U.S. FOOD AND DRUG ADMINISTRATION

MONOCLONAL ANTIBODY DEVELOPMENT

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PROCEEDINGS

MR. COX: All right. Welcome everybody and thank you for joining us today for public workshop on development of non-traditional therapies for bacterial infections. And if we, you know, we think about this area, we think about what's going on in the area of bacterial diseases. You know we are at a time when the antimicrobial resistance is getting ahead of us and we need new therapies in order to be able to meet patient needs.

We've seen an increasing interest over the last several years to development of what we're calling non-traditional therapies; so new types of interventions that we hope will provide new therapies for patients who need them; particularly, those with more serious infections and infections caused by resistant organisms.

Now folks who had been following this field may recall that there was a Duke-Margolis workshop a couple of months ago. That was a very helpful meeting to sort of get the landscape of the different types of products that are out there. And today, what we'd

like to do is continue those discussions and move beyond, in essence, the inventory and sort of a first blush look at the products and actually try and get into some level of detail with regards to the therapies, what they are, how they might be studied.

So you'll see we have a series of cases that we'll be talking about, which we hope will prompt a discussion on this very topic and we look forward to hearing the groups thoughts on the different development pathways. If we think about the term non-traditional therapies, I just want to reflect on that for just a minute. It's sort of an interesting name and some might even argue it's a misnomer. I mean if you think about early studies for type-specific anti-pneumococcal serum and other anti-sera that were used many, many years ago, maybe the smaller molecules are not -- they're non-traditional. And if we go back to our roots, some of the things that we're calling non-traditional actually were sort of the earlier therapies.

But I think what this reflects is that we're more accustomed to the use of small molecule drugs

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when we think about treating bacterial infections clinically. And one thing that John Rex and Kevin Outterson has taught me is that "It's very important for us to get all on the same footing." So we'll start out with a talk today from John and Kevin and they'll walk through an overview of non-traditional therapies and help us with some of this vocabulary about these various different types of products as we think through them that I think that helps us in our discussions if we have a similar footing. Then we'll also hear from Helen Boucher and Helen will give us a clinicians' perspective. What she's seeing out in the field. And that will remind us of the importance of the work that we're undertaking here. And really you know our real end goal here is to have new therapies for patients.

We will also walk through and group together issues of pharm tox, (inaudible) microbiology considerations that we think spans really the range of the different case scenarios we present -- that we will go on to present. So we try to group those altogether thinking that they'll be applicable in

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general to the types of therapies we are talking about.

And then you'll see that we have a series of cases and we'll try to make these interactive. We will, to the extent possible, welcome questions from the audience and from the folks at the table to try and really have a rich discussion. And we know too that folks are online. We're grateful for the folks online that have joined in. There is an opportunity to type in questions and we'll try and get to those as time permits.

So let me give you a few themes to think about and keep in mind as we go through the workshop. You know, I'll run through a couple of these and then also just give you my impression. So the first theme is just what we know about the clinical developments of the Phase III trials for small molecule antibacterial development drugs apply here or can it help us. And so I'll just pause a minute and think about that. If you think about what we're trying to do, we're really trying to impact, you know, the patient and the patients' disease process. So I would

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argue that a lot of what we know from the small molecule antibacterial drugs and clinical trials to show an effective a therapeutic is applicable, you know, almost regardless of the mechanism of the product. So we'll try and keep that in mind as something to learn from.

Obviously, there can be different considerations depending upon the molecule, how it acts. But there's a lot to be learned from what we've done already. And then next sort of provocative question. If the mechanism of action is known, should we focus on mechanistic studies in patients or should we be trying to show clinical benefit?

So I think mechanism when understood can be a very important tool and help us to understand what the therapy can do, which particular types of infections it may be able to treat or prevent. But as we think about development and you move from the early stages to the later stages, you obviously want to take an advantage of your knowledge of mechanism as much as possible. But ultimately what you want to do is, get to the point of being able to show clinical benefit

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for the patient. So there is this, I believe this is progression over time from mechanism to clinical benefit as you think about the development program.

And really the question is here I think "Can you demonstrate that the patient overall is better off when the patient receives the therapy?" This seems like really simple questions, but I think one of the challenges we face here is that we're dealing with a couple of different complex biologies. We're dealing with the complex biology of the human then add in disease, which leads to physiologic derangement, in addition you've also got the bacteria present. And if we think about bacteria even though they're single cell organisms, they're almost like the Swiss Army Knife in a single cell. Because if you think about it, they have to do everything to survive and to be able to do what they do just with a single cell. So this really does I think underscore the importance of looking at the clinical benefit of a product, you know, in the patient because, you know, the complexities here oftentimes will teach us new lessons that we didn't anticipate and we've seen this over and

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over with clinical trials. Things that we didn't expect pop up. Sometimes we can explain them and sometimes we're still left scratching our head.

So now moving from the philosophical mode of the logistical somewhat of a transition but for lunch in the back you'll see and it's all the way, so this is the C and the B conference rooms, and A is a different meeting beyond. But if you go beyond that and over to your right, there's a window there and you can check off on a paper if you'd like to get lunch served from the group there can sometimes help a little bit with regards to how quickly you can get lunch. They ask that you get that in, if you can by the break at 11:00, if you happen to be wandering out there, feel free to also grab the paper and submit that. The bathrooms are also just beyond and to the right. Online folks I've mentioned that you can type in questions and we will try and get to them as time permits.

The meeting is being recorded. So there will be a web recording available online, slides will be online, and also there will be a transcript for the

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meeting. We try to include in your packets in the very back you'll see disclosures, so folks have provided their work areas that may impact upon the work that we're discussing today. And this is a workshop and I think it's important just to remind folks of that. So this is really just for the purposes of discussion so that we can all learn from each other and it really is not about generating consensus.

So with that I want to thank you all for joining. There've been a number of folks that have worked very hard in putting this meeting together. I'm very grateful for all the work that folks have done. And the workshop and its value really comes from everyone who is here and from all their contribution, so for that I and we all are very grateful.

I'm looking forward to the day's discussions and look forward to learning from everybody. And with that I'll turn the podium over to John Rex and Kevin Outterson, who are going to start out with an overview of non-traditional therapies. Kevin?

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MR. OUTTERSON: Yeah. Thank you, Ed. If you notice, it's a lawyer and a doctor opening the session. It almost sounds -- we should have a bad joke about this job. A lawyer and a doctor walk into the FDA and what do we get. John and I have been in serious conversation about many of these issues for the better part of a decade. And so we are structuring this as a continuation of that discussion hopefully something that's fruitful.

We've had some challenging conversations over the years and we know that it'll continue to be that way today with this group. But our perspective, despite our academic backgrounds for both of us, is to be practical. You know, we're very interested in the science, we're also very interested in a practical answer that helps the industry move forward. We can't just wish this away.

We also don't think this is an FDA problem. You know, it's not that they're being intransigent or something. We need to pragmatically look and to find a way to move forward in this space. Particularly with all of the types of products, the non-traditional

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products that are coming to the market for the first time moving towards clinical trials for the first time, many of which are in the CARB-X portfolio.

So agenda for today; John and I, are going to split this up and I'm going to do a little at the beginning, John is going to do a lot in the middle, and then you'll see me again near the end. So the core problem is that in order to get, you know, approval from the FDA and then also later get paid by somebody who actually wants to use your drug, you have to show value, you have to show distinctive value. And we put it in red that this, we don't think this is a regulatory issue per se. You know, this is something we need to ask for any sort of product. And it's just uniquely difficult sometimes, you know, to show that with antibacterial products. And we're having a problem in the past few years in this way.

For antibiotics, it's been difficult to usually come up with a superiority sort of design. The sort of design that you would see routinely in many other drug classes. Last time the GAO looked at non-inferiority designs, a lot of them were in the

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anti-infective antibiotic space. And the reasons for that are relatively straightforward and we'll talk about that a little bit in the next slide. But the key is that FDA could accept a non-inferiority study. But what about the pairs, you know, what about the hospital formulary committees, what about the, you know, the folks who are making the decision on whether or not, when there is a choice between an antibiotic that's been generic for decades that has a cost per course of treatment of $120 versus an antibiotic which is new and has a cost of 10,000 to 12,000 per course of treatment. And the newer antibiotic only has a non-inferiority study; how do you make that case to a peer, how do you make that case to the formulary committee at your hospital, Helen?

And so you'd expect for the bad news quote here is that, you know, we need to be very clear that the FDA is not the finish line. Here the finish line is selling enough product so that the companies are incentivized to continue to doing research and development. And instead what we've seen recently is companies get FDA approval and then having to let go

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their early development folks in order to conserve cash to commercialize because they're not able to sell very much. And this is not just a regulatory problem is part of what we're saying.

So for antibiotics you know the paradox, we do want them, we need these drugs, we need new drugs for bad bugs and it's easy to show that in a lab because in a lab you can fill a Petri dish with, you know, resistant microbes and then try things to kill them. Finding those patients is the more difficult thing. And it's easier if you have a condition like cancer where you have days or you can refer to a referral center, or if it's a genetic condition that you can test and know exactly what you're dealing with and have some time versus a patient who is feeble and to delay an hour is malpractice you know. And you're going to have all sorts of other treatment.

And so the example we give here of limb-threatening infection due to MRSA, you know, we can't randomize, you know, methicillin versus the new. We have to do something like vanco instead. And vanco works most of the time. And so that's going to make

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the trial more difficult, right. And as soon as you know that vanco doesn't work, if you had a great diagnostic to show to this patient that vanco wouldn't work with what they have, you have to try something else. It becomes unethical to continue. And so this is why these trials it's difficult. I'm not saying impossible. Some people have tried. And occasionally, you know, there are superiority sort of results that they can generate as well. But it's just much more difficult than it is in many other drug categories.

And when you think about just how you know simple it is in other fields, I'll talk about this a little bit. You know why we have so many therapies on cancer in oncology, immuno-oncology and the ability there for them to be the 3rd or 4th or, you know, rescue treatment because they're able to identify the patients and they have a little bit of time to do that. And the fact that we're -- the victims, the whole sector is victims of its own success and the fact that most of the time the antibiotics we have including the older generic ones actually work, they

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cure the patient. And when you're doing the -- when the Standard of Care arm cures it's hard to improve up on that, right.

The core here is that we're not really measuring what we need in this area. The social value of antibiotics is not just today's patients, although Dr. Boucher will talk about today's patients. It's also about, you know, tomorrow's patients and having drugs available now or in the pipeline now to deal with whatever comes down the pike in 5 or 10 years. And it's very difficult to study the patients that might emerge in 5 or 10 years today. John is cackling. I think he thinks I understated that. All right, I'll turn it over to John for a bit.

MR. REX: I was actually smiling because you don't know how many hours of debate it took to learning to say those words in that way about why and what the problem is of why you are expected to solve it anyway.

