of 18 therapy.</p> <p>19 Selective pressure from antibacterial drugs 20 inhibits susceptible members of indigenous flora and 21 facilitates overgrowth of antibacterial resistant 22 flora which includes C. difficile. Drug Z-2 reduces</p>

<p style="text-align: right;">Page 198</p> <p>1 the concentration of beta-lactam drugs in the gut, 2 thereby potentially decreasing the incidence of C. 3 difficile infection which are referred to as CDI and 4 potentially decreasing the disruption of the gut 5 microbiome. 6 So known clinical studies in vitro rapid and 7 complete dissolution and release of drug Z2 from an 8 oral delayed release formulation to be used in 9 clinical and pharmacological studies was evaluated. 10 Stability of drug Z2 at different levels of the gut 11 environment, that is at the action site in intestinal 12 chyme and with intestinal contents has been evaluated. 13 In vivo studies include a 28-day dog safety 14 study with placebo versus varying doses of Z-2, that 15 is 15, 30, and 60 mg/kg/dose, administered three times 16 daily, so a maximum of 180 mg/kg/day. And in these 17 studies drugs Z-2 was well tolerated. There was also 18 a 14-day dog study with drug Z-2 and administered in 19 conjunction with beta-lactam drugs and no interaction 20 between the two was demonstrated with no significant 21 effect on the plasma PK of the beta-lactam drugs. 22 Once again drugs Z-2 was well tolerated. So</p>	<p style="text-align: right;">Page 200</p> <p>1 In addition, drug-drug interaction studies 2 were done with compounds that alter the PH of the gut, 3 such as proton pump inhibitors or the composition of 4 the gut microbiome, i.e., probiotics. 5 So for the Phase II study it was necessary to 6 have an endpoint that could be measurable. And 7 prevention of CDI was used as such an easily 8 measurable clinical endpoint. So in this study design 9 it was a parallel group double-blind placebo- 10 controlled multicenter trial conducted to evaluate the 11 effectiveness of drug Z-2 versus placebo for 12 prevention of CDI in hospitalized patients receiving 13 beta-lactam drugs for various non-GI infections. 14 So, in other words, it was used in 15 conjunction with beta-lactams. The duration of 16 treatment with drug Z-2 administered three times daily 17 was concomitant with and for 72 hours after the course 18 of therapy with beta-lactams and patients were 19 followed for about 6 to 8 weeks. 20 The efficacy endpoint was prevention of CDI 21 for 4 weeks following the start of treatment with 22 beta-lactam drugs. In this study 300 patients were</p>
<p style="text-align: right;">Page 199</p> <p>1 if we move onto the Phase 1 studies in healthy 2 volunteers, they were both single and multiple 3 ascending dose PK studies. So single oral doses of 10 4 milligrams to a 1,000 milligrams and multiple oral 5 doses of 10 to 200 milligrams administered every 6 6 hours for a week were evaluated. 7 Drug Z-2 was found not to be systemically 8 bioavailable except at the highest dose, that is 1,000 9 milligrams where systemic concentrations of 6 to 8 10 nanograms/mL could be detected. However, most plasma 11 concentrations were below the lower limit of 12 quantitation for the assay which was 1.5 nanograms/mL. 13 In the Phase Ib and IIa studies, clinical 14 studies were done to confirm the mechanism of action 15 in the human intestine. So in these studies healthy 16 subjects with functioning ileostomies were 17 administered drug Z-2 with serial sampling of 18 intestinal chyme to ascertain levels of drug Z-2 and a 19 variety of beta-lactam drugs. In these studies plasma 20 PK or beta-lactam drugs was found to be unchanged. 21 However, intestinal concentration of these drugs 22 decreased significantly with the action of drug Z2.</p>	<p style="text-align: right;">Page 201</p> <p>1 enrolled per study arm, 55 percent were male and the 2 mean age was 67 years. 3 The following results were observed in the 4 drug Z-2 versus placebo arms. There was lower 5 incidence of CDI in the drug Z-2 arm 3 percent versus 6 5 percent in the placebo arm, reduction of 7 colonization with C. difficile as well as Vancomycin- 8 resistant Enterococci, 5 versus 9 percent at 72 hours 9 when we looked -- when they looked at C. difficile. 10 And in addition colonization with extended spectrum 11 beta-lactamase producing gram-negative bacteria was 12 found to be similar between the groups and no 13 different from baseline. 14 Further there was no effect on the incidence 15 of antibiotic associated diarrhea, which was not 16 associated with CDI. So the questions for the panel 17 that arise from this case study are the following, 18 what are some important clinical trial considerations 19 for these kinds of products with respect to trial 20 design and endpoints? How does the expected higher 21 mortality in the population that might be at greater 22 risk for CDI factor into the endpoint?</p>

<p style="text-align: right;">Page 202</p> <p>1 Is being alive and free of CDI the only 2 appropriate endpoint? Besides reduction in CDI are 3 there other endpoints that we could consider as 4 clinically appropriate? What -- are there other 5 measurable benefits of such products and if so what 6 are they? And our study results from these trials 7 generalizable to populations beyond those evaluated in 8 clinical trials. So for example, to individuals who 9 receive other antibacterial drugs. Thank you.</p> <p>10 MS. NAMBIAR: Thanks Ramya. Dr. Kaleko -- 11 MR. KALEKO: Thank you very much. By way of 12 disclosure I am an employee of Synthetic Biologics and 13 I am familiar with the development of products similar 14 to Z-2. Z-2 is designed to be used prophylactically 15 to degrade beta-lactam antibiotics in the small 16 intestine to protect the downstream colonic microbiota 17 and could have potential benefits at three levels.</p> <p>18 At the level of the patient it could diminish 19 the risk of CDI, prevent colonization of the colon by 20 multidrug-resistant pathogens and prevent secondary 21 infections caused by these pathogens. At the level of 22 the hospital it could diminish the spread of CDI and</p>	<p style="text-align: right;">Page 204</p> <p>1 to 12, that's less measurable. 2 Finally, even studies with large cohorts run 3 the risk of low numbers for the primary efficacy 4 endpoint. Thus if patients lost a follow-up or 5 consider drug failures cases of CDI, this could 6 quickly bias the efficacy analyses. So I'd like to 7 suggest a strategy to deal with these limitations 8 specifically when considering the balance of risk and 9 benefit for Z-2 shift the emphasis to establishing 10 appropriate safety then bolster the efficacy outcomes 11 with ancillary information to establish a reasonable 12 expectation of clinical success.</p> <p>13 The basis for this proposal is that the 14 demonstration of safety is key especially for 15 prophylaxis. And due to the high mortality rate in 16 the target patient population should be achievable 17 with small cohorts. In contrast it's the efficacy 18 endpoint that's the one that requires the large 19 cohorts. So what ancillary data could be considered 20 to shore up the clinical efficacy data? Well let's 21 start with the microbiome. First, the bad news. To 22 the best of my knowledge there's no definitive</p>
<p style="text-align: right;">Page 203</p> <p>1 of multidrug-resistant pathogens. And at the level of 2 the population it could generally diminish the 3 delivery of antibiotics to the colon as if the 4 antibiotics were being used less frequently, like a 5 form of antibiotic stewardship.</p> <p>6 However since it's intended for prophylaxis 7 Z-2 faces hurdles in clinical development. 8 First and foremost, the primary efficacy endpoint CDI 9 is a rare event with an incidence less -- less than 5 10 percent in the placebo group. Thus to convincingly 11 demonstrate the Z-2 diminishes the incidence of CDI 12 may require prohibitively large phase three studies 13 and that's the crux of the problem, how do we diminish 14 the cohort sizes?</p> <p>15 Second, patients who are at greatest risk for 16 CDI are those who are most debilitated and have a 17 mortality rate that greatly exceeds the CDI rate, thus 18 it is necessary to separate the safety and efficacy 19 endpoints so that the high mortality rate does not 20 obscure a reduction in CDI. If for example CDI goes 21 from 5 percent to 2 percent, that's measurable. If 22 you roll in a 10 percent mortality and it goes from 15</p>	<p style="text-align: right;">Page 205</p> <p>1 microbiome or metabolome changes that predict 2 impending CDI in patients exposed to C.diff. So I 3 actually support the conclusion that the microbiome 4 does not yet provide a surrogate endpoint for clinical 5 disease.</p> <p>6 However, in Phase IIb Z-2 diminished new 7 colonization of VRE and C. diff. These endpoints 8 could be more predictive than microbiome analyses for 9 clinical outcomes. Since the 1950s we've known that 10 seeding from the gut can cause secondary infections, 11 more recently a 2012 paper from Eric Pamer's Group at 12 Sloan-Kettering showed that in bone marrow transplant 13 patients antibiotic mediated mono-dominance with 14 enterococci increased the rate of VRE bacteremia nine 15 fold and mono-dominance proteobacteria increase the 16 rate of gram-negative rods in the blood by fivefold.</p> <p>17 Additionally, four recent papers show that 18 colonization of the GI tract with multidrug-resistant 19 organisms and in particular new colonization was 20 associated with increased morbidity and mortality. 21 Taken in reverse, we can be confident that patients 22 who do not experience new colonization with VRE and</p>

<p style="text-align: right;">Page 206</p> <p>1 CDI are not likely to suffer infections with these 2 bacteria. So perhaps a diminution of such 3 colonization could be considered ancillary data to 4 support the clinical CDI results.</p> <p>5 Alternatively, could we bolster the efficacy 6 data with mechanism data, that is microbiome 7 protection. For example, for a product like Z-2, one 8 with which I'm familiar, protection from antibiotics 9 was first demonstrated with dog chyme and pig 10 microbiome studies. The same findings were then 11 reproduced in human chyme and human microbiome 12 studies. Thus the translational data across two 13 animal models and into humans support the mechanism of 14 microbiome protection and suggest that the CDI 15 efficacy data albeit with small numbers are in line 16 with what we predicted.</p> <p>17 So what I'm proposing is that with an 18 emphasis on safety perhaps we could use these 19 ancillary strategies to achieve sufficient comfort 20 with efficacy to circumvent the need for prohibitively 21 large Phase III studies.</p> <p>22 Of course the sponsor would need to provide a</p>	<p style="text-align: right;">Page 208</p> <p>1 of itself is difficult to interpret. However, 2 identification of this clinically relevant endpoint 3 related to the gut microbiome is problematic because 4 the exact definition of a healthy microbiome and its 5 variations is still unclear.</p> <p>6 The specific relationship between the gut 7 microbiome and disease, for example CDI but even other 8 conditions such as obesity, et cetera is undefined. 9 The measurable clinical significance of a quantitative 10 change in a particular bacterial species such as VRE 11 is still uncertain. The exact effect of antibacterial 12 drugs on the microbiome either as a class or 13 individually is unknown and therefore designing a 14 study or a clinically significant endpoint directly 15 addressing these issues is currently very challenging 16 and almost impossible.</p> <p>17 However, one might be able to infer the 18 potential for drug Z-2 to preserve the gut microbiome 19 at least partially by evaluating its ability to 20 prevent or reduce occurrence of CDI when drug Z-2 is 21 administered along with bacteria -- antibacterial 22 therapy.</p>
<p style="text-align: right;">Page 207</p> <p>1 commitment and plan for Phase IV studies to nail down 2 any efficacy questions and of course obtain additional 3 safety data. And then -- so I'd like to conclude by 4 thanking the FDA for convening this workshop to 5 explore ways of building flexibility into the 6 strategies to advance these potentially valuable 7 nontraditional therapies.</p> <p>8 MS. NAMBIAR: Thank you Dr. Kaleko. Ramya. 9 MS. GOPINATH: Thank you for your comments. 10 I'll try to present a little bit of the FDA 11 perspective on these types of products. So certainly 12 as we all know, and I think we got a taste of that in 13 the morning session, there is increased and rigorous 14 focus on the role of a balanced gut microbiome in 15 maintaining health. And conversely on potential 16 disruption -- disruptions or dysbiosis that may 17 contribute to disease causation.</p> <p>18 From a regulatory perspective, the evaluation 19 of a new product such as drug Z-2 intended to minimize 20 disruption of the gut microbiome poses challenges. 21 Most importantly, one has to identify a clinically 22 meaningful endpoint as change in the microbiome in and</p>	<p style="text-align: right;">Page 209</p> <p>1 CDI is known to be associated with overgrowth 2 of <i>C. difficile</i> bacteria and administration of 3 antibacterial agents especially the quinolones, beta- 4 lactam's and clindamycin and particularly for 5 prolonged durations is a major risk factor for 6 occurrence of <i>C. difficile</i> infection.</p> <p>7 We also know that older adults are at greater 8 risk for development to CDI and following resolution 9 of the first episode CDI may recur in as many as 15 to 10 40 percent of patients. A product that in some way 11 reduces the concentration of systemically administered 12 antibacterial drugs secreted into the gut may 13 therefore aid in prevention of CDI.</p> <p>14 However, designing such a trial presents 15 several challenges including the need to define an 16 appropriate study population in terms of age, 17 comorbidities, concomitant medications and previous 18 history of CDI, potential exposure to hypervirulent <i>C.</i> 19 <i>difficile</i> strains, the baseline rate of CDI in these 20 study populations, appropriate sample size and 21 appropriate endpoints.</p> <p>22 It may be challenging while it is a goal to</p>

<p style="text-align: right;">Page 210</p> <p>1 achieve a balance between trying to enroll the at-risk 2 population with those who have many comorbidities. As 3 my colleague, Dr. Kaleko, alluded to, if the baseline 4 incidence or prevalence or incidence of CDI in a 5 population is low it becomes difficult, so then you -- 6 one has to think of ways to potentially enrich a 7 population. 8 Trials for prevention of CDI by itself would 9 ideally be defined as placebo or active control -- 10 controlled superiority trials with the primary 11 efficacy endpoint being absence of CDI within a 12 predefined study period. However, the anticipated 13 increased mortality in hospitalized older adults 14 receiving systemic antibacterials who are also the 15 population most at risk for CDI needs to be 16 considered, i.e. if a patient dies during the study 17 period it is impossible to ascertain whether CDI was 18 successfully prevented in that individual. 19 In addition, a potentially small treatment 20 effect of drug Z-2 may be obscured by the background 21 rate of death or may necessitate a prohibitively large 22 sample size. Important PK considerations would</p>	<p style="text-align: right;">Page 212</p> <p>1 in addition to CDI. And the other one that I thought 2 that it wasn't clear to me whether you were on the 3 same point together was, you know, the issue of just 4 the methodological questions of patients' lost to 5 follow-up. You know, maybe I misunderstood, but it 6 seems like the rest of it, you know, you were both 7 ticking very similar boxes to me, which I find to be 8 encouraging. So help clarify if I'm confused please. 9 MS. GOPINATH: Thank you. So I think in 10 terms of the bacterial colonization, I mean, this is 11 something that really gets at the heart of the 12 discussions that we've been having, what is the 13 benefit. And currently I think you can approach it 14 from a clinical standpoint versus a regulatory 15 standpoint and I think that currently the FDA's 16 thinking on this is that we would approach it as a 17 exploratory endpoint because for the reasons that I 18 outlined in my remarks, it's a little unclear how 19 changes in the microbiome, although they can be 20 documented, what impact it has both to the individual 21 and beyond the individual. 22 MR. OUTTERSON: And on the methodology of</p>
<p style="text-align: right;">Page 211</p> <p>1 include identification of an appropriate nonclinical 2 model for prevention and very importantly evaluation 3 of systemic absorption of the product from both normal 4 as well as diseased gut. 5 In nonclinical Phase I as well as Phase II 6 studies evaluation of administration with food and 7 drug-drug interactions with agents that alter either 8 the pH of the gut such as PPIs or those that alter the 9 gut microbiome such as probiotics. In such a scenario 10 evaluation of the gut microbiome could be included in 11 some predefined way as an exploratory endpoint. Thank 12 you. 13 MR. OUTTERSON: So I wonder if -- thank you 14 for that -- if I could push back a little bit, trying 15 to find the places where those last two presentations 16 disagree. Because it seems like there's a lot of 17 agreement between the two, you know and we could run 18 through them, but I am -- I am more interested in the 19 gaps where there's not clarity between the two and so 20 for example, you know, how would the FDA view the 21 question of -- you know, he mentioned colonization as 22 being an intermediate, you know, additional endpoint</p>	<p style="text-align: right;">Page 213</p> <p>1 patients lost to follow-up and I don't know if, 2 Michael, if you have any comments either. 3 MS. GOPINATH: So I'll start. And so I think 4 that, you know, again this is -- I think it was 5 alluded to in one of the previous talks as well. This 6 is a difficult problem because the population that's 7 most at risk for CDI is also the population in who, 8 you know, if they're hospitalized for pneumonias or 9 they're hospitalized for some other infection, the 10 death rate is higher in this population and so as was 11 mentioned by Dr. Kaleko, I think if the treatment 12 effect is small, then we really struggle with this 13 because then in order to show that a preventive 14 therapy is working, you need a really large sample 15 size. So I think that's a topic that we're struggling 16 with and that it would be good to get people's 17 thoughts on. 18 MR. KALEKO: I actually agree that the 19 microbiome is not a primary endpoint. I think some 20 day when we have drugs that work in the microbiome, 21 we'll be able to look back and find those correlates 22 that provide predictive value that doesn't exist at</p>

<p style="text-align: right;">Page 214</p> <p>1 the moment. I feel a little differently though about 2 VRE and C. diff colonization because there really is a 3 wealth of literature that show that when you have new 4 colonization, you are likely to have a -- you're more 5 likely to have an infection, you're more likely to 6 have greater morbidity and mortality and that's even 7 as I said, I particularly pulled out Eric Paymer's 8 (ph) work because it's actually quantitative. 9 So I disagree a little bit about -- in that 10 regard. The way I look at this is mechanistically. 11 Now I used an example of another drug that's little 12 less hypothetical than this one where in dogs, the Z-2 13 like drug removed an antibiotic from chyme; and then 14 in pigs it protected the microbiome from loss of 15 diversity, overgrowth by expansion of antibiotic 16 resistance genes and then exactly the same thing 17 happened in humans, okay? The antibiotics removed 18 from the chyme in ileostomy patients and then the 19 microbiome is protected from loss of diversity and 20 there is less overgrowth of antibiotic resistance 21 genes. 22 So the mechanism is consistent all the way</p>	<p style="text-align: right;">Page 216</p> <p>1 this being almost impossible and the need to enrich. 2 I mean this is a very common infection; 500,000 cases 3 per year and that's probably an underestimate and I 4 think I just don't want us to get confused about risk 5 factors. You know, there are risk factors for relapse 6 that we talked about this morning being old or being 7 immunocompromised, but we have young healthy people 8 who get one dose of antibiotic for dental work. Young 9 healthy man who gets one dose of antibiotic for 10 prostrate biopsy. A lot of people get C. diff. This 11 is a common infection and I think that preventing in 12 those individuals is just as important as preventing 13 it in the people with the risk factors. 14 So I think one should consider even studies 15 in the so-called low-risk group, if that would ease 16 some of -- mitigate some of these concerns. The cost 17 in thinking about this at both the individual patient 18 and in the hospital and the population level is really 19 important and I think harkening back to some of our 20 discussion this morning, you know, the regulatory 21 issues are the regulatory issues right there. You 22 have to have -- you have to meet the standards, but I</p>
<p style="text-align: right;">Page 215</p> <p>1 through, so when you do see a drop in CDI, albeit with 2 small numbers, you can say, you know, this is via a 3 mechanism that we would have predicted. Therefore, 4 it's possible, highly likely -- not highly, let's say 5 likely, I mean I overstated, likely that it's true. 6 On the other hand when patients die, the 10 percent 7 mortality rate, they're also dying by a known 8 mechanism. They have infection. They have COPD. 9 They have high blood sugars. They have high BUNs 10 (ph). And those mechanisms are separate. So if each 11 -- the incidence of CDI and the deaths are taken in 12 the context of their mechanisms, we can actually keep 13 them somewhat separate. 14 Now that said, that's all hypothetical and 15 therefore, there is no doubt that one needs a large 16 definitive clinical trial to prove this, but whether 17 or not that clinical trial needs to be right up front 18 isn't clear to me as long as the drug really 19 demonstrates an appropriate level of safety. So those 20 are my thoughts. I hope that's in line. 21 MS. BOUCHER: Thanks. So I just wanted to 22 maybe push back a little bit on the comments about</p>	<p style="text-align: right;">Page 217</p> <p>1 think from a patient care pharmacy P&T approval 2 standpoint and getting uptake for a therapy like this, 3 addressing issues like decreasing resistance and 4 positive impact on the microbiome, whatever that is, 5 however we define it, I think those things are 6 important and the science is advancing so rapidly that 7 including that to the extent feasible would be 8 desirable in this kind of a study. 9 MR. RUBIN: The comment on the question about 10 lost to follow-up, I think these patients would 11 probably be censored and so not counted as a CDI 12 event, but I also think that it would be important for 13 the protocol to distinguish lost to follow-up from 14 death, lost to follow-up means you don't know if the 15 patient is alive and you don't know whether they have 16 CDI. Also, if you're dealing with the trial with a 17 very low background rate, then it's unavoidable that 18 if you have a nontrivial rate of lost to follow-up, 19 then that study is going to be very difficult to 20 interpret, so you'd probably need some kind of 21 streamlined outcome collection where for almost 22 everyone in the trial, you are able to determine</p>