So I'm John Rex from F2G and Wellcome Trust. Let me now talk a little bit about the question of what are we, you know, talking about today. And the

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question of what is a non-traditional has made our collective heads hurt. It's been around with us for a long time. I'm going to propose here an approach that's perhaps a little different than has been used in the past and that's to cook it down to 2 ideas. It's either a non-traditional structure or it's a non-traditional goal. And I like Ed's comment at the beginning about "non-traditional is kind of it's really what you are used to." It's a good way to say that. If you look at traditional versus non-traditional structures written down here, traditional is a typical small molecule, you know sort of, molecular weight 500 maybe up to 1,500, but it's a thing you can draw a stick figure of versus a non-traditional structure phage, lysins, monoclonals and charcoal. But if you look in that, you know, the monoclonals to antibodies, we've been using those for centuries. So what's non-traditional about that? Absolutely nothing whatsoever. It's a very traditional product if you will. But in the current context, it's a kind of a structure that we don't typically think about.

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And then there is another direction to think about here, as opposed to what does it look like; it's what is it you want it to do. And here the traditional end is treatment or prevention of a standard infection. No matter what's inside the box if what it's doing is killing some bacteria in a way that in theory should treat your pneumonia then that's kind of on the more traditional end, even though maybe the shape of it is unusual.

Something that we're -- I hope we are going to spend some time on today is the idea of non-traditional goals and what if your goal is to do something that is more at a community benefit at a level. So Kevin just talked about the patients of tomorrow, which is all of us, you know, one day we all of us are going to be -- will be pleased to not be carrying some highly resistant bacteria. So what if you were working on something that prevented the acquisition or the development of a resistant strain, or maybe there's something with your microbiome that had that consequence. And I thought it was interesting the way Ed asked the question here "would

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you look mechanistically or do you look in terms of a clinical benefit" and that's what this slide is about.

So when you're thinking about structure, the development fundamentals for many of things that are basically are in antimicrobials is pretty well known. You know, if it does something in a way that we're used to seeing a standard antimicrobial do, we have pathways for that. That's the good news. Pretty well developed. Now there are challenges that may come from the math of small numbers. What if you want to study one particular bacterium in the sea of possible causes of that syndrome? That gets harder. What if you want a particular just it's flat-out rare Acinetobacter but you want it to be rare. Then the hunt for that pathogen is hard. And ditto for rare events. When you get down into small numbers, you've got the problem of small numbers and I'll -- we'll loop back around in a minute to diagnostics as a possible aid here, but not the one you might wish for.

The idea of a non-traditional goal I think is under explored territory. So I've already mentioned the idea to consider a product or a method of use of a

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combination or anything else you want imagine that prevents resistant or prevents resist acquisition of resistance. Such an end point may lack immediate clinical correlate for me if I'm the one taking. Let me emphasis here what I'm talking about, not talking about TB where you know preventing resistance developing in the course of a 6 months course of therapy matters to me as an individual because if resistance develops, I will fail, my therapy.

What about something where it's over and done within a flash. With pneumonias reasonable use of short-term endpoints that's because most of it is over within a few days with skin infections. So it may be that my infection gets treated effectively. But what if I'm left, colonized with resistant strain, maybe in the future I get another infection or maybe in the future I hand it off to somebody else. How do I show the value of that to society? Is it adequate to show impact just by surveillance or do we need to prove fewer resistant infections?

A couple of bits of language that you need to be careful with today. Alternatives to antibiotics is

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a bit of language that I try not to use very much because it's such a broad term sometimes taken to be the same as non-traditional, sometimes taken as a superset of interesting physical devices like a super smooth catheter that nothing can stick to. I mostly just treat this idea as being non-traditional.

The phrase potentiator or enhancer is harder to get away from. But the difficulty with these is that -- these two words is that they tend to be applied to a variety of disparate situations and I generally find them too ambiguous. But if you have to use them because I'll find -- I'm going to use them in just a second on the slide -- you just have to carefully define what it is that you're talking about, just be careful that this word doesn't always mean to somebody else what you think it so obviously means in your head, just be careful with it.

There are some other potential benefits that get brought up for non-traditional products that I don't want to recognize now. They often have a very attractive intuitive feel to them. It's narrow, which is nice, less pressure on other bacteria. Its narrow

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can also be a problem for development. It works via the host and hence resistance can arise. It will have fewer side effects. All those things might be true, but you're still -- you got to prove those things and through that actually just show the core value that somebody should pay for. That is, it still needs to do something useful and we need to be able to say "who would get that benefit" and we need to be able to measure that benefit.

So potentiators and enhancers, two words I said I didn't want to talk about, but there you go, I have to talk about them and that shows how hard it is to get rid of these words. And a little bit about diagnostics. There are a lot of products that are functionally add-ons and I realized in working through the slide last night that I really should've labeled this about the add-ons. Where you take a base product of some sort and you add something to it, and I've labeled it here P for Potentiator, but E for Enhancer, and A for add-on. And that add-on thing improves the base product. And I think there are three useful subdivisions of this strategy to recognize. First is

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the one which you are going to restore the base product. The base product used to work some mechanism of resistance has risen and the add-on somehow undoes that, undoes that I'm sorry. So the classic here would be a beta-lactamase inhibitor and a beta-lactam. You're restoring a previously functioning drug to functionality by protecting it from beta-lactamase.

Category two is that of transforming. The add-on enables the base to do something really new. We have a lot of drugs for gram-positives where we know the target is present inside gram-negatives, but the drug just doesn't get there -- so if you somehow -- - or gets flexed out. So if you somehow cause the drug to either get in or stay in, you might transform a gram-negative drug with a -- sorry, gram-positive drug with a gram-positive mechanism into a gram-negative drug. So that would be an idea of transforming an existing tool.

The third category is the one that scientifically is the most intriguing. The first two you know they're mechanistically pretty straightforward and you know we have people -- we've

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either used those in the case of restore or in the case of transform they're being actively pursued. But the third category is one where I've not seen as much successful work. And that's the idea of an effect via the host where maybe it activates the immune system or it inhibits a varicose mechanism. Scientifically, I've always been intrigued by this and wish to see them work. They run into a problem however.

And these are the problems that occur when you get into these categories. For many of the products in this space standard tools generally seem to work like BL, BLIs, we've now got several of those studied and approved. But there are three specific recurring issues when you're looking at the add-on thing. The first is that of MIC. If the add-on doesn't create a measurable MIC, you have to come up with some other way to think about dose selection. And I've labeled it is a problem in this, but I think it's one that is more often solvable. I know Paul Ambrose has had some good thoughts on this. And you can probably solve it, but you still have to solve it for your product in some fashion.

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The second one is that of the rare pathogen and this is a hard numbers game and diagnostics will not entirely fix this. And I will devolve to a full slide of that in a moment. And the other thing that happens with rare pathogens is that the need for adequate empiric therapy may complicate the challenges showing the effect of the new product. Here what you're often looking for is the ability to provide some empiric coverage for other things, while look -- while your product is the only thing that treats the target pathogen.

So imagine a novel antipseudomonal compound. The only thing it does is to treat pseudomonas, which you need to wrap around it an empirical therapy that has a pseudomonad sized hole in it, just have a gap, just right for your product. So your product can fill in that one gap and all the other things that might occur in a patient can be covered by something else, but here the pseudomonas is left for you and you can do that for pseudomonas, you can do that for Acinetobacter. It's harder to do that for E. coli or Klebsiella. It's harder to do that for Staph aureus.

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It's tricky to find things that have exactly the right gap that they'll fit what you're doing so that you can provide empirical therapy for the first few days. An empirical therapy is just so often needed in this space.

And then finally the Augment category you're going to need to show an improvement on properly dosed base therapy and this can be hard to achieve. Let me emphasis that. If you look at the Augment category, the idea is the base product plus the new thing has to improve on the base and you're going to dose the base correctly. It has to be -- there is no cheating allowed here because nobody wants to be in an inadequate therapy arm if at all possible. You actually have to give a correct dose at a correct dose and then you have to improve on that. And if you imagine for a moment something that has a mortality outcome, you know, nosocomial pneumonia or maybe you've got a 15 percent rate of mortality in the clinical trial that you can do. So -- and that's with the correctly dosed therapy, the 15 percent mortality so further rise and 85 percent success rate.

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So in that 15 percent, if you're going to add something on to make the standard therapy better, it's got to take your mortality down from 15 percent to 10 percent or 5 percent. You've got a -- you've only got a small zone in which to work. And unfortunately, of those 15 percent who are going to die are in the standard trial setting and some of them are going to die anyway. They have nosocomial pneumonia for a reason. It's their underlying disease. So you may only have a few percent in which you can actually affect an improvement and that leaves you with a hard problem. I may believe you that it makes it better. It's just hard to measure it because you've got so little room left in the -- so little clear blue water left in the clinical trial.

Pathogens and Diagnostics. Unfortunately, diagnostics do not have the speed and efficacy of the Star Trek tricorder. I truly wish for one of those, but we're not there. And it leaves you with two issues. The issue number one is that diagnostics do not create cases. If the bacterium is rare, it is rare. So if its only present in 1 of a 100, you still

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have to screen 100 to define that 1 and it is just you know straightforward. It took me a long time to understand that idea, diagnostics don't create anything, you still have to pay to look through all those cases.

And issue number two, Kevin alluded to this, is that time is ticking and referral is really not a path. In cancer and rare diseases, we don't dawdle, but there is time to make a diagnosis and refer as needed. You've got days or weeks to get that sorted out and get somebody to the right place.

With trials of anti infectives, the acute illnesses so not hepatis C, not TB, you've got to treat -- you've got to enroll people at that study site and put them on therapy right now. And you can't really drive them -- maybe you drive them across town. That's about as far as you could go in general. So they have to actually present at the site that's got study going on. And that just magnifies the problem of finding those rare cases. And it leads you into what I call the multidrug-resistant center of excellence problem, which is that hospitals work hard

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to not be the hospital that has the billboard on front it says "We have the worlds most resistant bacteria but don't worry, right on in and get your heart transplant because we have a great trial." Now, nobody wants that sign out in front of the building and I used to be the hospital epidemiologist facility where I worked really hard to eliminate resistant bacteria and yes, we might have one or two cases. And then a couple of weeks later we would have none because I would have been all over whatever the infection control problem was that had to led to those cases. So we used to have them, but I don't have them anymore. So we're trying to enroll these cases a little bit like chasing the phantom menace and it just we want to make them go away.

So non-traditional goals. Pretty much everything I've been saying has been presuming a standard goal of treating or preventing a standard infection. And most of the examples to be discussed during the workshop seem to fit here with a few twists and turns. And Ed posed the thematic question of, do the ideas that apply for standard development, you

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know, of pneumonias, are they correct? Do they apply here or is there some variation that's required? I think we should listen for that theme.

But what if the goal is really different? What if the goal is benefit not just to the patient or maybe even almost no benefit to that human being, but rather a benefit to the community as a whole by preventing the selection for resistance or the spread of resistance.