<p style="text-align: right;">Page 218</p> <p>1 whether they had CDI or not. I don't think it's that 2 different from what you see in these large 3 cardiovascular outcome studies where it's known going 4 end of the study that if you have a lot of people 5 where you don't know whether they have the event that 6 it's going to be hard to interpret when you finish. 7 I agree with the comment, there was a comment 8 earlier in the day about big data and I think this 9 could be an area where it could be useful to try to 10 enrich for patients who are at low or high risk for 11 CDI to make -- possibly make the trial more feasible 12 possibly by including patients who've had CDI before 13 and for whom you're looking at recurrence. And then 14 also this is an area where there have actually been a 15 few very large vaccine studies, I think Pfizer and 16 Sanofi, someone correct me if I'm wrong, over 10,000 17 patients for preventing CDI. And ideally you'd like 18 some of these studies to be done to validate some of 19 these surrogates that we're talking about like 20 colonization or changes to the microbiome to show that 21 a treatment effect on an endpoint like this will 22 actually translate into an effect on -- of clinical</p>	<p style="text-align: right;">Page 220</p> <p>1 that went on behind closed doors was the whole issue 2 about surrogate markers and how the colonization was 3 still just a surrogate for the prevention of more 4 serious bacteremia disease associated with ifesium 5 (ph). 6 So the question would be, there is a 7 mechanism within the FDA for approving drugs based 8 upon a surrogate with the ability then to do a 9 subsequent definitive trial and I think that's sort of 10 -- in some ways there was some of that discussion of 11 committing the company to doing that. So -- and then 12 as pointed out, there was that pretty large trial with 13 a C. diff vaccine that you could look at what the 14 colonization rates and so on if they did those studies 15 properly, but I'm just wondering if there is an 16 opportunity in this regard with a drug that may have 17 some real benefit for society to look at the surrogate 18 marker concept. I recognize that it was a difficult 19 discussion back then. I don't expect that it would be 20 any easier than it was previously. 21 MS. NAMBIAR: So thank you for your comments. 22 I mean I'm sure you know where we had a discussion on</p>
<p style="text-align: right;">Page 219</p> <p>1 outcomes. 2 MR. KALEKO: Can I add briefly that I 3 actually dropped my little spiel on enrichment that I 4 had here and the reason is because it's -- the way I 5 view it, it's a curve that goes up, has a maximum and 6 then comes down. As you enrich with sicker and sicker 7 and sicker patients, yes, you'll have more CDI, you 8 probably also start diminishing your effect-size after 9 a while and you'll be increasing your mortality rate. 10 So the two things that confound the data actually 11 increase while you're enriching. So I think there 12 probably is a maximum, but mathematically I don't know 13 where it is. 14 MR. RUBIN: Wayne will take it. 15 UNIDENTIFIED SPEAKER: Can we get a value? 16 UNIDENTIFIED SPEAKER: Okay. 17 MR. DANKER: So I have a bit of experience 18 with this from a closed door session years ago, so I 19 can't talk about that, but there was a discussion when 20 I was with another company looking at the use of a 21 drug to reduce the colonization for ephesia (ph) which 22 in cancer patients and if I remember the discussion</p>	<p style="text-align: right;">Page 221</p> <p>1 microbiology as a surrogate endpoint just last week at 2 an advisory committee meeting. And so I think it 3 really depends on what data one has for a particular 4 organism and a clinical outcome for that particular 5 condition. So I think last week's discussion was 6 around nontuberculous mycobacteria and whether or not 7 sputum culture conversion correlates or it is likely 8 to predict clinical benefit. And you know, there was 9 a lot of assumption that it might, but when you 10 actually look at the data more closely, you realize 11 the shortcomings of the data and even though in that 12 instance, you know, it's become part of clinical 13 practice, the data that support a correlation between 14 microbiologic surrogate and the clinical outcome for 15 that particular clinical entity are pretty weak. 16 So I cannot comment on the adequacy of the 17 data for this particular instance, but you know, we 18 would have to take a look at the literature very 19 closely and see if in fact there is support. I mean 20 we've used microbiologic surrogate endpoint for 21 tuberculosis, the approval of Bedaquiline a few years 22 ago was based on a surrogate endpoint, but a lot of it</p>

<p style="text-align: right;">Page 222</p> <p>1 really depends on how reasonably likely it is to 2 predict clinical benefit, and if the treatment benefit 3 on that surrogate endpoint will hopefully translate 4 into clinical benefit or not, so. I wasn't part of 5 those closed door discussions, but I think I know what 6 you're talking about and --</p> <p>7 MR. KALEKO: May I add one other quick point? 8 And maybe somebody could help me figure out how to do 9 this. I suspect that a drug like Z 2 at the hospital 10 level actually diminishes CDI very much the way 11 vaccines work mathematically with herd mathematics. 12 If you -- every time you get rid of a case of CDI, you 13 diminish diarrhea, you diminish the spread of spores 14 and then you diminish other cases of CDI. So how can 15 you -- normally in your clinical trials, you look at 16 the effects in the patient. How do you look at the 17 effects in the hospital which might be amplified?</p> <p>18 MR. COX: So maybe I'll just start and I'm 19 thinking maybe Dan and Scott have additions to this 20 one, but -- so it sounds like what you're looking for 21 is -- it feels like the way you'd try and answer this 22 question would be like a cluster randomized trial and</p>	<p style="text-align: right;">Page 224</p> <p>1 questions about what actually did it, and you know, 2 would the drug do it or was it, you know, room 3 cleaning and other things and so all these other 4 factors are always sort of part of it. So it can be 5 hard to attribute what actually the cause is, but 6 usually for a drug claim, I mean you want the 7 evidence-base that supports that the drug actually did 8 it, so -- but you know, I mean we can always look and 9 see what somebody's got, but it's at least one way to 10 think about it.</p> <p>11 And it's hard, you know, for some of these 12 conditions where there are multiple different things 13 that are impacting upon, you know, why a C. diff rate 14 is going down, it's always hard to dissect what was 15 responsible for why that rate went down.</p> <p>16 MS. NAMBIAR: Yes, Mary Beth.</p> <p>17 MS. DORR: So I wanted to comment about the 18 impact on the hospital. I mean it makes a lot of 19 sense. The same thing with quality of life. If you 20 can prevent C. diff, then you should be able to 21 improve the quality of life of the patient if you're 22 preventing recurrences for example. But in the</p>
<p style="text-align: right;">Page 223</p> <p>1 you'd randomize healthcare institutions, that would be 2 your unit of analysis and you would give -- some 3 healthcare institutions, you know, would have access 4 to the product that you're talking about. And then 5 you would look for, you know, lower levels of cases of 6 C. difficile infection in the hospitals that receive 7 the experimental therapy compared to the hospitals 8 that did not have a therapy available. Does that 9 sound right or no?</p> <p>10 MS. BOUCHER: I guess the question is do you 11 need to do that? I mean the data exist that 12 decreasing rates of C. diff decrease rates of C. diff, 13 right? That data exist. There's no -- every hospital 14 epidemiologist knows this, that's why they push like 15 they push. So the question is do you need to do that? 16 That's almost like an epidemiology study you're 17 describing or would -- showing that this drug 18 decreases C. diff in individual patients, would that 19 be enough to make other more general conclusions?</p> <p>20 MR. COX: Yeah. No, I mean, there are times 21 when you can make general conclusions based upon the 22 data from other studies. And you know, there's always</p>	<p style="text-align: right;">Page 225</p> <p>1 hospital environment, payers don't want to pay for 2 prevention. So you can show that your drug prevents 3 something, but how are you going to get that 4 reimbursed? So we can't forget about at least in the 5 United States how we're reimbursed for our drugs. So 6 it's something that we all need to consider when we're 7 developing drugs.</p> <p>8 The other thing I wanted to talk about is the 9 impact of this enriched population. Your population 10 is already enriched because they're getting a high- 11 risk antibiotic. What we saw in a subgroup analysis 12 for the modified trials, in those patients who were 13 getting a high-risk antibiotic, their mortality rate 14 within 90 days, which was our follow-up period, was 10 15 to 15 percent, so that's high. So I really do agree 16 that you need to consider that because your population 17 is already enriched even if you're enrolling those 18 younger people who had clindamycin after a dental 19 procedure, that's an enriched population who has a 20 high mortality rate.</p> <p>21 MR. KALEKO: Can I quickly ask a question 22 about the payer issue? It was my understanding, and</p>

<p style="text-align: right;">Page 226</p> <p>1 please educate me if I'm wrong, that in the U.S. 2 hospital-acquired CDI is paid for by the hospital. So 3 as long as the total cost of diminishing CDI is lower, 4 I'm getting this straight, than the actual cost of the 5 drug; did I get that right or did I get it backwards; 6 the hospital should be interested in it and that's 7 even without bringing in the quality of life and the 8 liability and all the other things that hospitals have 9 to suffer when patients get CDI. So -- but I think 10 your point is well-taken. The issue of payers is one 11 that needs to be addressed. 12 MR. EVANS: I think a couple of points, and I 13 think it's very admirable to the forward thinking 14 about future patients and you know, very thoughtful to 15 be thinking ahead that way. I think we need to 16 marriage it or think about what that means to today's 17 patients, in particular patients that come into 18 trials. So the surrogacy we're talking about that may 19 have effects on future patients or the rest of the 20 population ecologically is different from the 21 surrogacy we traditionally talk about in trials where 22 you're talking about something you can measure on me</p>	<p style="text-align: right;">Page 228</p> <p>1 necessarily you have to study more healthy patients in 2 order to see those effects. We've -- there are at 3 least some studies we've done in which for many of 4 these diseases, the sensitivity occurs in the most 5 sick patients. That's where you find -- if your drugs 6 have an effect, that's where you find the effects. 7 Now so -- and in a very pragmatic setting, if 8 that's where the drug is going to be used, that's 9 where you want to know what the -- what your effect is 10 in those populations. So you know, I think there are 11 ways to deal with the mortality issue is, you know, 12 that's a -- you have a randomized study, you cannot do 13 any better than that. You're going to compare how 14 patients end up on a randomized study in that fashion 15 and I'll stop there, thanks. 16 MS. EAKIN: All right, thanks. I think 17 William made a point earlier this morning about 18 possibly there being a need for new animal model 19 development. And you know, one of the things that 20 we're interested in at NIH and I know also colleagues 21 at FDA and BARDA, we're interested in trying to make 22 investments in the spaces to, you know, meet where</p>
<p style="text-align: right;">Page 227</p> <p>1 today that may tell you about a clinical event that 2 happened somewhere down the road that's too far down 3 the road for you to measure today. And that's a 4 little bit different than the surrogacy of preventing 5 something for -- not necessarily for me, but for 6 somebody else and what that means to the patient 7 coming into the study when you're consenting them that 8 you're talking about a benefit that may not benefit 9 them, but may benefit somebody else, and how that 10 might affect how they look at things. 11 I don't think the -- in many ways, I think 12 we're turning to this door discussion this morning is 13 a discussion about the mortality and so forth. 14 Causality is measured by a contrast of randomized 15 regimens. It's not measured by adjudication of what 16 somebody believes is the reason for something. You 17 measure causality by contrast of randomized regimens. 18 So you can set up an ordinal level endpoint where 19 you've got death on the bottom and levels above it 20 are, you know, survivors that either have CDI or not 21 and that helps to deal -- that's the way you deal with 22 the competing risk of death. And I don't think that</p>	<p style="text-align: right;">Page 229</p> <p>1 there are gaps in the science with new animal models 2 for instance. And one of -- this is one of the areas 3 we've at least been talking about internally and I'd 4 just be interested to hear more whether people think 5 there is a need for more animal model work to try to, 6 you know, recapitulate what's seen in say Eric 7 Paymer's studies and clinically in an animal model 8 setting that might be used to strengthen some of these 9 new products. 10 You know, particularly I know there are 11 animal models looking at, you know, colonization and 12 microbiome diversity et cetera, but really taking 13 those models forward to look at, you know, gut- 14 derived, you know, bacteremia and things like that to 15 actually strengthen some of these arguments and of 16 course I can't imagine it ever replacing the clinical 17 evidence, but if it would strengthen that, I'd be 18 interested just to hear what people think about the 19 value either in discussion today or as follow-up 20 discussions. 21 MR. TRUONG: Yeah, I just want to make a 22 comment about prevention versus treatment in some of</p>