And you could easily imagine this on the basis of a combination therapy designed right now to prevent the selection of resistance. We know that if I treat your nosocomial pneumonia, gram-negative pneumonia, there is a small but measurable rate of at the end of the treatment, the end of the successful treatment of your nosocomial pneumonia. Your E. coli is gone, you feel better, but you actually now have a resist -- strain that is resistant to what I treated you with. So you are better, the war is over, but you're now carrying something that the next time would be harder to treat. What's the value in that and how do you measure it? And actually one, and actually

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couple of cases we're going to explore this thing. And I think with that it's back to Kevin.

MR. OUTTERSON: So as a lawyer sometimes your -- your goal is to tell clients hard news, right. And not that they can't do something, but they have to do it maybe a different way or that things aren't the way that they're hoping. And so for CARB-X, you know, we have a lot of things going and we ask, well, why are we involved in this? And actually the first person that I called when we thought about creating CARB-X on the outside of the government was, John. And John and I put together the original proposal to BARDA. And this is what we're doing now. You know we've, I guess, it's $504 million now over 5 years, we're focused on supporting preclinical work all the way up to and including the SAD/MAD studies in Phase I for the priority drug resistant bacteria.

We're doing that through grants, non-dilutive awards to companies all around the world. We've 34 companies under contract as of today, dozens more in process. We had over 400 applications in 2018 that we're still processing at this moment.

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And in that pile includes both traditional and non-traditional. We have -- probably by the end of this year we'll have certainly more than a dozen non-traditional products in our portfolio. Most of those are non-traditional products, non-traditional goals, but some have that as well.

And so for CARB-X the thought is that we're investing in things for which the regulatory path is not entirely clear. If I was a venture capitalist maybe I'd be more worried about that, from a CARB-X perspective we thought it would be useful to prepare the ground for all the companies and for whichever ones make it, you know, to FDA approval. And to begin to have this conversation, not for the benefit of any one company, but for the benefit of the sector. So that's our interest. CARB-X is nonprofit. You know, it's non-dilutive, but our goal is to try to support what's happening across all of the research that's happening.

And so this is, you know, a complex chart of -- each of these dots represents a CARB-X company that has been funded. And on this chart wouldn't be

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anything that we received for an application for 2018. Like I said over 400 applications we'll be announcing those awards beginning later in this year. But you get a sense of, you know, we have some products that are a known class and a known mechanism and we rate those as lower risk, but not as innovative. Some of the known mechanism, but there's a new class, right, so there is additional risk, because it will be the first time that that class made it through. Some are both a new mechanism and a new class, right. And some are completely non-traditional there's never been that particular type of thing approved by the FDA.

And the sense of this slide that you should take away is that CARB-X wants to invest in things across all of these ranges, you know, lower risk and higher risk and that we have an interest in, in supporting all of these. People ask all the time, which is your favorite CARB-X company and I have four daughters it's like asking me which one is my favorite daughter, right. You know, we love all of our companies and we want this sector to succeed.

So we're helping the ecosystem. We've had

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these discussions many times with the folks at the FDA and one thing that we hear back from folks at FDA is, "Don't give us hypotheticals. Let's talk about actual companies and actual products." But we don't want to wait until the company has already designed their Phase II trial or is having trouble raising money for the Phase II trial, because of the lack of regulatory clarity. So we're trying to help that with some real-life examples today and tomorrow. And to give the FDA, you know, the information it needs in order to write draft guidance, but also the companies to begin helping them think through it. Many of the companies that we deal with at CARB-X don't have a Regulatory Affairs Department. They're still just serious science teams, you know they're all about, you know, moving the science forward. They don't want necessarily to be thinking about these issues. We're trying to do some of that work, you know, for this sector ahead of the time.

And some of these thinking to explore and, John has alluded to some of this population level benefits, you know, what can sort of clinical benefit.

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So one of the examples John used is maybe your nosocomial pneumonia was cured in you, but now you carry a resistant bacteria. But move that even more to a population level what if the only value for this additional product or the primary value was that it reduced, it bent the curve of resistance in the population at large. Is that a viable product? How do we measure that value? How do we, you know, put that into a study that the FDA recognizes as good science, right?

And we see some of this with the HPV, you know, it's impossible or difficult to run a clinical trial that would run 20 or 30 years to see really the HPV developing all the way into full blown cervical cancer and it wouldn't be ethical to allow that to go on. And so there's intervening markers and we're also able to trace now the population level impact of things like the pneumococcal vaccine and the HPV vaccine, you know, outside of the patients themselves population level benefit.

And so could these be benefits value that we attribute to some of these products and that gets

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worked in.

And this is the bad new slide. You know that FDA approval is no longer the finish line. It's not for this sector might be for others, because it does not result in sales. The adoption curves have been very flat and very challenging for the developers. And this is the reason why some of the developers upon approval of their drug have to conserve every ounce of cash, because they know that they're not going to be making much cash on sales, at least in the first couple of years. And so if we had a way to do what's in red here to have data that was compelling, not just to the FDA, but to payers so that the companies could be reimbursed, you know, adequately for this innovative therapy then that's going to be very useful.

Of course, we're in the context of good stewardship, which is another way of saying we're -- we're not going to over market, we're not going to inappropriately sell, but from a company perspective this is the CDC and CMS and physicians and the entire subspecialty infectious disease docs trying

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desperately not to use your product right. It doesn't happen that way in other drug categories.

And so many of us in the room, you know, work extensively on trying to get other incentives, pull incentives, market entry words for things like them in order to solve for some of these problems outside of the scope of today, but this is the sort of thing that's required. A couple slides to kind of drive this point home.

This is from Alan Carr, Needham and this shows all of the FDA approvals for antibiotics since 2009. And the most successful of these would be considered a very lackluster immune-oncology drug. And if you drew a line across, and this is all of the drugs, this isn't a cherry-picked sample, this is all of them. If you drew a line across at about the $4 million sales per month, you know, and drew that across, I think that, you know, I don't have any data from these particular companies, but it would be hard to have a, you know, a sales force -- I'm looking at, John and a plant that was producing the drug and doing better than breaking even at $4 million, you know, in

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monthly sales. And so it's another way of saying that only two or three drugs approved since 2009 are breaking even, okay. That's a crisis, right, because we're not able to demonstrate value to the people who buy the drugs in order to drive the sales, dollar volume not unit volume, that we need to keep this sector afloat.

And so thinking about, you know, two compounds and maybe this is an unfair comparison, but they're, you know, it's similar in terms of their timing. And, you know, they both had kind of markers of FDA attention, right fast track, priority breakthrough and on Plazomicin, QIDP and LPAD. They both go after serious things, important things. These aren't trivial drugs. The number of patients randomized actually Achaogen had a larger trial. They were able to do a superiority to the standard of care versus for Plazomicin was noninferior to Meropenem. It did have a superiority result against Colistin. Plazomicin is life saving, not to diminish the life enhancing, right, but it's lifesaving. You see the other results here the number of patients, you know,

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the kind of in the same range of category, one is chronic, one is acute and then you see that the payments at the bottom that are put in the red box. So, you know, just a dramatic difference in how much is being paid and dramatic difference in the market capitalization. I think this is a partially -- our inability collectively to articulate the value of these drugs to the people who buy them. And some of that is the topic of today, but like, John and I've said in many sectors this is not per se a regulatory problem, this is a designing a trial to demonstrate value to the people that need to understand the value; the FDA as well as the payers. Back to, John.

MR. REX: So this is the last slide. And we didn't get up here to say all these difficult hard things just to be obnoxious difficult curmudgeons, all right. That, you know, I am as a clinician these some of these tools are just a -- they feel like they ought to be really helpful. You know, it feels like it's a good thing to do. I want them to work. But come back to Ms. Swanson the CEO of Raytheon who said, you know, beg for the bad news. You really need to know what's

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going on and plan for it so that, you know, tears today versus tears tomorrow it's another to say it. So we really have to be clear on the non-traditional nature of the product and whether that's even relevant; the fact that it's monoclonal is that even at all relevant to your development pathway.

And I think that more often than when it's -- if the NT (ph) component is the structure, I think that more often you can use traditional tools. And we're going to talk about that and see to extent to which that's correct and whether there are places where we need to broaden our view on that.

The idea of a non-traditional community-oriented goal, I think is something that we're only now beginning to know how to talk about. And we are going to have some discussion of that. And exploring and refuting and expanding these ideas is a value to the whole community. And, you know, we -- you know, Kevin I have both worked long and hard to make it possible for companies to find money to bring products forward and we are desperate just to figure out ways for them to show their value in the marketplace long

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term, because, you know, deep down, you know my, the reason I stand here is that I'm an ID doc who got frustrated with infections I couldn't treat and so I moved into industry to see if I could do something about it. Ditto Kevin's story is that he got fascinated by the prom resistance many years ago and patent law and those things are actually quite interwoven, ask him that story if you can at the break, it's a -- yes, we're both here for the same reason. We see the problem of developing these products and we want to solve those problems.

And so let's turn this over to the next speaker, but that's actually the setup for today is to think about how to actually make things work in a pragmatic way. And I believe next up is the world famous, the internationally renowned, Dr. Boucher.

MS. BOUCHER: Thank you very much. Let me see. Thanks so much and good morning everybody. I am delighted to be here and thank you so much for the invitation. My disclosures are shown here, I'm really non-relevant to today's discussion. I'm going try to pick up on what John and Kevin talked about and

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provide a little bit of clinical insight and really a number of questions, because I certainly don't propose to have the answers.

I think as we heard we heard some sort of general kind of requirements for these non-traditional therapies and I just thought as a clinician, well what would we need? We need these medicines to work. So they need to be effective and they need to be acceptably safe. Do they need to be better than traditional antibiotics? Do they need to be additive to traditional antibiotics? I don't know and we'll talk about some examples.

There needs to be a feasible path to both double study and use these things. And I think it's really important to think about how we would use the stuff that we're talking about in the real world in the clinic. Because changing behavior is really hard thing we've learned a lot about that in stewardship, but I think, you know, docs do things the way we do them and so when we're thinking about a new therapy it's important to think about; well, what would be, what we have to do to use it? And then there needs to

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be some kind of reasonable reimbursement in order for my hospital to take it on board and use it.

So I may start with an example. I have two sort of potential exemplars to present for non-traditional therapies and one is for external wound infections. These are really common infections that happen after surgery and have risk factors that we know and are very well established. So being a woman, being obese, diabetic, a smoker and having a complicated surgery are all known risk factors for these infections.

So the lady I'm going to tell you about is lady I took care of several years ago, 50-year-old lady who was obese, a smoker with poorly controlled diabetes who had about a coronary bypass. And she comes back 2 weeks later is in a pretty classic way with high fevers and puss from her sternum, kind of the worst of the worst, she has MRSA. She has the usual therapy, which is an attempt to debride it with antibiotics and then she goes back to the operating room and has to have titanium plates placed, because there was not enough substance to close up.

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Unfortunately that didn't work, the wound broke down again, back to the operating room for more surgery. Now we're, you know, month and half into this she is on appropriate antibiotics with Vancomycin, still doesn't work. She still draining and still has MRSA. They have to go in and take out the plates and close her up again, another long course of therapy that goes till August. So 8 months of therapy here. And guess what? That doesn't work still, she comes back in again with chest pain. She has more osteomyelitis and now there is bacteria in her blood. So there's no doubt that we've got a failure and indeed she has endocarditis. So she gets an IV and more long-term IV antibiotics. Twelve more weeks of therapy we finally calm her down. There is no more surgery to be done, because she's had so much surgery now and the plan is lifelong antibiotics. So this lady who presented in 2007 end up living until 2018, 11 years after surgery and she actually lived reasonably well. I wish I could tell you that she changed her lifestyle, she did not. She smoked until her death and ended up dying really of lung disease. But she lived another 11

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years after this horrible thing.

So what if we had something to impact on this kind of an infection. These are, as I pointed out, they're common, they're very morbid. This lady was at the -- at the extent of morbidity I would say and some are fatal. So the question is how much is it worth to prevent one of these? Certainly to this lady it would have been worth a lot. To my hospital it would have been a lot. This lady was a big user of our ICU and operating room for a year and then to society. I think those are all questions that we're grappling with.

So I'm going review briefly a study that we did not many years ago that was actually a failed study that I think may be instructive. So the idea was that maybe we could vaccinate these high-risk people before cardiac surgery to prevent these infections. So Merck did a study of vaccine against Staph aureus and it was a big undertaking, a yearlong study where people were vaccinated 2 weeks before surgery. We see those patients at that time so we can vaccinate them. And then they were followed for a

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year. And the idea was to see who -- who got an infection treated with vaccine versus placebo. We enrolled 8,000 patients in the study and found out that there was no difference in the infection. So the same number of patients who got the vaccine got placebo got infection. So that was disappointing, but what we didn't expect, to allude back to, Dr. Rex's and, Kevin's comments about we find things that we expect and things we don't expect. We found that the people who were vaccinated were actually more likely to die from their Staph aureus infection have multiorgan failures so that was completely unexpected. So maybe something was negative about the vaccine. So the conclusion was that the vaccine didn't work even though there was a robust antibody response I'm not showing you all those data and that we had this increased mortality among vaccinated individuals.

So the reason I'm presenting all this to you is that this was a study that was extremely well done in a reasonable amount of time, in a population that would benefit. So it can be done and this publication was back in 2013. So we do have exam, I'm presenting

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this is an example of a study that could be done in a very high-quality way in infection where a therapy like this could make a big difference.

So let's look at something else. Now let's change gears and look at C-diff, C. Difficile. So this is an infection, it has a huge burden in the United States; 500,000 infections per year. There is lots of national efforts going on to prevent and control C-diff. We have public reporting. We have pay for performance. We know that there's a high risk of recurrence up to 25 percent and we again have well described risk factors being older, comorbid illnesses, the need to continue antibiotics are all associated with recurrence.

So now I'll tell you about another lady patient of mine. This is -- now 58 is a bad age by the way. These lady is about 58-year-old lady with giant cell myocarditis who had a heart transplant back in 2013 and she showed up 2 years later with refractory clustering difficile colitis in CMV. Her heart was working fine and she had had no recent rejection. So she had had a complicated course 2

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years ago when she presented, giant cell is a very bad disease. She was in shock. She had external wound infection with her first surgery. Her transplant itself was somewhat complicated. She had pneumonia. She had kidney failure. She had a lung rehabilitation course and some early rejection, but then she got better. And so she shows up to us back in 2013 with sort of watery diarrhea and has a diagnosis of Clostridium difficile made and this goes on and on and on. So she is in November of '13 she comes back in April of 2014 with diarrhea again. This time she has two problems Clostridium difficile as well as cytomegalovirus. We see this co-infection not infrequently in heart transplant. She had no rejection and she makes her way all the way to the summer with recurrent diarrhea. She had total of five different episodes of Clostridium difficile. And we have been talking about what to do for her. We tried Fidaxomicin, which was then a new antibiotic that she would get a little better then she'd get worse. And we started to talk about doing fecal transplant, but at that time, as it still isn't, you know, approved by

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the FDA there was a lot of concern about doing non-FDA approved treatment. And then there was a concern in a transplant patient about making her back to remik (ph), because that's been seen in immuno compromised people. So we hesitated to do it, but finally in January of the following year we finally did it and it was successful and she's been well today. So again a huge amount of morbidity, but this therapy was effective in this lady.

So I think both of these cases teach us that, you know, as we already know infections caused by resistant pathogen is really bad it can happen to any of us. And the traditional antibiotics, even if we had all the antibiotics, we wanted it wouldn't be always successful. That having these non-traditional therapies is useful to our patients and to us. That it's possible to study them. I think the study I showed you is a study that could be done. And that preventing infections is important. I think in either of these cases anybody would agree if you were the family member or these patients you would be happy if we could have prevented that. Certainly I would be

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happy if we could prevent it.

Again preventing, I don't get paid necessarily to prevent infections, to use expensive therapies, to prevent infections in individual patients, but if we could fix that I think that would be very useful.

So doing these trials is hard as Dr. Rex and Outterson pointed out, and I think we have -- we don't have a lot of templates to use certainly preventing pneumonia is an area that's been studied and FMT is now been studied a little bit for Clostridium difficile, but we need a path and that's why we're all here as, Kevin and, John pointed out.

Coming back to the sort of requirements I put up in quotes to begin with. The feasible path to study uses is important and I think stewardship here can be very helpful. Now that we have stewardship programs in all U.S. hospitals, we have a mechanism by which we could use these therapies in a safe and ideally hopefully most effective way in hospitals. And hopefully in long-term care facilities and in the outpatient as well. And I'm just pointing out here we

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certainly hope to see the CMS condition come through, its still sort of pending, but the joint commission has made stewardship mandatory in hospitals and long-term care facilities, which is a great step forward.

We also have a lot of data that stewardship works, this is just one study showing the affect on antibiotic resistance of having stewardship in place. And then finally the reimbursement just one -- one comment on that because we at IDSA have been so active in this area. In principle, we hope that incentives are robust, understandable and predictable to motivate industry and private investors. We hope, as was pointed out earlier that they target the greatest areas of unmet need and that they're aligned with stewardship as well as maintaining access so that all of our patients could take advantage.

We are grateful for all the push incentives including CARB-X that we saw earlier. And then in terms of pull the biggest need is in pull and things like market entry rewards, per day review, tax credits and others, the licensing model presented by Dr. Gottlieb recently between CMS and FDA is very

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interesting and we hope to learn more about that shortly.

So in closing, you know, in 2018 as I showed in these cases, we clinicians are forced to use drugs and non-traditional therapies with extremely limited and often negative data. We have case reports for Phage, which I'm sure we'll hear more about it and we have small series for things like FMT and some monoclonal antibody therapies, but we need more.

The development is not going to be straightforward as we heard the difficulty with non-inferiority and superiority trials. And I think it's likely that small clinical studies are going to be needed and the best we can do and so the quality of that data is very important. Clinical trial networks I think are a way we could advance this ball. And then maybe thinking about feasible studies focused on more pragmatic endpoints things like the desirability of outcome ranking or DOOR that's being developed and has had some success already.

And then I just wanted to say my personal pitch for always thinking about looking at multiple

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body sites and infection sites and the utility of that to us as clinicians as we think through this complicated problem. And with that I'll just remind everybody why we're all here. It's for our patients and say thanks again for the invitation.

MR. COX: Thank you, Helen. And thank you, John and Kevin too also for the talks. I think that it really has helped to set the stage for the discussions today. And while Owen is making his way up to the podium let us go around the table too and start with introductions. And if we could we'll start with Ed Weinstein on my right-hand side. Ed?

MR. WEINSTEIN: Sure. Ed Weinstein, Clinical Reviewer in the division of anti-infective products.

MR. POTGIETER: Peter Potgieter, President of Clinical Development and Medical Affairs at Locus Biosciences.

MR. DANKNER: Wayne Dankner, Chief Medical Officer, Atox Bio.

MR. BURD: Edward Burd, Head of Regulatory Affairs, Rebiotix.

MR. PEREZ: Toni Perez, Chief Medical Officer

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at Combioxin.

MS. SUVARNA: Kalavarti Suvarna, Clinical Microbiology Reviewer in the division of anti-infective products CDER, FDA.

MR. EVANS: Scott Evans, Professor of Epidemiology and Biostatistics at George Washington University.

MS. EAKIN: Ann Eakin, Senior Scientific Officer at NIAID.

MS. GHOSH: Mayurika Ghosh, Medical Officer FDA.

MS. DORR: Mary Beth Dorr, Merck, Product Development Team Leader for bezlotoxumab, ZINPLAVA and Clinical Director.

MR. BLACK: Todd Black, Executive Director of Antimicrobial Discovery Research at Merck.

MR. REX: John Rex, Chief Medical Officer, at F2G Ltd. and Expert-in-Residence, Wellcome Trust.

MR. COX: Ed Cox, Director of the Office of Antimicrobial Products, CDER, FDA.

MS. NAMBIAR: Sumati Nambiar, Director of the Division of Anti-Infective Products, CDER, FDA.

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MR. OUTTERSON: Kevin Outterson, Boston University and Executive Director of CARB-X.

MR. IARIKOV: Dmitri Iarikov, Deputy Director, Division of Anti-Infective Products, FDA.

MR. DUBOVSKY: Filip Dubovsky, Head of Clinical Development for Infectious Disease and Vaccines at MedImmune/AstraZeneca.

MR. RUBIN: Dan Rubin, Office of Biostatistics CDER, FDA.

MR. HOPE: I'm William Hope from the University of Liverpool.

MS. DAS: Shampa Das from the University of Liverpool.

MS. WEI: Tracy Wei, Clinical Pharmacology Reviewer, CDER, FDA.

MR. AMBROSE: Paul Ambrose, Institute for Clinical Pharmacodynamics.

MS. BOUCHER: Helen Boucher, Tufts.

MS. GOPINATH: Ramya Gopinath, Clinical Reviewer in the Division of Anti-Infective Products CDER, FDA.

MR. KALEKO: Mike Kaleko, Head of Research at

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Synthetic Biologics.

MR. MELNICK: David Melnick, Chief Medical Officer at Spero Therapeutics.

MR. TSE: Brian Tse, I am a Project Officer in Antibacterials Program at HHS/BARDA.

MR. LARSON: Joe Larson, Senior Vice President, SMI.

MR. KIM: Wes Kim, Senior Officer at Pew Charitable Trusts.

MR. TRUONG: Vu Truong, Chief Executive Officer, Aridis Pharmaceuticals.

MR. COX: Great. Thank you. And now my colleague, Owen McMaster, will talk to us some about pharmacology toxicology considerations. Owen?

MR. MCMASTER: Good morning and welcome. My name is Owen McMaster. I'm a pharmacology toxicology reviewer in the division of anti-infective products at FDA. And this morning I'm going to present the pharm-tox perspective as we look at the development of non-traditional therapies for bacterial infections.