<p style="text-align: right;">Page 230</p> <p>1 these nontraditional, you know, we are developing as 2 pseudo-mono-clonal antibodies and when we take a look 3 at the -- whether we should be developing these 4 clinically to prevent or to treat, we gravitated to 5 treatment primarily because in some of these 6 indications such as pneumonia, we don't have good 7 command on what is the attack rate. So for example, 8 if we're trying to develop these monoclonal to prevent 9 pneumonia episodes in colonized but asymptomatic 10 patient, we actually don't have a good feel for what 11 is the prevalence of progressing to pneumonia of a 12 staph aureus pneumonia at-risk patient or pseudomonas 13 pneumonia at-risk patient because the -- some of the 14 data we're seeing is for either one of these bugs 15 which represent the most prevalent gram-negative and 16 most prevalent gram-positive in nosocomial pneumonia, 17 you're looking at somewhere between 20 to 30 percent 18 attack rate.</p> <p>19 So if that's the case, we have to set at 20 effect sizes very large. Let's say you set a 50 21 percent effect size, would a 25 percent attack rate 22 means that for every 8 patient or 10 patient that one</p>	<p style="text-align: right;">Page 232</p> <p>1 to 100 percent. And so I think as we decide whether 2 or not develop these drugs for prevention or for 3 treatment, I think some of the epidemiological data is 4 going to be very important to make that decision.</p> <p>5 MS. NAMBIAR: Are there any questions from 6 the audience? No, all right, I tried.</p> <p>7 MR. REX: A comment and then a question. So 8 the comment is that I think we're hearing a number of 9 times a statement about the effect is really small, 10 it's going to be hard to show where a large trial and 11 I think we need to think carefully about what does it 12 mean to say that an effect -- if the effect is really 13 small, then who cares, right? You can make the 14 argument that there's -- there can be small effects 15 that you may -- maybe you do a study of 100,000 people 16 and you show you -- the number needed to treat is 17 50,000 to produce some benefit. Is that actually 18 something that you want to chase.</p> <p>19 Now -- but small -- preventing one case of 20 Ebola however may have a different consequence than 21 preventing one case of C. diff. One case of Ebola 22 would set off a global panic if it were to occur in</p>
<p style="text-align: right;">Page 231</p> <p>1 treat, only one would benefit and so from the payer's 2 perspective, you have very difficult commercialization 3 risk. Conversely, in the treatment mode, which is 4 what we're developing, we're using the adjunctive 5 therapeutic treatment modality as a way to develop 6 these drugs. There the risk is different. There the 7 risk is to show that incremental benefit, right, what 8 is the effect-size over, above what the standard of 9 care antibiotics could afford. So there we -- you 10 know, when you ask, you know, the physician, what's 11 the effect-size as clinically meaningful to you, there 12 is a significant difference if you're doing prevention 13 because if you ask physician if I have a drug that I 14 could prevent X percentage from relapse in pneumonia, 15 what is clinically meaningful to you? If you ask that 16 same question to the payer, the response is actually 17 very different.</p> <p>18 From the clinician's perspective, you tend to 19 hear about 10 to 20 percent prevention, meaning 20 effect-size would be clinically meaningful and 21 valuable. If you ask the payer based on the attack 22 rate, they're going to tell you somewhere between 50</p>	<p style="text-align: right;">Page 233</p> <p>1 this room whereas one case of CDI would -- you know, 2 it would have a different consequence. So this notion 3 of small effect-size, I think it is important for 4 developers to stay focused on things that have 5 reasonable effect-size, but you can keep in mind the 6 severity of the thing you're chasing. So the question 7 I want to get at though is this, we've beat around the 8 microbiome a lot and what evidence would we need to 9 show that microbiome pattern 1, whatever you want to 10 define that to be, is in some ways safer or better 11 than microbiome pattern 2. Have we ever debated that 12 question? Another -- to turn it around another way is 13 to say under what circumstances is detectable carriage 14 of organism X, fill in the blank, an infection in and 15 of itself that merits either treatment or prevention, 16 under what circumstances for example would -- is 17 carriage of VRE something that I should treat as an 18 infection that I should seek to treat or prevent?</p> <p>19 And some other thoughts for you would be, for 20 example, group A strep and a surgeon who is not sick, 21 but is carrying group A strep, that's actually a 22 problem if he or she is shedding the organism into his</p>

<p style="text-align: right;">Page 234</p> <p>1 or her patients. Group B strep and a pregnant lady, I 2 suggested that one to third trimester, that's not an 3 infection of her so to speak, yet it is an infection 4 we actually actively seek to treat that. Carriage of 5 neisseria meningitidis in the nose is considered to be 6 a thing that you want to prevent. It's not an 7 infection, but it's bad news when it occurs. So is 8 there a way to use those models as some sort of a tool 9 that would let you get at this broader question of 10 when is your microbiome -- when should you say out to 11 your microbiome and what is the metric for that that 12 would be useful to us as a community so that when 13 Michael is developing his next product, he actually -- 14 he has a tool already qualified that defines the 15 definition of the point at which the microbiome is 16 painful. How about that one? And have, you know, 17 worked on that? Any work on that? I mean I -- 18 MS. EAKIN: We work on just about anything, 19 so in some fashion. 20 MR. BURD: We've been working on recurrent C- 21 diff. And as part of our data gathering on our 22 patient populations, we've been looking at what's</p>	<p style="text-align: right;">Page 236</p> <p>1 MR. KALEKO: Can I ask you a question? First 2 of all, I should mention that's why I said to the best 3 of my knowledge. Are these profound changes? There 4 are ones that your -- that your therapeutics are 5 creating. If you were to look at just the general 6 population who haven't been on antibiotics, and who 7 would not be at risk for CDI, do they come in with 8 those change, with those profound improvements and 9 then lose them with antibiotics and then you bring 10 them back? 11 MR. BURD: But -- so we have not done those 12 studies. 13 MR. KALEKO: Or those profound changes 14 specific to your therapeutic? 15 MR. BURD: So what we've done is that we have 16 a cohort of healthy individuals that we look at. And 17 this cohorts being compared to larger bodies of work 18 that's been done I think in part by the NIH. And you 19 get a population distribution of a variety of groups 20 of bacteria. When you look at those groups and you 21 look at them in the context of recurrent CDI, you see 22 a profound inversion of the predominant species in</p>
<p style="text-align: right;">Page 235</p> <p>1 their microbiome constituents when they walk in the 2 clinic and then what happens to them after treatment. 3 And we're seeing some very profound patterns that 4 arise out of that that are predictive of success. And 5 I heard earlier that they are not measures that we 6 could use, but the work that we're -- body of work 7 we're gathering, which will be published soon, really 8 does suggest that there are ways to look at the 9 baseline of your patient population coming into the 10 clinic, and then the effects upon the microbiome 11 following your treatment. And these are predictive of 12 both short-term efficacy as well as long term. 13 And so we talked earlier about how you would 14 go about validating those surrogates and that's sort 15 of the problem that everyone's going to have. Until 16 we get a validated surrogate, we have a chicken and 17 egg problem. So for our company at least, we're 18 thinking about this prospectively with the idea that 19 eventually we will have to develop this as a surrogate 20 and validate it in randomized controlled studies. But 21 there are ways to do this and there is a body of data 22 being developed.</p>	<p style="text-align: right;">Page 237</p> <p>1 normal or healthy individuals versus in those who are 2 having recurrent CDI. We can talk about the specifics 3 of the data offline. 4 MR. KALEKO: So is that a legitimate now 5 secondary endpoint for a Z 2 trial? 6 MR. BURD: It very well could be. I mean one 7 of the questions is how do you enrich your patient 8 population when you have these low rates? This is one 9 way to think about it. Patients that are coming in 10 the door that are very near normal in terms of the 11 distribution of these families of microorganisms 12 aren't much -- are potentially at much lower risk of - 13 - of having an infection. 14 So if you want to enrich for patients that 15 are on that sort of, steady slope of losing normal 16 control of their microbiota and moving into dysbiosis, 17 this would be a way of enriching for them reducing the 18 number of patients I think for some indications, but 19 not all. 20 MR. KALEKO: Yeah, I think it makes for a -- 21 for a really interesting endpoint. The problem with 22 the Z 2-like trial is patients come in, they're</p>

<p style="text-align: right;">Page 238</p> <p>1 infected, the emergency room docs got to get them on 2 their antibiotics immediately. The clinical trial 3 doesn't really have time to enroll. 4 MR. BURD: Right. 5 MR. KALEKO: But for an endpoint, I think 6 that would be very interesting. 7 MR. BURD: Right. So one way to think about 8 it is, if you're able to get a sample at the time the 9 -- they start treatment, the question is have you made 10 them worse at the end of it. So you don't have to 11 look at from normal to total dysbiosis, but you could 12 look at stability of that profile over time because if 13 it's still degrading, then you have -- then you know 14 that they're worse off than they were. 15 MR. DUBOVSKY: So I thought it was very 16 interesting that this competing risk of death was as 17 troublesome for the CDI-enriched population as it was 18 for the back population this morning. And it occurs 19 to me that it's going to be same for any product 20 you're testing in patients of high acuity, that if you 21 count those as failures, it's going to drive down your 22 point estimate of efficacy. I'm still not sure I've</p>	<p style="text-align: right;">Page 240</p> <p>1 diff pressure as it's called is a tremendous risk 2 factor. And the -- I think the way that one gets at 3 that and this is going to sound terrible, but you find 4 hospitals that are having breakouts or have actually a 5 long historic -- long history of breakouts as you 6 know. The problem is those are the hospitals that are 7 likely to actually have cleaned up by the time you 8 actually get going with your clinical trial. 9 MS. DORR: Right. Long-term care facility 10 patients, you know, they're going to have an increased 11 risk of being colonized and a PCR (ph) test to show a 12 patient's colonized is pretty rapid and most hospitals 13 can perform those studies within a 24-hour period. 14 The test takes an hour, but if they batch it, you 15 know, could take as much as 24 hours to get the result 16 back. 17 MR. KALEKO: Agreed. Thank you. 18 MR. OUTTERSON: All right. We're almost -- 19 we're at the end of the time I think for this session. 20 I was going to give a 60-second summary of just some 21 of the things that we talked about. We talked a lot 22 about surrogate markers and I think, you know, the FDA</p>
<p style="text-align: right;">Page 239</p> <p>1 heard a really good argument why you can't look at 2 that as a safety feature. In other words, if he is 3 able -- if product Z is able to prevent CDI infection 4 and doesn't increase death, it still seems like that's 5 a clinical benefit. Whether -- but if it were flipped 6 and you had increased mortality in the active group, 7 it seems like that would not be licensable. So is 8 there a downside to looking at it that way? 9 MR. KALEKO: I think that's reasonable. 10 MS. DORR: I wanted to make another comment 11 about the enrichment. Like the example that we had 12 this morning where for the VAPP study, they were only 13 enrolling patients who were colonized with staph 14 aureus. Have you thought for Z 2 just in randomizing 15 patients who were colonized with C. diff at the time 16 that they start their antibiotic or X number of days 17 after they start the antibiotic? 18 MR. KALEKO: I can't speak for Z 2 per se 19 hypothetically. But the way similar studies are run 20 is patients come into the emergency room and they're 21 enrolled as quickly as possible and so you don't have 22 time to figure out if they are colonized. Clearly C.</p>	<p style="text-align: right;">Page 241</p> <p>1 it seemed to me was saying that, you know, we're open 2 to surrogate markers. Show us the scientific evidence 3 of clinical, you know, connection or clinical benefit 4 on that. We had a I thought a interesting back and 5 forth on what if there's an Epi benefit in the 6 hospital and then the response was close to -- close 7 to randomization. 8 And then the response from Dr. Boucher was 9 why bother, we know it's right. We know this is how 10 it works. But I like the thought of this is one way 11 for us to think about how to measure the positive 12 externality of the treatment of this patient, is one 13 way to measure value beyond the individual person, 14 right? And so that's a good thought. I love to -- 15 first question I always ask is how is it going to get 16 paid for, right? It goes back to my training. And so 17 all of these discussions, you know, one question I 18 would leave out there is how is this study that we're 19 designing any better than the study that was done for 20 deficit which sells about \$7 million per month in the 21 United States? You know, so we have to do better than 22 that, right?</p>

<p style="text-align: right;">Page 242</p> <p>1 And so John needs to pull the magic -- pull 2 incentive out of his hat. He doesn't have a hat. Bad 3 example. I liked what Scott had to say about -- Scott 4 Evans on the surrogacy that we're talking about is 5 really surrogacy for other patients, right, as 6 opposed, you know, this is a different type of 7 surrogacy. It's not the patient X and then at time, 8 you know, plus 6 months we are doing a surrogate 9 marker of how this individual will be in 6 months. 10 We're really talking about surrogacy in some fashion 11 about other patients, right? And that has ethical 12 implications and other, you know, we need to have that 13 mindful. 14 And there was a discussion as well about the 15 who is going to -- what the payers and the providers, 16 you know, or, you know, the payers -- providers are 17 okay with a 10 to 20 percent, you know, Delta whereas 18 the payers want -- a 100 percent, you know. And those 19 are very interesting, you know, differences there. 20 Thank you for your attention. We have a break of a 21 few minutes, much longer than the last break. 22 MS. NAMBIAR: Fifteen.</p>	<p style="text-align: right;">Page 244</p> <p>1 Asia, but not exclusively. And they screened them all 2 before they went on their travels and they screened 3 them again, screened their stool when they came back. 4 And what they found was that of a 100 people who set 5 out, 24 came back carrying an extended spectrum beta- 6 lactamase in their stool. And then they followed them 7 a little bit longer. And of those 25 percent, 25 8 percent of them were still carrying ESBLs 6 months 9 later. So I'd like you to remember those numbers. A 10 fourth of them came back carrying a more difficult to 11 treat gram-negative and 6 months later a fourth of a 12 fourth were still carrying that organism. 13 And another one where I think the title says 14 it all, included it just for another demonstration, 15 this -- the ECDC carbapenem producing OXA-48, 16 Klebsiella pneumoniae in travelers previously 17 hospitalized in Gran Canaria, Spain. So, you know, we 18 wind up in the hospital there, the organism is present 19 locally. You can come back to your home based in 20 Europe carrying the organism that you picked up. 21 In high prevalence areas, a high fraction of 22 the CRE, so here I stepped up from ESBLs to</p>
<p style="text-align: right;">Page 243</p> <p>1 MR. OUTTERSON: Fifteen minutes. Enjoy your 2 time and come back for case study 3. 3 (Recess) 4 MR. REX: Okay. Boys and girls, ladies and 5 gentlemen, I think we're going to get started. Kevin 6 is waving at me saying it's time to rock and roll and 7 -- okay. So for the final act on this rainy slightly 8 sleepy afternoon, let's look at this case, case Z-3, a 9 case that looks at the idea of reducing risk of 10 infection due to a metallo-beta-lactamase producing 11 organism by preventing the acquisition of said 12 organism. And I'm going to acknowledge Patty Bradford 13 is not here today, but who helped me a lot with trying 14 to make this into actually a credible concept. 15 So two bits of background. The first is that 16 travelers are at risk for becoming colonized by 17 resistant gram-negative bacteria, and in particular 18 you can demonstrate that you can get colonized by 19 ESBLs and CRE by traveling. So look at two bits of 20 data. First is a paper by Tang et al from 2010 where 21 they looked at a 100 travelers from Sweden who were 22 setting off to travel outside of Sweden, mostly to</p>	<p style="text-align: right;">Page 245</p> <p>1 carbapenemase-resistant Enterobacteriaceae, so that's 2 a variation on ESBL. High fraction CREs are metallo- 3 beta-lactamase producers. And here are the data, I 4 have one paper, I was looking for nice surveys of this 5 and the best one I found 2017 Mohanty et al looked at 6 carbapenemase production in Enterobacteriaceae 7 bloodstream isolates. And two-thirds of the CRE were 8 metallo-beta-lactamase producers NDM-1, that's a very 9 high prevalence. 10 And then 2011, an earlier paper, one of the 11 papers that has almost started it all, New Delhi 12 metallo-beta-lactamase from a travel returning to 13 Canada. So, you know, makes sense. The organism is 14 out there. If you eat the wrong thing, you can pick 15 it up. Nothing magic about that. So this leads us to 16 product Z-3 which is a hypothetical non-absorbable 17 prodrug that doesn't do anything in its prodrug state. 18 The prodrug conjugate however can be hydrolyzed by a 19 metallo-beta-lactamase and this interaction is 20 specific to the beta lactamase activity of bacteria. 21 It's not affected by human-derived metalloproteases. 22 Upon cleavage by the metallo-beta-lactamase</p>

<p style="text-align: right;">Page 246</p> <p>1 in the periplasm, a peptide is released that kills the 2 metallo-beta-lactamase expressing bacterium. Z-3 has 3 been studied pre-clinically and in phase I data and we 4 have the information required to permit daily dosing 5 for up to 3 months in human beings. So with this in 6 hand, we set out to do a phase II study of travelers 7 from Northern Europe to Southeast Asia or India, and 8 we enrolled 200 healthy adults, half men and half 9 women from Northern Europe who have travel plans to go 10 to Southeast Asia or India for 4 to 8 weeks.</p> <p>11 They are all screened prior to travel and 12 found in there's -- that their stool is free of ESBL 13 and MBL-producing strains of Enterobacteriaceae by 14 culture on selective media and by next-generation 15 metagenomic sequencing. They are randomized one-to- 16 one to begin daily oral dosing with Z-3 versus an 17 identical placebo beginning at the time of travel and 18 to continue this for 2 weeks after their return.</p> <p>19 One month after return, that is 2 weeks after 20 stopping Z-3, rectal swabs are again tested. And lo 21 and behold 24 percent, exactly like tanged in 2010, 22 are found to be carrying CRE in their stool. And this</p>	<p style="text-align: right;">Page 248</p> <p>1 group developed urinary tract infection during a 6- 2 month observation. I had a hard time getting a really 3 strong number for this, and the 1 in 50 could be a 4 overestimate of the frequency of this in these 5 otherwise healthy female travelers.</p> <p>6 So this leads us to the questions to debate. 7 Z-3 is not going to keep you from getting an 8 infection, but the infection that you do get cannot 9 possibly due to an MBL if you're not carrying one. 10 It's gravity. Can or how can these data be translated 11 into a large-scale demonstration of utility? And 12 specifically is demonstration of reduced rates of 13 infection due to an MBL producer required for proof 14 that not being colonized prevents you from being 15 infected with an MBL, do I have to prove it? If I do, 16 why do I have to prove it? Okay. If I -- it's almost 17 like one of those jumping out of the airplane 18 parachute questions, right? You know, I don't really 19 feel like I have to test the importance of wearing a 20 parachute when I jump out of an airplane.</p> <p>21 On the other hand, if it's not required to 22 prove clinical efficacy, why is that not true?</p>
<p style="text-align: right;">Page 247</p> <p>1 is true for both groups, both the placebo and the Z-3 2 treated. They have CRE. Of those CRE, 8 percent 3 which is a fictitious number taken as one-third of the 4 number I found in India just sort of reflect a rate of 5 travelers of the study -- of the subjects in the 6 placebo group and 0 percent in the Z-3 arm are found 7 to be carrying an MBL.</p> <p>8 So you've got a fraction of them who come 9 back colonized with an MBL. And that's chosen because 10 it's an irritatingly close p-value to 0.05, but one 11 you might choose to disbelieve. P equals 0.04. Six 12 months later, again just like tanged in, a quarter of 13 those who were colonized are still colonized, and 14 they're still carrying it in proportion. So there are 15 six people still carrying an ESBL and two still 16 carrying an MBL. So the persistent MBL rate is 2 17 percent.</p> <p>18 Two infections occurred during this 6-month 19 period, one in each study arm, both were uncomplicated 20 UTIs in women. Both were due to a -- an ordinary 21 Enterobacteriaceae, not a CRE, just what these women 22 were carrying. Hence 1 in 50 women in this traveling</p>	<p style="text-align: right;">Page 249</p> <p>1 Because, you know, this is a product with a potential 2 side effect, and you know, it feels like we ought to 3 do the -- ought to study it. And so one way I thought 4 about this was, well, the number needed -- maybe I can 5 do this based on urinary tract infections. So if you 6 do the math, the number needed to treat for women is 7 1,250. If 1 in 50 develop a urinary tract infection 8 and the proportion due to an MBL is the mean of the 8 9 percent rate when they came back right at the end of 10 their trip, and the 2 percent rate they have 6 months 11 later. So it's sort of picking a midpoint. I have no 12 idea if that's right or not, but 50 over 0.04 is 13 1,250.</p> <p>14 So if I want to show that I reduce the rate 15 from 1 in 1,250 to a smaller number that is 16 statistically meaningful, my very crude sample-size 17 calculation was I needed to have 30,000 people, 15,000 18 in each arm to produce the -- to prove a reduced rate 19 of urinary tract infection in women. Men aren't going 20 to get it at that rate. So it's only in women. So if 21 I do this study and it's positive, is Z-3 now 22 indicated for preventing acquisition of MBLs in women,</p>

<p style="text-align: right;">Page 250</p> <p>1 but not in men?</p> <p>2 Finally would you pay for this if it was</p> <p>3 available for \$500 at CVS and you're about to go to</p> <p>4 someplace where you could pick up an MBL? Would you -</p> <p>5 - would you be willing to buy it? If so, which of</p> <p>6 these data sets would you require before you would put</p> <p>7 your \$500 on the table? That's it. Ed is shaking his</p> <p>8 head at me. I don't know why.</p> <p>9 MR. OUTTERSON: Can we buy it for \$50?</p> <p>10 MR. REX: No, because the plant that</p> <p>11 manufactures it, you know, I have to run that darn</p> <p>12 thing and you know, and it's -- you know, these things</p> <p>13 aren't entirely free to make. So I guess I'll add</p> <p>14 that we invented this case to be as clean as possible</p> <p>15 a question about a community-level benefit. I mean,</p> <p>16 there are lots of ways you try to get at the question,</p> <p>17 but this one was meant to try to take away everything</p> <p>18 but the community-level benefit. I'm seeing stunned</p> <p>19 silence here. But good for you.</p> <p>20 UNIDENTIFIED SPEAKER: But doesn't it then --</p> <p>21 MR. COX: Too though, right?</p> <p>22 MR. REX: Well, so --</p>	<p style="text-align: right;">Page 252</p> <p>1 prevention. We do have some data there.</p> <p>2 MS. BOUCHER: Yeah, no, we have some data for</p> <p>3 surgery for example with chlorhexidine bathing and</p> <p>4 mupirocin for 5 days before open-heart surgery that</p> <p>5 it's beneficial.</p> <p>6 MR. DUBOVSKY: Right. But my guess is those</p> <p>7 weren't a licensing phenomenon.</p> <p>8 MS. BOUCHER: Right. I don't believe that's</p> <p>9 a licensed indication, but I defer --</p> <p>10 MR. REX: But is my use of -- is</p> <p>11 chlorhexidine a drug? I mean is it --</p> <p>12 MS. BOUCHER: Yes.</p> <p>13 MR. REX: -- do I have to have somebody --</p> <p>14 MS. BOUCHER: Mupirocin is a drug. Mupirocin</p> <p>15 is a drug.</p> <p>16 MR. REX: Mupirocin, but --</p> <p>17 MS. BOUCHER: So we use mupirocin.</p> <p>18 MR. REX: But to use the chlorhexidine bath,</p> <p>19 that's not a --</p> <p>20 MS. BOUCHER: That's not a drug, but the</p> <p>21 mupirocin is, that's a prescription.</p> <p>22 MR. COX: Yeah, I think -- I think it is. I</p>
<p style="text-align: right;">Page 251</p> <p>1 MR. COX: Yeah, so what I was -- I was asking</p> <p>2 John about was this, doesn't it benefit the patient</p> <p>3 some too? What do you think?</p> <p>4 MR. REX: Well, yeah, you know, I guess and</p> <p>5 what I thought about this, you know, why would I be</p> <p>6 willing to buy this before I take my trip? And the</p> <p>7 reason is that I'd rather not be colonized with the</p> <p>8 metallo. You know, I think my chance personally of</p> <p>9 getting, you know, sick with infection in the next 6</p> <p>10 months are relatively small, but if I'm -- don't have</p> <p>11 a metallo, I won't have a problem with it and I won't</p> <p>12 spread it to anybody else. I mean I think those are</p> <p>13 the two things that seem straightforward to me about</p> <p>14 it. But I think the likelihood that I personally</p> <p>15 would benefit is going to be really small because my</p> <p>16 chance of an infection in the next 6 months is really</p> <p>17 small.</p> <p>18 MR. DUBOVSKY: Is there anything to learn</p> <p>19 from other decontamination things like chlorhexidine</p> <p>20 or mupirocin?</p> <p>21 MR. REX: So Helen's going to have to help me</p> <p>22 a little bit on this in terms of hospital or infection</p>	<p style="text-align: right;">Page 253</p> <p>1 I think it's handled by our nonprescription products</p> <p>2 group, yeah, and it's -- I don't know the division</p> <p>3 between what's handled under monograph and what they</p> <p>4 handle under an NDA, but it -- it is a drug from what</p> <p>5 I recall. But I think what you're talking about are</p> <p>6 probably studies that are done, you know, by the</p> <p>7 academic community for at least some of these studies.</p> <p>8 And they are using approved products and they're using</p> <p>9 them, you know, perhaps as combinations or mixtures to</p> <p>10 look at, you know, in various different infection</p> <p>11 control measures.</p> <p>12 And they're in the published literature, but</p> <p>13 they may not be done by, you know, the pharmaceutical</p> <p>14 company. They may not be something that's connected</p> <p>15 with the pharmaceutical company. So they may not lead</p> <p>16 to supplements that would come in to us that would</p> <p>17 lead to changes in the product label. But they could.</p> <p>18 MR. REX: I mean I don't -- I may not be</p> <p>19 looking it up correctly, but I just found there's a</p> <p>20 chlorhexidine oral rinse that seems to have a -- some</p> <p>21 sort of an FDA label. But I didn't find one for skin</p> <p>22 prep.</p>