The first point I would like to make is that throughout this process sponsors are encouraged to

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talk to the review teams, because this is very complex development process and individual reviewers even though they try as best as possible to adhere to ICH guidelines et cetera, the review team for your specific drugs is the best source of guidance regarding the particular development product.

So this morning I'm going to outline the traditional nonclinical safety assessments that would normally occur during drug development and along the way I'll point out the special considerations that must be taken care of for non-traditional therapies. And then my final slide will look forward to the future of non-traditional therapies as we try to address these issues. So nonclinical pharmacology and toxicology really plays a central role in hazard identification, characterization and risk assessment. Pharma-Tox allows us to identify the target organs and adverse events of special interest in addition to determining what doses, durations, routes of administration and exposures are associated with specific toxicities. These all go together to inform the dose selection for clinical trials.

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This slide describes the regulatory guidances, which form the context within which nonclinical studies are conducted and the first two are really the most important ones ICH M3 and which describes the nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. And ICH S6, which refers to biotechnology derived products. There is a reference in FDA guidance there as well and I refer you to FDA.gov and ICH.org for further information regarding these guidances.

So ICH M3 describes the studies that must be conducted prior to first-in-human studies. The -- they include pharmacodynamic, safety pharmacology, PK, gene-tox and general toxicology studies. The first two pharmacodynamic studies, which may be conducted in vitro and in vivo provide us with the information regarding the mechanism mode of action of the drug. Safety pharmacology studies evaluate cardiovascular effects, CNS effects and respiratory effects. And both of these are identical for traditional and non-traditional products.

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Pharmacokinetic information is always useful to predict margin of safety as we plan clinical trials and there are -- these data are expected for traditional drugs. For biotechnology derived products there are no specific guidelines. For non-traditional drugs we need to be quite careful, because there are differences which may impact our interpretation of the data.

For example, delays in expression of pharmacodynamic effects relative to the pharmacokinetic profile for example for cytokines may -- affect our interpretation of the data, also prolonged expression of pharmacodynamic effects relative to plasma levels. And very importantly, alterations in the PK profiles due to immune mediated clearance mechanisms, which may affect the kinetic profiles and interpretation of the toxicology data.

Traditional metabolism or biotransformation studies are not needed for non-traditional drugs. Traditionally genotoxicity studies would be conducted prior to single dose clinical trials and the Ames assay is one that we would need before clinical study.

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For multiple dose trials, we would expect in vitro chrome assay to be completed. For non-traditional drugs genotoxicity studies may not be needed.

Biopharmaceuticals are not necessarily always expected to direct with -- to interact directly with the DNA or chromosomal material and especially for dealing with large quantities of peptides or proteins these may yield un-interpretable data.

Many biotechnology derived pharmaceuticals are immunogenenic, not all but many are and if such antibody responses should be characterized in repeat dose toxicity studies. The detection of antibodies should not be the sole criterion for early termination of preclinical safety study or modification of the duration of the study, unless the immune response neutralizes the pharmacologic and/or toxicological effect. In most cases the immune response to biopharmaceuticals is variable as with humans and I recommend that you consult ICH S8 for further information.

So ICH M3 decides the general studies, general tox studies, which are required to support

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early studies, early clinical trials. These are usually conducted in two species and it should include the most relevant species. The high dose should be selected based on the maximum tolerated dose, the maximum feasible dose, the saturation of exposure, the limit dose or large exposure multiple depending on what applies for your specific case. The duration of the general tox study should be equal to or greater than the duration of the proposed clinical trial.

I mentioned relevant species in the previous slide and by relevant species I mean species, which -- within which the test material is pharmacologically active based on the presence of a receptor or an epitope and based on demonstrated tissue cross reactivity, which would be similar to tissue -- to human tissues. There are instances where there are no relevant species in which case transgenic animals expressing the human receptor maybe considered as well as use of homologous proteins. There are however cases where there are no relevant species and no transgenic animals available and no homologous proteins available. In these cases a limited toxicity

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study in a single species up to 14 days may provide important information for off target effects.

We generally expect two species, but one species may suffice, if for example there is only one relevant species that can be identified or if the biological activity of the biopharmaceutical is well understood. Also if two short-term studies have been conducted and the tox profile has been shown to be similar in the short-term study then a single species may be used for the longer-term study.

Non-clinical toxicology combination studies are recommended in special circumstances in particular if the individual agents are intended only for use in combination. So for example, if drugs are going to be co-packaged or if there is a fixed formulation also for cases where there are recommendations for co-use. Also if the nonclinical development programs have not been completed for the individual entities, so we would need co-packaging plus and the absence of a complete nonclinical program to require nonclinical combination studies. We also need them for two early-stage studies if there are specific significant

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toxicological concerns for example, if the two drugs have a similar target organ so that the combining of the two products would be expected to produce some enhanced toxicity that might be unacceptable, then we would need combination studies; also if they're low margins of safety or if the adverse events are difficult to monitor in humans.

By Stage 3 we would generally expect clinical studies to be supported by a nonclinical combination toxicity study if the above conditions apply. But again, as I mentioned before, please consult with your review team regarding the need for these studies. If necessary these studies should be conducted prior to clinical trials if there is a significant toxicological concern, but these need to be conducted only in a single relevant species for up to 90 days.

It's not recommended for early stage entities or for too late stage entities with adequate clinical information. Also if the individual agents have been studied for gene-tox, safety pharm and carci then we wouldn't recommend combination gene-tox studies or combination safety pharm or combination

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carcinogenicity studies.

So at the end of the pharm-tox studies we end up with some very useful parameters, which may be used to help guide the clinical trials that are conducted. So for example we get the no observed adverse effect levels, which is the highest level of drug, which does not produce adverse effects. For biologics we pay more attention to the minimum anticipated biological effect level. We also look at the pharmacologically active dose. We will have theoretically at least defined anticipated therapeutic dose range as well. And these all are considered and factored in as we plan the first-in-human clinical trials.

So for late Phase, as in Phase III clinical trials, we need to consider the issues of reproductive toxicity and carcinogenicity if the conditions apply. Reproductive toxicity studies are outlined in ICH S5 and these need to be conducted according to the principles outlined in those documents. The evaluation of toxicity to reproduction should be conducted only in pharmacologically relevant species. For products directed at a foreign target such as

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bacteria and viruses, reproductive toxicity studies may not be required. Again please consult with your review team regarding the specifics. There may also be public information based on the class of drugs that you're evaluating.

Carcinogenicity studies are conducted for regimens, which are long term or if there is a significant concern for carcinogenic risk. So for example for drugs that are administered for 6 months continually or repeated intermittent dosing they should be conducted -- they should be supported by carcinogenicity studies before the marketing of the drug. If there is a significant -- I will add at this point that we have under many circumstances received carcinogenicity studies post marketing. If there are significant concerns for risk then the -- for carcinogenic risk, then the study should be conducted to support the clinical trials. Please refer to ICH-S1a and ICH M3 for additional information.

So as we look to the future one a -- one idea that's been raised by the ICH is the idea of using animal models for disease in toxicology studies.

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Traditionally, we do toxicology studies in healthy animals, which allow a very clean unconfounded view of the toxic effects of the drug. I recently had one drug where the disease caused certain effects and the drug also caused the same effects. And we had to look to the pharm-tox, which very clearly pointed out that the animals, which were obviously healthy and did not have this disease also had this finding and clearly therefore that this was a drug effect as opposed to a disease effect.

The animal models may be useful in evaluating new parameters. So traditional studies would allow us to evaluate pharmacokinetics and pharmacology route effects, the treatment regimens, durations, but there are special cases where and I -- I'll refer to, Dr. Boucher's example just now, where there was a case where the expected treatment was not in fact to improve, but actually to make worse the outcome. Animal models of disease provide an opportunity, if toxicology studies are conducted in these animal models, to evaluate whether or not there is any undesirable promotion of disease progression in the

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context of these studies. These are not very often submitted to the agency so I would caution that if, if tox studies are conducted in diseased animals that scientific justification should be provided and that concurrent control, historical control and base line data be provided as there's not much experience with these approaches. I also refer to ICH S6 for further information.

So in summary the nonclinical program for non-traditional drugs should be as similar to that for traditional drugs as is feasible or scientifically justified. And perhaps the most important thing is that sponsors should consult with the reviewing division very closely in order to develop the nonclinical programs. Thank you.

MS. NAMBIAR: Thanks, Owen. Our next speaker is Tracy Wei, is a reviewer in the Office of Clinical Pharmacology and she's a member of the team that provides support to the division of anti-infective products. Tracy?

MS. WEI: Hi. Good morning, everyone. My name is, Tracey Wei. I'm a clinical pharmacology

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reviewer in the Office of Clinical Pharmacology in CDER, FDA. So I'm going to talk about the overview and the development considerations from the clinical pharmacology perspective. So here's my disclaimer. So the non-traditional therapy is a broad term and covers a variety of products. So some products exhibit direct bacteria effect and can be used as monotherapies. However most of the non-traditional therapy do not have the antibacterial properties that enhance the efficacy of standard of care and have microbials in adjunctive therapies by interacting or binding to different targets.

The biologic and peptide drugs such as peptides, lysins, monoclonal antibodies and recombinant proteins account for the majority of this type of non-traditional therapy. MIC based the PK/PD targets are not relevant for most of these drugs. So in this presentation I will focus on biological and peptide drugs used in non-traditional therapy.

First, I'll talk about pharmacokinetic considerations. For those non-traditional therapy under the current development, linear PK has been

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observed within the therapeutic dose range. However, differences in PK behaviors were observed in infected patients compared to healthy subjects. For example, faster clearance and shorter half-life was observed for some monoclonal antibodies in infected patients. While some peptides showed us lower clearance in higher exposures in infected patients than in healthy subjects. In addition, PK differences may exist among the sub set of patients, such as the patients with different type of infections. As the big molecule foreign agents, immunogenicity is observed in most biologic and peptide drugs for non-traditional therapy. Most exhibit low incidence of the positive and high drug anti-body response. However, higher positive anti-drug antibody rate was observed for some lysins following systemic administration.

According to the FDAs guidance for immunogenicity, monitoring immunogenicity should be considered across the entire drug development program and the neutralizing antibody assay needed to be developed. It is important to understand the tissue distribution of this biologic and peptide drugs

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because multiple barriers may exist for such big molecules to distribute to the site of infection. The tissue sample connection for PK assessment or conducting the dedicated tissue penetration study need to be considered. With regard to the pharmacodynamic considerations, since the MIC based PK/PD approach does not apply to most of these non-traditional therapies. It is important to identify and evaluate the mechanism based PD biomarkers from the infected patients. For some peptides with a very short PK half-life accessing the long-lasting PD effect is even more critical. The examples of the mechanism based PD biomarker may include the characterization of the binding of the antibody to antigen such as measuring the antitoxin neutralizing antibody if the drug targets two exotoxins or to determine the option of exocytic killing effect, if the drug targets the exopolysaccharide on the cell surface of the bacteria.