<p style="text-align: right;">Page 254</p> <p>1 MR. HOPE: So John, isn't there a literature 2 on invasive procedures in men after they come back 3 traveling? So there's -- I think there's literature 4 published on prostatic biopsies for example, where -- 5 that's the first point I just want to make. And then 6 the second is I just want to say something about 7 precision of language, which I know that you're very 8 interested. And it goes right through this 9 afternoon's discussion about the distinction between 10 infection and disease.</p> <p>11 And so that the -- those terms are being used 12 interchangeably where I don't think that you -- I 13 mean, so VRE infection, we're all infected with VRE in 14 the sense that we -- it's present, but it's not 15 causing disease. And that is just -- well, maybe 16 semantics, but an important distinction here sorting 17 out because we're really interested in clinical 18 endpoints in disease rather than in infection. So -- 19 and you know, it's the same in fungal diseases as well 20 because we're all infected with aspergillus right here 21 and now, but we don't have aspergillus disease.</p> <p>22 MR. REX: So if I may pick up on both of</p>	<p style="text-align: right;">Page 256</p> <p>1 series of outbreaks of prostatitis in Southeast Asia. 2 And so it's possible for that sort of thing 3 to occur. And the link here I -- I was trying to come 4 up with a way to do this that didn't require anything 5 special to happen. I was looking for a very -- 6 something that I could imagine doing. I mean I can, 7 you know, I could see that, you know, all -- 8 everything about this case was something that, you 9 know, I'm having trouble seeing that you could 10 actually do it if you really wanted to.</p> <p>11 MR. HOPE: So maybe I'll just comment a 12 little bit. So I mean, if we think about, you know, 13 the surgeon who has group A strep, I mean, you know, 14 it's been a while since I've done the infection 15 control sort of stuff. But you know, maybe you have 16 three or four patients with post-operative infections 17 with group A strep and that sends you looking for the 18 source. And if you find out that they all had the 19 same surgeon or the same surgical team, then you start 20 to culture. So I think what you have there is a, you 21 know, a fairly strong epidemiologic connection 22 between, you know, an event and then an actual</p>
<p style="text-align: right;">Page 255</p> <p>1 those. First, earlier when I used -- when I asked the 2 question, is there some definition of microbiome that 3 you should treat as if it were an infection, I meant 4 it deliberately in that sense, that -- and I meant I 5 should -- maybe I should have said disease and it's -- 6 Neisseria meningitidis in my nose is probably 7 something I would treat as a threat to me that I would 8 like to do something about, even though at this moment 9 it's not replicating in my CNS.</p> <p>10 So I -- to my mind, that's -- it's not -- I 11 can't feel it, but it's certainly scary and I suppose 12 a correlate would be you can't feel colon cancer for a 13 long time, and yet when you discover that you have a 14 polyp, you get it taken out. So I think there is a 15 sliding scale here for some of these things that have 16 a long period -- a long runtime before they eat you 17 kind of a question. And your comment about men and 18 prostatitis and gram-negatives, absolutely there is a 19 relationship there. Jason Gale wrote a series of 20 articles about how the use of antibiotics and shrimp 21 farming has led to carriage in shrimp of multi-drug 22 resistant E. coli which led to a pretty clearly linked</p>	<p style="text-align: right;">Page 257</p> <p>1 infection in patients.</p> <p>2 So I think John's on to something when you 3 started to talk about, you know, how close is the 4 connection because as that connection starts to become 5 closer between the clinical event and the state of 6 carriage, then I, you know, then I think you're in a 7 better position to understand, you know, if you alter 8 the state of carriage that you may reduce infections. 9 And you know, same thing if, you know, the -- somebody 10 comes in with a Neisseria meningitidis infection and 11 the person who intubated them has been, you know, 12 exposed to secretions and all that is a presumably a 13 high risk.</p> <p>14 I mean, I haven't looked back at the primary 15 literature there, but presumably is it sufficiently 16 high enough risk of infection that it's worth 17 prophylaxing those folks, so that -- I mean, so it 18 does seem, you know, what is the information that 19 connects the event to that -- either that at-risk 20 exposure state or that carriage state leading to a 21 clinical infection? And to the extent that you can 22 figure that out, it certainly helps to understand, you</p>

<p style="text-align: right;">Page 258</p> <p>1 know, what an intervention might do as far as 2 altering, you know, state of what may be carriage or 3 colonization and as far as actually leading to the 4 reduction of a clinical infection. 5 MR. REX: So I can't -- I'm not going to back 6 the slides up, but you've got slide 6 in front of you. 7 Set it up so that there actually was a p less than 8 0.05 for our demonstration that you prevented 9 acquisition of metallo-beta-lactamase producers. Can 10 I bring you a dataset on the real version of Z-3 and 11 get an indication for Z-3 is indicated for the 12 prevention of acquisition of metallo-beta-lactamase- 13 producing organisms while traveling to Southeast Asia? 14 MR. COX: So it's always hard to talk about 15 the approvability of a hypothetical NDA (ph) in the 16 spot, but he's done a series of slides. But -- 17 MR. REX: Do you mean yes? 18 MR. COX: Well, it's a maybe. Would you take 19 a maybe? 20 MR. REX: Yes, okay. 21 MR. COX: So it sounds like what you're 22 telling me and I'm not entirely clear on this, but if</p>	<p style="text-align: right;">Page 260</p> <p>1 where everybody was going. And then nobody had a 2 clinical event. So I think you really have to -- you 3 have to be able to tie what's going on here to the 4 clinical event in a very sort of solid way. That's 5 the hard part. Because, you know, if you're treating 6 something, it's going to go away 2 weeks later on its 7 own anyways, and you're going to have no clinical 8 events, I think you have to start to ask the question 9 of what am I doing. 10 MR. REX: Yeah. 11 MR. COX: If you -- if the carrier state 12 persists and you have clinical events, then I think 13 you've got a connection with, you know, preventing a 14 clinical event. And this is what's so difficult and 15 so challenging about, you know, these issues of 16 carriage. And so that's just sort of the hypothetical 17 talked about at the high sort of theoretical level to 18 make it even -- you know, which makes it even more 19 complicated that's why it's very helpful to have the 20 clinical events to help sort this all out. You know, 21 how often do you culture, what's your level of 22 detection with the culture, you know, are people</p>
<p style="text-align: right;">Page 259</p> <p>1 you actually have a clinical trial and it sounds like 2 it's a lot of patients that you actually show 3 reduction of, you know, the event of clinical urinary 4 tract infection with MBL organisms, then you might 5 have something there, so. But there's always the -- 6 oh, you don't have that. 7 MR. REX: No. I personally -- well -- 8 MR. COX: Okay. 9 MR. REX: -- I'm asking you, yeah, this right 10 here. So this is as far as I've gotten. I haven't -- 11 I've done a 200-patient trial and I come back with 12 this, okay? And maybe I do a 2,000-subject trial, but 13 basically you -- this is all you've got and nobody -- 14 and I don't go to the trouble of doing a 30,000- 15 subject trial. It's, you know, it's -- all I really 16 ever show in real time with this is that it keeps you 17 from -- it keeps you from coming back with an MBL that 18 I can detect in your stool. 19 MR. COX: Right. So again, I mean -- you can 20 come up with a gazillion different hypotheticals. So 21 I can then postulate that these people were all 22 cultured 3 weeks later and they all -- all their MBLs</p>	<p style="text-align: right;">Page 261</p> <p>1 transiently positive and transiently negative? 2 I mean there's just a lot of questions that 3 come up and these are all -- I mean if you can get to 4 the actual clinical event and show the reduction in 5 the clinical event, then some of these difficult 6 questions in essence are eclipsed by the benefit that 7 you've shown to the patient. 8 MR. REX: So that I -- you know, I put you on 9 the spot, but it's -- actually it's not a regulatory 10 issue in a sense. I mean if I -- even if it were 11 approved, would you pay for it? You know, I'm looking 12 at Kevin Outterson as our -- as a patient rep in 13 effect. 14 MR. OUTTERSON: With a preventative care 15 taskforce. 16 MR. REX: With a preventative -- 17 MR. OUTTERSON: Care would be. 18 MR. REX: Right, yeah. Say that again? 19 MR. OUTTERSON: But would the prevention care 20 taskforce give it an A or B rating and therefore -- 21 MR. REX: Yeah. 22 MR. OUTTERSON: -- require, you know, U.S.</p>

<p style="text-align: right;">Page 262</p> <p>1 insurance policies to cover it.</p> <p>2 MR. REX: Right.</p> <p>3 MR. OUTTERSON: Yeah.</p> <p>4 MR. COX: And then let's add in that it has</p> <p>5 some adverse effects.</p> <p>6 MR. REX: No. No, no.</p> <p>7 MR. COX: So then -- you know, then the</p> <p>8 benefit risk gets a little complicated too so --</p> <p>9 MR. OUTTERSON: No. That's not on the hypo.</p> <p>10 MR. COX: Pardon?</p> <p>11 MR. OUTTERSON: That wasn't on the --</p> <p>12 MR. COX: But it wasn't on the slide.</p> <p>13 MR. REX: Yeah. But you know, I made it as -</p> <p>14 - I made it very clean. But nothing is ever that</p> <p>15 clean.</p> <p>16 MR. OUTTERSON: Right.</p> <p>17 MR. REX: You know, there would be something</p> <p>18 that it does though occasionally and so you might feel</p> <p>19 like you wanted to see the next level of proof, but</p> <p>20 the next level of proof is a big study.</p> <p>21 MR. COX: But there are -- people travel a</p> <p>22 lot. There's no reason why, you know, 30,000 people</p>	<p style="text-align: right;">Page 264</p> <p>1 \$500. But how many people are you going to have that</p> <p>2 would personally spend \$500 because how many people go</p> <p>3 to Southeast Asia? So I think, you know, it does come</p> <p>4 down to economics and whether or not it's worthwhile</p> <p>5 to even bring such a drug to the market.</p> <p>6 MR. KALEKO: At the risk of violating again</p> <p>7 the constraints of hypothetical scenario, wouldn't</p> <p>8 this particular therapeutic be useful? It seems that</p> <p>9 the greatest issue with MBLs is that they will expand</p> <p>10 under selective pressure from antibiotics. So</p> <p>11 wouldn't the best use of this be to give it to</p> <p>12 everybody who comes into a hospital knowing that 50</p> <p>13 percent of them by the time they leave the hospital</p> <p>14 will have been on antibiotics. Or someday have it in</p> <p>15 -- on a formulary at your local drug store so that</p> <p>16 everybody who gets an antibiotic gets it. So that</p> <p>17 eventually you stop the expansion of MBLs and then</p> <p>18 they will by their very nature drift away.</p> <p>19 MR. COX: So that may be a studiable</p> <p>20 question.</p> <p>21 MR. KALEKO: Yeah. It might be.</p> <p>22 MR. COX: You know, you could try and figure</p>
<p style="text-align: right;">Page 263</p> <p>1 could be accrued.</p> <p>2 MR. BLACK: So taking this comment, John,</p> <p>3 because I meant the study that you described, you say</p> <p>4 you want to focus on the community benefit. The</p> <p>5 component that you haven't really addressed here is</p> <p>6 what then is the transmission rate of these people?</p> <p>7 So is it really just local cluster that's at-risk or</p> <p>8 have you prevented further environmental dissemination</p> <p>9 and then it becomes more like, you know, a vaccine</p> <p>10 herd assessment of how many people do I need to treat</p> <p>11 to really prevent enough carriage to then have an</p> <p>12 impact on a cluster analysis-type of study I think on</p> <p>13 progression of disease. And that's not necessarily</p> <p>14 captured here if it's going to be kind of treatment as</p> <p>15 prevention.</p> <p>16 MS. DORR: I was just going to comment from</p> <p>17 the perspective of if it wasn't paid for by my insurer</p> <p>18 or by my company if I was traveling on business, would</p> <p>19 I pay for it. If I was paying out of my pocket to go</p> <p>20 to Southeast Asia, I'm probably spending \$10,000 or</p> <p>21 more dollars to go on vacation and if I'm educated and</p> <p>22 I know this is a bad thing, I personally would spend</p>	<p style="text-align: right;">Page 265</p> <p>1 out if the effect that you're postulating the drug has</p> <p>2 can be demonstrated in a clinical trial and that is in</p> <p>3 fact the effect that the drug has.</p> <p>4 MR. REX: You know, I guess I was thinking</p> <p>5 this was -- in this case it's going to be food-borne</p> <p>6 acquisition of organisms in a healthy traveler. And</p> <p>7 in a nosocomial setting, hospital setting, you've got</p> <p>8 other ways of acquiring pathogens who -- so that is</p> <p>9 you took the stuff by mouth and it works in your gut</p> <p>10 to keep the colonization recurring seem to me to be</p> <p>11 part of the storyline. But the notion of a prevention</p> <p>12 -- well, but that actually is like a -- that's a</p> <p>13 standard infection prevention question, isn't it? I</p> <p>14 mean, it's the -- you know, what kind of hand-washing</p> <p>15 and gloves and carrying on prevents you from acquiring</p> <p>16 a difficult organism.</p> <p>17 I didn't -- you know, this one isn't set up</p> <p>18 to -- if you've gotten -- if you've already gotten an</p> <p>19 infection due to an MBL, it's not going to help you at</p> <p>20 all because this only works -- this made-up thing only</p> <p>21 works in the gut. But it's really we're back into a</p> <p>22 very standard infection prevention question there.</p>

<p style="text-align: right;">Page 266</p> <p>1 MR. DUBOVSKY: But John, in this case people 2 who go to hospital could be screened, know they have 3 it, they could be decolonized, right? 4 MR. REX: Well, I guess that's true. This is 5 a -- you know, in theory if it -- you know, the way 6 it's invented, if you're carrying this in your stool 7 and you took some of this in theory it would -- it 8 might clear you I guess and no reason why not. 9 MR. KALEKO: What percentage of people who 10 have it in their stool also have it in their 11 nasopharynx or someplace else? 12 MR. REX: I don't -- I didn't really dig deep 13 there, but the main place where you carry the gram- 14 negatives -- well, you could certainly carry them in 15 your mouth and your dentition, you can if you've got 16 bad teeth. No question the way to get and the way I - 17 - the way this one was invented, unless you did a 18 swish and swallow, I mean, I -- you know, we're kind 19 of -- we're getting very inventive with it here. But 20 the notion here was about the reason the pay-in I 21 thought maybe you could make this work was, 22 acquisition is going to be oral, this got to stuff in</p>	<p style="text-align: right;">Page 268</p> <p>1 known to occur. 2 MS. DAS: I can't -- I keep thinking about 3 the synergies as an anti-malarial here and can't you 4 think about development on those terms? And you know, 5 if you are developing it, is it of greater use in the 6 countries where you have more MBLs prevalent, you 7 start to decrease the instance of MBLs? 8 MR. REX: Well, I mean that's why I had the 9 travelers go from Northern Europe to Southeast Asia 10 we've discussed at the low because I knew the rates 11 were higher there. You know, that's the -- there was 12 -- it wouldn't be a point doing it from Sweden to 13 Norway. 14 MS. DAS: No, but I guess my point is that 15 was why you're developing an anti-malarial because, 16 you know, I take anti-malarials when I go to a foreign 17 country, but I'm not the person that primarily 18 developed for and I'm not the cost-benefit argument I 19 guess. So could you develop this drug actually for 20 use -- for greater use in the countries where you have 21 higher rate of MBLs and added advantage of it is that 22 the new travelers can use it?</p>
<p style="text-align: right;">Page 267</p> <p>1 your gut at the time that you are exposed to organisms 2 and they just can't stay if you've got this in your 3 gut. 4 MR. MELNICK: But John, once you've 5 established that a carriage state is associated with 6 infection downstream, you know, and it could be this 7 trial or another, the cost benefit of using it in 8 patients who are known to be colonized becomes very 9 different. So the scenario of somebody coming into 10 the hospital, getting screened and then found to be a 11 carrier and treated, that's a different cost-benefit 12 equation. 13 MR. REX: Can't argue with that. It -- here 14 this is -- I was trying to create something or to 15 create a storyline that was about a question that was 16 as close as possible to I as an individual can get 17 almost no benefit from this. The benefit -- yeah, 18 there might be some and I -- sorry, I didn't throw in 19 something about transmission because you can certainly 20 look at your family, partners, and see if it had 21 little bit of spread locally because, you know, that's 22 how these things get around, right? It certainly is</p>	<p style="text-align: right;">Page 269</p> <p>1 MR. REX: Oh, oh, oh. So the primary market 2 for this is people who are living in a high-risk area 3 and in that group you would have -- they would be at 4 risk for all the things that happen to human beings in 5 ordinary course and that would give you potentially a 6 larger pool of things, it wouldn't be as hard to find 7 the people -- you know, finding the subjects actually 8 would be a more straight -- it would be a simpler 9 trial to do in many ways, wouldn't it? 10 MR. OUTTERSON: Yeah, but you make most of 11 your money on the travelers' market. 12 MR. REX: Presumably. 13 MS. NAMBIAR: So -- 14 MR. REX: Because I better get busy and 15 invent this stuff. 16 MS. NAMBIAR: So I think if it draws a 17 similarity with malaria, I mean that's how malaria 18 studies are done, right? Very often we would study it 19 in semi-immune population, people who live in endemic 20 areas. We try to study it also in a non-immune 21 population, which really would be the travelers. But 22 the use is really for -- for the vast majority will be</p>

<p style="text-align: right;">Page 270</p> <p>1 people who are traveling from non-endemic areas to 2 endemic areas.</p> <p>3 MR. BLACK: So just ask another hypothetical 4 around this, so let's say my Merck chemist make a nice 5 safe prodrug version of this and it becomes the best 6 therapy for treating, you know, expressing 7 pseudomonas. Would you want to continue using your 8 drug in this manner? Because this is an antibiotic, 9 right, and it has the same potential risks of being an 10 antibiotic and can be developed into a more 11 therapeutic version.</p> <p>12 MR. REX: Well, the way that this one was 13 invented, it's limited to the gut. I did -- where 14 there's a way to give it systemically, I -- you know, 15 maybe there is. But in order to use it as a 16 therapeutic, you would have to deliver it 17 systemically, right? And I didn't think -- well, 18 maybe it could.</p> <p>19 MR. BLACK: I'm just saying -- I'm just 20 commenting, it is a novel antibiotic that you've 21 discovered and described and if we could progress 22 that, would you still want to use it in this way, is</p>	<p style="text-align: right;">Page 272</p> <p>1 sufficient? And the analogy, one analogy could be HPV 2 which, you know, it wasn't shown to reduce cervical 3 cancers, to reduce, you know, carriage of the subtypes 4 plus pre-cancerous lesions. Could you accept a 5 smaller study with and what would you want the other 6 thing that was done by somebody else to say?</p> <p>7 MR. COX: Yes. So I mean, I think again it 8 gets back to these issues of, you know, limits of 9 detection, when are you looking, you know, have you 10 actually shown that, you know, treating will actually 11 reduce the infection? If you don't have direct 12 evidence of that, how good is the other evidence that 13 you have that you're relying on? In essence you're 14 looking at a surrogate. I mean there's just a lot of 15 questions here that are very difficult to answer in a 16 very hypothetical way and it wouldn't, you know, if I 17 say "Yeah, yeah, sure we can do that," I haven't done 18 anyone any favors because we haven't really thought 19 through the issues. And I think, you know, one of the 20 things that this case brings up to me is that whenever 21 we talk about idealized situations and then you move 22 into the real world, there's a lot of things that pop</p>
<p style="text-align: right;">Page 271</p> <p>1 what I'm asking? And so --</p> <p>2 MR. OUTERSON: Yeah, I feel the room is -- 3 John, you've beat them into stupor or something with 4 the type of it. You have a future in law school 5 teaching if that's -- what you're doing now doesn't 6 work out for you. So I want to press -- I want to put 7 my good friends to the right of me here on a little 8 more pressure. So looking at this study that John is 9 recording 30,000 people and really if you want to 10 power it for men, you know, and get things other than 11 UTI, you know, there might be 50 or 100, you know, 12 there's going to be a lot of people in the study. The 13 previous slide showed a much smaller study, say 200 or 14 2,000 people. So my question, you know, pushing back 15 what John said earlier, what other evidence would it 16 take for you to approve it based on slide 7? And so 17 I'm assuming that if there was, you know, a good 18 study, various studies out there saying that MBL 19 carriage results in 1 out of 1,000 or 1 out of 500 20 with X and 1 out of 500 with Y, and X and Y are bad 21 things; you know, would just the fact that it's 100 22 percent efficacious in eliminating MBL, would that be</p>	<p style="text-align: right;">Page 273</p> <p>1 up that maybe you thought about, maybe you haven't 2 thought about, that are really important in 3 understanding the connection between, you know the 4 disease state, the intervention, and the clinical 5 outcome that you're trying to figure out.</p> <p>6 So I mean you can see what we're trying to 7 get at is, is the patient better off or not and some 8 way to really figure that out. And you know, usually 9 that's in bacterial diseases where the outcomes happen 10 in a relatively short term in most of the situations, 11 usually we're trying to get direct evidence of that. 12 You know, if there is really, really strong evidence 13 and you've shown that, you know, that reduction of a 14 carrier state is associated with reduction in disease 15 and that should happen with agent A, agent B, agent C, 16 and you can, you know, demonstrate that that surrogacy 17 is in essence, you know, valid, you know, then that 18 can be helpful.</p> <p>19 But you know, that's why we're really sort of 20 interested in trying to see that we're really 21 impacting patients with a clinical outcome. And you 22 know, the discussion has been interesting here</p>