As Dr. Ed Cox mentioned earlier today, we also need to understand the benefit from the mechanism to the clinic. So it's also desirable to determine the clinically relevant downstream pharmacological

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effect in the patients. For example, the effect on the change of the cytokine levels by immunomodulators following it's binding to CT28, in the impact of non-traditional therapies on the anti-bacteria effect of the concomitantly used antibiotics in the adjunctive therapy.

With these PD results they can be integrated with PK information and explore the clinical PK/PD relationship analysis to support the dose selection. So dose selection is a bigger consideration during the drug development program. For most traditional -- for most non-traditional therapy, dose selection needed to be rely on the PK/PD approach that is not MIC based. Such PK/PD data are usually first determined from the in vitro or animal studies. Such pre-clinical PK/PD information is useful for the Phase I or Phase II dose selection. However, PK/PD results obtained from patients prefer for the Phase II or Phase III dose selection.

Phase II dose ranging studies are usually conducted to facilitate dose selection, and the multiple dose levels are usually tested in such

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studies. For combination therapy, multiple dose ratios may also need to be tested. This Phase II dose ranging study can then be utilized to determine the mechanism base and clinically relevant PD effect from the patients. Exposure response analysis is commonly used clinical pharmacology tool to assist dose selection. PK/PD relationship analysis, exposure efficacy analysis, and the exposure safety analysis are usually conducted. In some cases, drug exposure at the site of infection rather than in the plasma maybe more informative for the ER analysis to support the dose selection.

Now, I'm moving to the considerations on the clinical pharmacology studies. So most current non-traditional therapies are still at the early development stage. The clinical pharmacology studies needed for each non-traditional therapy should be assessed on a case-by-case basis. We also encourage the sponsors to consult with the FDA at each early stage.

Since most of non-traditional therapies are used in the combination therapy or the adjunctive

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therapy, the risk of the drug/drug interaction may need to be assessed in the clinical studies. In the potential of therapeutic protein drug/drug interaction needed to be considered for those cytokine or cytokine modulators. With regard to the PK studies in the special population, hepatic impairment usually does not affect the PK of monoclonal antibody, but some exceptions were observed recently. Renal impairment may alter the PK of therapeutic proteins with molecular weight less than 69 kilodalton.

It is important to assess the risk of the drug on the QTC interval. Generally, monoclonal antibodies are not associated with clinically meaningful effect on the QTC interval. However, this may not be the case for other biological and peptide drugs and other assessment needed to be conducted for these drugs. Depending on the specificity of each drug development other clinical pharmacology studies needed to be considered on a case-by-case situation. For example, the lung penetration study for the indication of pneumonia need to be considered. Or for the Gard locally acting drug, the drug/drug

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interaction study with a proton pump inhibitor or a further effect study may need to be considered.

So comparing to the conventional therapy with small molecules, we are facing several challenges in developing non-traditional therapy for bacteria infection. The drug disposition of non-traditional therapies may not be fully understood in the infected patients. More data needed to be collected to characterize the immunogenicity and understand its impact on PK/PD safety and efficacy.

Problems may exist to determine the drug distribution to the site of infection taking account the problems to access the infected tissues and the questions on the representation of some surrogate tissue samples. Currently, we have limited experiences in understanding the drug effect of non-traditional therapies to support the Phase III dose selection. More work needed to be done to identify the appropriate PD biomarkers and to understand the clinically relevant pharmacological effect of non-traditional therapies in affecting the antibacterial activity of the concomitantly used antibiotics.

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For most non-traditional therapy under the current development, pre-clinical PK/PD data were used for dose selection. So we may have the challenge to translate this pre-clinical PK/PD data to human if this information is not available from the patients. So I just listed this several challenges but we can continue to discuss these challenges or the further thoughts in the next several sessions in the context of the case studies. But I'll be happy to answer any questions on my presentation at the end of this session. Thank you for your attention.

MS. NAMBIAR: Thanks, Tracy. So next speaker is Kalavati Suvarna. Kala is a microbiology reviewer in the division of anti-infective products.

MS. SUVARNA: Good morning, I'm Kalavati Suvarna, clinical microbiology reviewer in the division of anti-infective products. Today, I'll go over some of the microbiology considerations. Thanks. So today, I'll go over some of the microbiology considerations in the development of non-traditional therapies for bacterial infections. In general, the microbiology evaluations include mechanism of action

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studies, evaluation of the spectrum of activity, resistance development, interactions with other anti-bacterial drugs, and confirmation in an in vivo animal model. Coming to the mechanism of action with non-traditional products, there are products where we know the mechanism of action, we know the specific target on which the product acts. Those include the antibodies lysins, anti-microbial peptides, antivirulence products and anti-resistance products, even with these products you might know the target but may not have a full understanding of all the upstream effects.

Then you have a second category where you don't know the mechanism of action because it acts not on the pathogen but on the host, these include the immunomodulators or for lack of a better word, I've used microbiota modifiers. You might be using a product which inactivates the drugs or absorbs the drugs, in this case you need to have a good understanding of the site of action and how the drug is metabolized.

In case of spectrum of activity over the

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range of non-traditional products, we have those that are pathogen specific, those that are narrow spectrum and those that are broad spectrum. For the pathogen specific ones, it's important to understand antigen variability using -- looking at large number of strains from different geographical areas, looking at different serotypes, ribotypes, things like that.

The products as mentioned before, Dr. Rex mentioned, we have some products where MIC is not applicable, those includes antibodies, immunomodulators and biofilms here, you then have to develop a different type of functional assay to show spectrum of activity and these can include cell based assays, opsonophagocytic killing assays, biofilm eradication concentrations, and to look at maybe cytokine effects and the cytokine levels.

In some cases the MICs may not be very predictive and may need additional standardization as applicable to lysins and antimicrobial peptides. Here because of the rapid affect of the product, time kill type of assays are more informative. And the next category is the one which is very difficult to

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interpret because there's no effect on the pathogen, you're looking at other markers of, like, normal flora assessments, measurements of the host immune response or say, how the drug degrades in the human and how that impacts the disease or how that gives you a clinical benefit.

The next is looking at resistance development. Here in the case of antibody products, what you're looking at is changes in epitopes and or antigenic drift. These have not been really well studied for this class because some of them have been developed as single dose. The other products which -- where you can't use the traditional testing methodologies because of its impact on growth kinetics and the study design has to be modified, and then it begs the question of what other methodologies can be used for these products because they don't all perform in the same traditional manner.

In terms of interactions of a traditional drugs, for most products that have an MIC type of MIC value, you can use the time kill assays either in static or dynamic conditions. For those that don't

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have MICs usually animal models are used to show the effect of the combination versus a single agent. In other cases, biochemical or biophysical assays have been used. However, this only shows the interactions, it does not translate to what the clinical effect would be. The various animal modules that have been used to confirm in vivo activity, these include animal modules of pneumonia endocarditis, sepsis, thigh infection, catheter implants, systemic infections, they've all used -- all of them always test with immunocompetent and immunocompromised animals, but sometimes these are not very predictive, especially we've seen that with the anti-body class where you can have some host specific immunevasion mechanisms or virulence factors produced by the target bacteria that prevent you from translating the in vivo efficacy to humans. So to summarize with the challenges and I've put them into three categories, one is the design and interpretation. So how you design the functional assay and how you characterize the activity when the mechanism of action is not well understood, how would you characterize the upstream effects so the --

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basically relates to interpretation of the functional assay. A third category is when you're looking at the microbiome data, how do you interpret that because that's still a very exploratory analysis.

The next category is where there's limited characterization, these include basically what would be useful in the clinical studies, the potential for resistant development and interactions with traditional antibacterial drugs that maybe used in combination or a standard or care. The third challenge relates to translation of the preclinical data to what would be clinically relevant, we already mentioned about the lack of some predictive models for antibody class, what would be the natural levels of antibodies to a pathogen of interest, what would be the impact of the neutralizing antibody on the activity of the drug, what would be the impact of heterogeneous populations or changes in the target of virulence factor expressions, how do you evaluate some redundant effect or functions, what is the activity of the drug at the site of infection or intra cellular activity. So these challenges will be discussed

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within the context of the cases that I discussed today and tomorrow during this workshop. So that's the end of my talk. Thank you and if you have any questions, I'd be happy to answer them.

MS. NAMBIAR: Thanks, Kala. So what we'll try to do in the next few minutes or so before we take our first break is see if there might be any clarifying questions or comments from panel members or from members of the audience. Then we can check to see if there might be comments online as well.

MR. COX: So, I'll start out with one. And this is a pharm tox question I'll ask Dr. McMaster. So I'm a company and I've got a new molecule. I'm not ready for an IND yet, but I've got some questions about my toxicology studies. Is there a mechanism and the people to contact us often about these sorts of questions. And then is there something that a company should do to make this most productive, if they want to interact prior to the point of an IND? So I'll throw that one out to you Owen and welcome your comments.

MR. McMASTER: Hello, thank you. So yes, we

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do get these inquiries all the time. There is a mechanism for companies that are in the middle of drug development who want to make sure that they're really fulfilling all these, which can become quite complex guidances, and we try our best to provide a forum within which they can express the problems they're having and also provide guidance, guided largely by the ICH, but we also have FDA guidances as well. If I could be specific, can I point to my slide 6 please? Because that goes through the expectations from a company that's coming in with a product that has not conducted any clinical trials as yet. So for a company coming in, we would explain to them that we expect pharmacodynamic studies and Kala just went over detail of what kinds of studies we would expect. We'd expect safety pharmacology studies, some PK data but as I mentioned in my talk, this can be very complex and so the expectations for this kind of product is limited.

Gene-tox studies, we absolutely would need for traditional products, although again these maybe complicated depending on the chemistry of the molecule

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and then general-tox studies, the durations of which would be guided by the proposed clinical trial. So we do provide a context within which companies can come into the agency and seek guidance, and we encourage people to do that. Thank you.

MR. BLACK: So I had a question kind of similar to that. So because of difference in reactogenicity in different animal species, what guidance do you give on surrogate antibodies and for instance to do the tox studies relative to the actual human product, and I think particularly in the context where you're making half-life extending modifications or other modifications that may alter that in the humans?

MR. McMASTER: So this is a very, very big problem. And sometime, as I mentioned in my talk, it's insurmountable. So sometimes there are no relevant species, sometimes there are no transgenic models, sometimes there's no homologous protein that you can create that's going to model what you're trying to look at. And in those cases, we simply recommend that a short-term tox study is done because

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even these agents may have off target toxicities which we will be able to evaluate in a short-term study. But this is a very complex problem and sometimes there's just no way to address it. And we realize and sometimes if that's it then we, you know, we base this on the scientifically available data and there's no point wasting animals if there are -- there's no point to it.

MS. NAMBIAR: If I can just add to what Owen said, in terms of seeking advice from the division, I think we highly encourage you to reach out to us, pre-IND is an appropriate way by which you can seek advice from the division. We can respond in writing, we can meet with you in person, we can have a call. And discussions at these meetings, while a big focus is on the pharm tox data package, I think, I just want to be clear that we are willing to discuss the overall development program. And to a point that Kevin made earlier, it's much easier for us to have a discussion when we actually have a product in hand rather than hypotheticals.

Even if you are very early in development but

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to sort of have the long-term discussion, and some of these are very challenging because we don't have a lot of prior history to go by. So it might necessitate a fair bit of discussion between the company and us. So starting the conversation early and building upon it might need more than one discussion. I think we in the division are very open and welcome you reaching out to us to have these conversations. So just wanted to make that clear. Thanks.

MR. COX: And I'll throw in one more piece too and I'll look to Owen to make sure he agrees with me but our experience has been too to the extent that the person coming in and asking for the pre-IND consultation has thought about things you know to a fair degree and has put out a plan. There may still be questions, they may not have all the answers that can certainly help to move the discussion along and get to a good answer sooner. So did I get that right, Owen?

MR. McMASTER: Yes, you did. Also because we see so many more of these applications, we may often be able to refer you to mechanisms which may be able

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to address your very complex issue. More questions, and folks from the audience feel free too if you've got a question you can come up to the microphone.

MR. DUBOVSKY: I have a point, which came to my mind both when we were looking at the pre-clinical discussion as well as the clinical one. And for pathogen specific approaches, it's pretty easy to envision combination products, where you either need to target different serotypes or different virulence factors in your bacteria of choice. And that kind of raises a conundrum for us in how we handle that and how we approach it, you can do a matrix approach either pre-clinically and clinically but those become almost impossible to do in difficult to study diseases. An alternate approach is just to take your combination all the way through efficacy and examine a global benefit risk ratio for eventual licensure and if the sponsor makes a mistake and makes it too complicated, too expensive a combination, that just leaves space for competitor to come in and own that space. So I make this comment in with the realization that we're all trying to advance as many products as

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nimbly as possible and the development stream is a real driver of cost and return of investment. And I'm also aware of the recent experience of people in this room around this but I just propose there may be an alternative for us, especially if you're dealing with three, four, five, different entities.

And I guess the final comment is our colleagues in CBER deal with this all the time. They do pathogen specific multi-antigen vaccines and they have a pathway which is a little bit lighter than the one which some people think we need to follow.

MS. SUVARNA: So along those lines I also wanted to have some discussion about what additional tools can be developed. Yes, so there's also one thing to have some discussion about what additional tools can be developed that could be used by multiple companies so as to advance this field with non-traditionals. You had a comment there, Vincent (ph)?

MR. TRUONG: Vu Truong, Aridis, given that we know the types of or the classes in non-traditional anti-infective under development, does it make sense for the FDA to generate a -- prepare a guidance for

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the industry in terms of PK/PD studies, pharm-tox, comparability studies; for example, when we switch cell line (ph) and so on?

MR. COX: It may. So it sounded like if I understood correctly, you're talking about how the product is produced, right? You're talking about switching cell lines so that would be manners of production or did I get that wrong?

MR. TRUONG: Certainly that would be helpful but also provide guidance on how many animal models you need to test for, let's say, an antibody development right? The relevance of some of these animal models for PK/PD or toxicology is not very scientifically useful or clinically predictive. And so to provide guidance on how to develop license, how to establish tox studies for antibodies or other peptides, so on. I think that might be very useful for the industry.

MR. COX: Yeah. So, I mean, we do take the issue of guidance and recognize it as something that's very important. And in essence the workshop is in that spirit to try and answer questions. And as you

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can see there's a broad range of topics and I know some of the guidances but I wouldn't claim to know them all, and that's why we have a multi disciplinary team that looks at things. You know with regards, you know, to manners of production, and I guess really the first question is, is do we have anything out there that would address the questions, and if not, then maybe there is a gap that would need to be filled? And then you're talking about animal models and I'm thinking -- I was initially thinking toxicology but now you also mentioned pharmacokinetic studies. And yes, I mean that may be another area. And then just listening to your comment too, you also brought up the topic of what's the state of the science in a particular area. Because obviously it helps most to write a guidance document in a setting where there is at least some scientific information that allows us to write something that's meaningful. If it is an area where there's a need for more foundational science then it may be that the foundational signs would need to be done first before any of us could come up with recommendation. So we appreciate your comment.

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Guidance development is an area that we've been quite active in and will we'll continue to be active in to try to address the questions that are out there, and we'll continue to find areas, and we appreciate your comments because that helps us to , you know, look at particular areas where there may be a need for guidance or guidance may benefit drug development. So we'll keep your ideas in mind and see where it falls on the priorities, see where it falls in essence with the state of rightness if you, with regards to the foundational science that would allow us to write a guidance.

MR. AMBROSE: Hi, I guess from our perspective having worked with some non-traditional things, a lot of folks they have a model that they believe they're going to use to forecast what an effective human dose might be. But because of that model's expense or for some other reasons they study one or two bacterium and everything hinges on how the drug responds against those two and it may be in the case where we don't have things like MICs, we need to get much more comfortable with studying a lot more

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because what kills drugs is variability, right, in biologic response? And maybe we're not doing a good enough job of accounting for that.

MS. WEI: I have a follow-up comment regarding to the discussion on the potential. Yeah, so follow-up comments regarding the discussion on the guidance development. I think regarding to the PK/PD consideration especially using the animal model, so what we should be aware that this is a non-traditional therapy, it's across a very broader range of the drug, like, for the some peptide, lysins, monoclonal antibodies, that have very short half-life but it's not like monoclonal antibody have like about three weeks, even longer half-life. And their targets may be very dependent on the mechanism. So it will be, like, maybe some targets would be to the pathogen itself or just to the host or immune system. So regarding the guidance it maybe quite complex to cover the current these targets. So I was thinking if we have something will be very general or just very high level.

MR. REX: So if I could pick up on the point

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you just made that there's a broad range here. And we use the word non-traditional to mean so many things. So write a guidance for non-traditionals, summarize the history of the Western world, be brief. It's not -- there's such a breadth here. And I am concerned that we can spend all day talking in very vague terms about, "Oh I want a better animal model for non-traditionals" and make zero progress because we haven't cooked it down to the point where the answerer actually tells you what to do next. And is there a better language that we could be using, I like Tracey, your division on your slide of the -- you have these -- some nice boxes and do we need to chop it up a little bit into some agreed upon subunits and talk about each one of those individually. Some of the cases kind of do that but I'm not sure that we have created the right conversational boxes and I am reminded of conversations in the past where we would spent an entire meeting arguing about what we were going to talk about and only in the last 30 minutes did we finally get to where we had agreed upon language for that day. And the next time we start we

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had to have the entire day again of defining what we're talking about. So I really can -- is there a better nomenclature for non-traditional, I have to say the word but I'd like to now structure it a little bit. So that's my question, what is the correct structure for the conversation? What should be the boxes that we're discussing?

MR. BLACK: Well, I think it's a critical point because I guess when you segment these out, you do have these direct acting types of non-traditionals which I think do fall into a little bit of the category of our understanding, whereas if you're relying on a host response, where we know particularly in these patients that almost likely have these multi-drug resistant infections that can be highly variable and so then how do we make sure we capture that variability for bringing in antibody effects or host components to the efficacy. So I do think you could segment that on how much the host response is needed for efficacy as opposed to how much is really directly related to the activity of the entity being tested.

MR. DUBOVSKY: I guess another obvious box.

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John, I guess you cover this a bit is, can you measure a direct clinical benefit in a reasonable way versus not? So can you actually measure what most drugs are licensed upon now or are you really hoping to license then something which is broader, has phenomenal public health impact but may not be possible to measure the clinical benefit to the individual?

MR. BLACK: And history of the Western world, you know at a -- I'm sorry -- at a recent Vaccine Congress, it's just amazing to point out that we essentially have two effective biologic therapies for infectious disease. We have the RSV, which is a neutralizing antibody that impacted the host cell interaction in infection, and then Merck had anti-toxin antibodies for C. Diff. recurrence just three years ago as the second biological proof for in infectious therapies. So I think it does show the challenge of how we're utilizing these approaches in infectious diseases. It's not for lack of trying but it's really something simplistic as neutralizing toxin and neutralizing a virus is -- maybe a little bit more straightforward and direct and as soon as we start

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bringing in then more complexity that's where we're, I think, really being challenged right now.

MR. KALEKO: Seems to me that, listening to the discussion the description of traditional are those things that can be developed through predetermined algorithms. And things that are non-traditional, can't. Now if you have a universe or space, I should say, of traditional development, the universe of non-traditional is infinite, probably even bigger than the Western world. So the question is how can you set up algorithms for what is an infinite variety of opportunities? And I think the question really boils down to how do you deal with individual opportunities on a case-by-case basis without algorithms?

MR. REX: Looking around for others with wisdom on that.

MS. EAKIN: Well, I'll turn my mike on --

MR. REX: You go for it, just speak, say it clearly, here we go.

MS. EAKIN: Well, I'll try. So I guess one observation, and I don't know if this helps with the

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traditional and non-traditional definitions but I think I certainly have used in the past a sales pitch for antibiotics development that are pre-clinical non-clinical models, of such high quality and so predictive of clinical success that it allows, sort of, the early risk assessment. So early clinical development you get to Phase I, you know your safety, in PK, where you can you know almost guarantee success in later stage clinical development. And whether that's true or not, it home could be up for debate but I think we've used that. And so that to me is a traditional approach for antibiotics anyway, whereas some of these non-traditional approaches are waiting for much deeper into clinical development where you have biomarkers where maybe you don't even know what the clinical indications are going to be until much, much later and you see the clinical results. So that puts it into a very different realm of risk, which I think has some impact as well as I guess of particular interest of mine is are there tools, I think you mentioned that, that we could do better models so we can invest in earlier to maybe help clarify that risk

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earlier, even for these less direct acting traditional approaches.

MR. COX: And maybe I'll throw one out too to try and offer maybe a different sort of way we might look at this, which is, you can look at it from the standpoint of the molecule. What's the nature of the molecule and how you're going to develop the molecule, that may impact your tox studies and other things along the way. Then as you get into later development, you might look at it from the standpoint of what will this molecule do for patients and, and if you think about that second sort of angle of looking at things, not -- so it's not just what the product is but it's the other angle of what is the product going to do for patients. Well, you could imagine the study that Helen showed, there was a vaccine study to try and reduce Staph aureus infections, and that maybe a study design that could be utilized, there'd be some slight differences that would be applicable to different types of products. You could have a vaccine, that might be one way to do it; another type of product might be a monoclonal antibody, and maybe

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would have an infusion of a monoclonal antibody at some period of time prior to the surgery the patient was going to undergo. Maybe what it would -- the product that you would give would be of a Phage Lysin, and you would do that. So you can start to see that depending upon which angle you're looking at things there may be things that are more applicable or not. It's not that any one model is necessarily going to be perfect but there may be a lot of foundational work that can be drawn upon that teaches us important lessons and that sort of guide how we look at these products, and they may not be from the standpoint of benefiting the patient. There may be paradigms out there that are applicable. So it's just another way to sort of think of things and look at this particular area.