<p style="text-align: right;">Page 274</p> <p>1 because, you know, as this case was developed, it went 2 towards a low-frequency event and then we also heard 3 some comments from Shampa saying, you know, is there a 4 possibility of using this in a scenario where, you 5 know, this event maybe something more frequent. 6 So again it gets to the idea of enrichment 7 and we've heard several people talk about, so is there 8 another way to look at this, that's another thing to 9 think about when you're -- when you're trying to show 10 a clinical effect for a drug, is there a population, 11 is there a circumstance and I credit the folks that 12 have come up with this idea of, you know, maybe 13 there's a more frequently, you know, a population in 14 which the infection will occur more frequently. So 15 enrichment is always something to think about and 16 maybe I'll just stop there, let's see. 17 MS. NAMBIAR: If I can make a comment. I 18 think we've seen the same discussions happen, not just 19 in the context of decolonizing the gut. You know, you 20 can -- you know, we've seen products come through and 21 there is interest in seeing -- applying it in the 22 nares and having some degree of decolonization in the</p>	<p style="text-align: right;">Page 276</p> <p>1 data, right, those -- the infection prevention teams 2 analyze the data, they come up with the best strategy 3 that we can feasibly implement in our institution. 4 And my institution is different than yours and the 5 next one. 6 I think the question that's here that I'm 7 hearing is do we know with certainty even the period 8 of risk. So if we could surmise that this product 9 decreased colonization sufficiently or made it go 10 away, whatever we agreed upon, for 30 days, 60 days, 11 you know, what's the period of greatest risk to that 12 individual for getting infected and potentially 13 passing it around? And some of that is knowable, 14 right, because we know about the cases that have come 15 here that have been imported and we know when they 16 were, wherever they were, that where they presumably 17 acquired the organism. But then maybe some of that is 18 what needs to be known. But it -- is it enough -- 19 could it be enough, that's the question back to you. 20 Could it be enough to know that? Yeah, you could only 21 decrease colonization or make it go away for 60 days 22 or 30 days. You know, is that enough if it was</p>
<p style="text-align: right;">Page 275</p> <p>1 nose, is that good enough? And what is the benefit to 2 the patient and I know Helen mentioned in practice 3 mupirocin is used, but you know, prior to 4 cardiothoracic surgery. But in some of the clinical 5 studies, the treatment benefit, which is a clinically 6 meaningful benefit, I think wasn't that clear-cut in 7 those studies that were done. I mean it was a certain 8 subgroup in which you actually demonstrated a benefit. 9 So I think this issue goes beyond just say 10 decolonizing the gut for a travel, but it can be an 11 effect on a bacterium that is just part of your flora 12 for the most part and whether or not that offers a 13 benefit to the patient. 14 MS. BOUCHER: So John's question, part of it 15 was about the benefit to the population, right? And 16 so as we think about things like decolonization and 17 procedures that we do before big surgeries, that's for 18 the patient undergoing surgery, but it's also for 19 every other patient in that unit because we know that 20 if patient A gets a staph infection, the patient next 21 door is likely to get it from my hands, you know. So 22 those decisions that are made on less-than-perfect</p>	<p style="text-align: right;">Page 277</p> <p>1 knowable that that was the period of greatest risk. 2 MR. REX: Well, I obviously don't have any 3 data to show you the -- I was keying off the idea that 4 the time (ph) and data suggests that you could acquire 5 certain organisms when you lost them over time for 6 whatever reason. And so presumably there is some 7 period of, you know, some people go persistent and 8 others get rid of it. And that there is a finite risk 9 of an infection during the period when you are 10 colonized. And that is one going to prevent you from 11 getting an infection, it was just going to prevent you 12 from having an infection due to something that was 13 harder to treat and that was the only -- that was the 14 only value. If you have a UTI, it won't be due to an 15 MBL if you're not carrying one. 16 And that -- and I did think a little bit at 17 the time, but I obviously didn't write it down about 18 the fact that also your spouse, your child can't have 19 that organism as well obviously if you didn't bring it 20 back from your travels. So this -- that's as far as I 21 could make it go. 22 UNIDENTIFIED SPEAKER: Can we --</p>

<p style="text-align: right;">Page 278</p> <p>1 MR. REX: But that felt to me like that was 2 potentially an interesting benefit for a community as 3 a whole and if what that did over time was -- you 4 know, right now we're seeing these rates of -- and I 5 chose the MBL because certainly we've seen how ESBLs 6 crept into the rest of the world and as ever 7 reasonably that MBLs are just as pathogenic, there's 8 no obvious loss of that, so will we see a time 20 9 years from now when MBLs are meaningfully more common 10 because they have continued to live around the world. 11 You know, maybe the WHO global action plans will slow 12 that down. 13 But you know, the odds aren't bacteria smart 14 and they have lots of chances to replicate and move 15 around the globe and so you'd think you'd begin to see 16 little bits, you know, more and more of this. And the 17 idea that you might do something that would slow it 18 down struck me as attractive. But it just -- it 19 seemed to ask an interesting question that made me not 20 sure what the right answer was. So before -- I think 21 we're getting close to quitting time as they say. 22 I've been trying to come up with a list of strong</p>	<p style="text-align: right;">Page 280</p> <p>1 together or is it mixed human stool and does that 2 change your strategy whether it's a single thing or a 3 combination of things. The third one I almost wrote 4 down biology versus not, but I ended up concluding 5 that wasn't right. I looked for it. So it's 6 immunogenic versus not. And maybe even that's not 7 right, I don't know. 8 But things that are immunogenic seemed to 9 have a set of toxicology issues and possibly short -- 10 maybe the product itself can be -- it gets neutralized 11 in some fashion, I don't know whether that's right or 12 not. And then the fourth one is the one we've just 13 now been debating, which is direct clinical benefit 14 versus not. And those categories seemed -- so host 15 versus non-host; combination versus single thing; 16 immunogenic versus not; and direct clinical benefit 17 versus indirect clinical benefit seem to me to be 18 boxes that might enable you to have specific 19 conversations where you try to sort stuff out about 20 how you might take a product forward. 21 So those were the thoughts that I had and I - 22 - and if people have stuff to add to that, this -- now</p>
<p style="text-align: right;">Page 279</p> <p>1 factors that it will cut points if you will in terms 2 of the non-traditional, what are the things that need 3 to be debated and how would you divide it. 4 And I'm just going to read off the list I've 5 got right now and if you think of something else, let 6 me know because it feels to me like one of the real 7 valuable outcomes from today would be if we identify 8 some subset of the concept of non-traditional that we 9 can articulate is a place where a good, in-depth 10 conversation would be instructive, that would be a 11 useful output from this. And so the list that I've 12 got right now has four things on it. One is the 13 difference between it works for the host versus 14 working at a non-host level. So that could be immune, 15 but you know, broadly it works on you rather than on 16 the pathogen. 17 The second one is that it's a combination of 18 things versus being a single thing. And we talked 19 about that in terms of monoclonals versus polyclonals, 20 but also the idea of, you know, FMT (ph), is it a 21 thing, is it a single organism or is it something that 22 you -- is it 19 organisms that you choose to pull</p>	<p style="text-align: right;">Page 281</p> <p>1 or later or tomorrow if you think of something, I 2 would be very interested in trying to make a better 3 version of that list with the thought that that might 4 identify buckets of things that would be worth more 5 detailed debate. 6 MR. KALEKO: It might be too late in the day 7 for me at this point, but can you clarify the 8 difference in 1 and 4 on your point list? 9 MR. REX: Well, my list number 1 was host 10 versus non-host, that is it's working. You know, 11 something that it works at the host level would be 12 activating my immune system to throw off to -- as 13 opposed to something that kills the bacteria directly. 14 And maybe variance factors probably fall into that 15 category as well. That's -- that would be host -- if 16 it doesn't kill the bacteria, just somehow slows it 17 down or -- and then my list number 4 was direct 18 clinical benefit versus not. And so Z-3, a lot of its 19 benefit presumably is an indirect benefit as opposed 20 to the monoclonal prevent staph aureus pneumonia. If 21 I'm at risk for staph aureus pneumonia, I can get it - 22 - I personally can get a benefit directly from that.</p>

<p style="text-align: right;">Page 282</p> <p>1 And here with Z-3 maybe I can -- there's a little bit 2 of possibility that I get a benefit, but not a lot. 3 And so that was the pole I was thinking about. 4 MR. OUTTERSON: We've had a lot of comments 5 up here, but is there anyone in the audience who wants 6 to step up to that microphone and boldly ask a 7 question or make a comment? 8 MS. NAMBIAR: Okay. I think I got somebody. 9 UNIDENTIFIED SPEAKER: Dr. Dan -- 10 UNIDENTIFIED SPEAKER: So John -- is that 11 working? Yeah. So John, the other area is which I 12 thought you were talking about in number 4 is, that's 13 come through a lot of these surrogates as well, so 14 that's K1 (ph) that seems to be running through nearly 15 everything is a way of doing that to make it useful. 16 MR. REX: Yeah, so it's hard to hear a little 17 bit, but you're saying that you could extend the 18 concept of direct versus indirect benefit to talk 19 about surrogates for subsequent presumably direct 20 benefit. But where you actually though -- as you well 21 hear and see -- 22 UNIDENTIFIED SPEAKER: And if you could get</p>	<p style="text-align: right;">Page 284</p> <p>1 that the FDA is willing to entertain stories about 2 surrogacy and about, you know, complex stories, but 3 they need to be things that are routed in actual hard 4 science, not just fanciful leaps of logic that and -- 5 but you know, we were open -- you know, there's an 6 openness to at least exploring some of these ideas of 7 a population-level benefit of surrogacy in both of the 8 ways that has been expressed and just opening the 9 boundary of what -- you know, John frequently talks 10 about, you know, is it going to benefit this patient 11 and we're broadening that discussion, is it benefiting 12 this patient now versus later in this patient versus 13 the population as long as the clinical evidence of 14 that or the science evidence of that is robust. But 15 that's my summary, not the FDA's summary, so I'll let 16 -- if you want to say anything to close up today? 17 MS. NAMBIAR: No, it's -- I know when we 18 started talking about this hypothetical case, we did 19 think it was going to be difficult. But honestly I 20 didn't think it would be so difficult. I think you've 21 really got the panel members and most of the audience 22 fairly perplexed and thinking and I think this is --</p>
<p style="text-align: right;">Page 283</p> <p>1 direct benefit as a surrogate that for a longer term - 2 - 3 MR. REX: Right. Here in Z-3, you could say 4 that the surrogate is absence of colonization with an 5 MBL for the long-term benefit of no infections due to 6 an MBL, right. 7 MR. EVANS: Yeah, my comment on that was when 8 you talk about direct clinical benefit, I think 9 there's really two pieces of that puzzle, when you -- 10 direct clinical benefit is really two pieces of the 11 puzzle, part number 1, for whom? And whether that's 12 the person who is being randomized and treated or 13 whether that's beyond that. And how do you interpret 14 the beyond that stuff? The second thing is the 15 surrogacy and in some ways it's connected to the first 16 one because if you're going to talk about surrogacy, 17 am I talking about surrogacy for the patient in the 18 trial or am I talking about surrogacy for a population 19 level outcome that's happening, and what level of 20 validation of that surrogacy has to happen in order 21 for, you know, feel comfortable to move forward? 22 MR. OUTTERSON: So my 30-second summary is</p>	<p style="text-align: right;">Page 285</p> <p>1 it's a particularly hard one to address. But having 2 said that, I think there's no harm to wrapping up the 3 day a little sooner than we had planned. Many thanks 4 to everybody who participated today, presented 5 discussions, and we start tomorrow at 9:00 as well. I 6 think registration is prior to that, but the first 7 session which will be the last case study for this 8 workshop will be tomorrow morning, we'll talk about 9 the lysin products, I mean other interesting 10 discussion. So thank you everybody for joining us 11 today and we'll see you all tomorrow. Thank you. 12 13 14 15 16 17 18 19 20 21 22</p>

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