MS. NAMBIAR: I think we have one question on line, before we go to that, I want to check if any questions or comments from members of the audience. No, not yet, okay. So Tracy, there's a question online for you. The question is the current theme of antibiotic drug development usually avoid dose finding

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studies. Can you highlight any value that you've seen conducting exposure response if we have a valid preclinical target?

MS. WEI: Yeah, because in my presentation, I also mentioned that if it is also preferable that we can identify the PK/PD target from the human -- from the patients. So we think the -- only using the preclinical PK/PD target may not be sufficient in some cases. Especially, if from the animal model they use some end point that it's difficult to translate to human such as like the -- a survival of animal or like reduction of the disease severity, sometimes it may not be predictive to the human. Therefore, we prefer that during the drug development in the clinical stage, it is encouraged to the sponsor to collect the more PK/PD data especially using the dose ranging study, so you can have exposure response relationship to identify the optimum dose.

MS. NAMBIAR: Paul, maybe you want to add to that -- we will get to you in a minute.

MR. AMBROSE: Yeah, let me add to that, let's pretend that there's a valid pre-clinical model for

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efficacy like the questioner asked. So another reason to do it might be some of these compounds might have target mediated drug disposition, in other words binding to the target is a mechanism of clearance since so, therefore, clearance can be much, much faster in a patient than in a volunteer and that might be a reason to conduct that study as well.

MS. NAMBIAR: Go ahead, thanks.

UNIDENTIFIED SPEAKER: I just had a question targeting the pharmacokinetic tox. I was interested in the reliance on PK with PD readouts in the setting when there --

MR. COX: We may get you to get a little closer to that microphone so it picks up a little better, thank you?

UNIDENTIFIED SPEAKER: I am sorry. So, I was interested in the pharmacokinetic tox that you gave in the reliance on PD biomarkers for your readout, so I'm wondering in the setting, where you don't have a mechanism based PD biomarker such as even blood stream impacts on infections where culture clearance is your readout, but maybe at the time of dosing the patients

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aren't bacteremic anymore but we know that you need prolonged therapy even in post clearance of culture. How you look at things like dose finding or even efficacy readout in absence of PD biomarkers?

MS. WEI: So, yeah -- so you mentioned that maybe in your case, there's the lack of mechanism based PD bio marker, but I think in the other point maybe you can use some microbiological endpoint, so that maybe -- also be -- can be categorized to be as the -- one of the clinical endpoint. So, we just want to have something to link of your -- the mechanism or the working of the drug to the clinical end points. So especially in the early drug development stage, in the Phase II then the patients -- the sample size is not big enough to interpret a clinical outcome. So some of those endpoint like microbiology reading or some sort of (ph) endpoint may help you just to confirm the -- like proof concept the drug or to give you some hint for the dose selection. Hope I answered your question.

MS. NAMBIAR: Didn't -- sorry, looks like you've follow-up come?

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UNIDENTIFIED SPEAKER: Yeah. Well, I think the challenge is for something like bloodstream infection, where at the time of dosing in a trial a patient may no longer be bacteremic, but it's challenging in those situations where there is no PD biomarker and even pre-clinically for dose selection, where -- for example, if you have intracellular target you can't measure activity at your site of drug activity.

MS. WEI: So in that situation, where we -- yeah, we welcome the case by case discussion to reach out to the FDA to our group. We can just look at each specific case and then to see how the PK/PD approach or if that there is a lack of the data as I mentioned as in one of the challenge, how do we solve that. But we welcome more of this case discussion at the early stage.

MS. NAMBIAR: So, if there are no more questions or comments, we'll take our first break. We'll reconvene at 11:15 a.m. And just a reminder that if you're interested in getting lunch, I think you have time now to sign up at the booth. So thank you, we'll see you back in 15 minutes.

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(Recess)

MS. GHOSH: Good morning, my name is Mayurica Ghosh, and I'm a medical officer in the division of anti infective products. I'm going to discuss today a hypothetical case of a monoclonal antibody for prevention of a bacterial disease. It's an injectable humanized immunoglobulin the IGG-1 capa. It has an exogenous target, it binds specifically to the alpha toxin of Staphylococcus Aureus blocking alpha toxin pore formation in the target cell membranes and that's protecting the cell from lysis. It is of narrow spectrum and it has no activity against other pathogens, it is being developed for the prevention of Ventilator Associated Bacterial Pneumonia by Staphylococcus Aureus. In terms of the non-clinical studies, in a murine model of Pneumonia, prophylaxis with a murined version of the product reduced disease severity with an EC90 of 200 micrograms per milliliters.

A two week repeat dose toxicology study in rats showed no evidence of toxicity. However, a six

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week repeat dose toxicology study in monkeys showed evidence of immune complex arthritis. A tissue cross reactivity study was negative, it crossed the placenta, hence, reproductive toxicology studies were performed, and a single dose pharmacokinetic study in monkey showed positive anti drug antibodies.

A Phase I first in human study was completed. The terminal half life was 90 to 110 days. The serum concentrations maintained above the PK target for 30 days. In terms of clinical immunogenicity, 5 percent of the subjects tested positive for anti drug antibody during the study and 35 percent developed infusion reactions. A Phase II dose ranging study in ventilated subjects colonized with Staphylococcus Aureus in their lower respiratory tract was completed. The primary efficacy endpoint here was incidence of Staph Aureus Pneumonia during the 30 days post dosing.

A PK analysis showed a half life of 40 days, lower than healthy subjects as the clearance was higher in patients. And a dose of 4,000 milligram achieved the PK target, which was the same concentration of 200 micrograms per milliliter.

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Antibody concentration in tracheal aspirates was measured. Adverse re events of urticaria and rash were noted and there was one case of laryngeal edema, which was thought possibly secondary to a hypersensitivity reaction. A Phase III randomized double blinded placebo-controlled superiority trial with a sample size of 582 subjects in ventilated subjects colonized with Staph aureus in the lower respiratory tract was completed. The inclusion criteria were tracheal or bronchial sample positive for Staph aureus PCR within 36 hours prior to randomization and no diagnosis of new onset pneumonia within 72 hours prior to randomization. The primary efficacy end point here was incidence of Staph aureus pneumonia during the 30 days post dosing. This was based on clinical signs and symptoms and microbiologic cure.

Culture: The secondary efficacy endpoint was all-cause mortality at day 28. Safety was assessed by adverse event monitoring through 30 days, 90 days, and 190 days post dose. The incidence of pneumonia in the treatment group was 23.4 percent compared to 29.9

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percent in the placebo. The difference in rate was 6.5 percent with a 95 percent confidence interval of negative 0.7 percent to 13.7 percent, and a two-sided P value of 0.08. Forty five deaths occurred in the treatment arm versus 35 deaths in the placebo arm at day 28.

Some of the questions which can be discussed later this morning would be, how would you address the challenges of designing such a prevention trial including the need for a large sample size, identification of the at-risk subjects, challenges with the diagnosis of pneumonia itself, and confounding of safety assessments by underlying co-morbidities. What other study designs and indications would you suggest for this or a similar product? Thank you for your attention.

MR. IARIKOV: And now Mary Beth Dorr from Merck and she's a Clinical Director, I would remind you, of clinical research in infectious diseases, would provide industry perspective. And then Dr. Ghosh will provide FDA perspective on the subject of monoclonal antibody development. And before we

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proceed, our webinar participants kindly asked us to speak up a little bit because they have problems hearing us. Thank you.

MS. DORR: Well, first, I'd like to thank the FDA for inviting my colleague Todd Black and I to come and provide our perspective on drug development of monoclonal antibodies for infectious disease therapy. So our experience is based upon the development of basil toxin MAb, a monoclonal antibody for prevention of C. Difficile infection recurrence. So it's a little bit different than this case in that this case is for primary prevention of a disease, where we studied prevention of a recurrence. So our drug is given as adjunctive treatment to antibiotic therapy.

So, we Merck end licensed this product after Phase II. Phase II was robust proof of concept it was a combination product that was studied in Phase II based upon two toxins known to be virulent factors for C. Difficile infection, largely based upon animal models. And so, the first thing I want to say is that development of monoclonal antibodies for infectious disease targets is complicated, and we encountered

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many challenges through the development. We were fortunate that at the end of the day we had -- we achieved regulatory success but as people have mentioned and if you noted our drugs in Plava (ph) was on a slide that was shown earlier, that doesn't translate necessarily into marketing success. But -- so that others can learn from our experience, we offer some comments for your consideration.

So first is what is the appropriate target? For us, you know toxins for C. Diff, toxins make sense because they are the virulence factor but which toxin? And if you are looking at a bacterium that have more than one virulence factor, you need to consider that. And then, if you are going to look at multiple virulence factors it's important early on to understand the relative contribution of each one of the antibodies because as many of you are familiar with our situation, we moved forward with a combination based upon Phase II-B, but the FDA, in their wisdom, required that we also study each antibody separately, and at the end of the day, we found that only one of those antibodies was

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contributing to the efficacy of the product.
And so, that was a very costly lesson to learn, very late in development. Our development program was 2,800 patients that was our target. We ended up being able to drop the single antibody arm after an interim analysis, so at the end of the day we enrolled 2,650 patients, very large clinical development program for monoclonal antibody.
So, again that goes back to the idea of animal models, so is the animal model reflective of the clinical situation? Nobody knew what the relative contribution of each toxin was in the human, it was these monoclonal antibody studies, that we conducted, that found that toxin B was the relevant virulance factor in humans.
The other question is, can animal models help inform potential furmuter (ph) genecity. So you know, what is the right animal model to study that? And then for prevention studies, if you're trying to prevent a disease, even like for us, it was secondary prevention but if you're trying to prevent something, you need to enroll patients who are at high risk. In

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our situation, we were fortunate in that 75 percent of our population had at least one risk factor for C. Difficile recurrence, but if you don't enroll enough patients with risk factors then you're going to dilute your true effect size. And so that's really important to understand what the risk factors are before you embark upon a large Phase III clinical development program.
So also the definition of the end point is really important. If you've got a soft end point it's going to be more difficult for you to show a difference. What we found is that we used an algorithmic approach based upon a patient's symptoms and also microbiologic. So we didn't ask the investigator what they thought, so we called some patients failures, who weren't even treated for their infection because they had a single day of diarrhea and they had a positive PCR test.
So then that brings us to the PCR test. The PCR test can detect patients who are colonized but that doesn't necessarily mean, at least in the situation for C. Diff. that the patient has toxin in

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their stool because C. Diff. sporelates and PCR picks up the spores as well. So patients can be decolonized and their diarrhea could be due to the taco they ate the day before.
So that brings us to the definition of the end point really should include the physician's decision to treat the infection, because the symptoms could be due to something else and if that was ruled out then it should not be attributed to as -- to the specific disease that you're studying. But, when you're talking about an infection where you treat empirically before you have your microbiologic results that can get a little complicated.
So another thing that was brought up is the difference in PK between healthy's and patients. So, what we found with our monoclonal antibody, which is something that's known for monoclonal antibodies in general, is that there was a correlation with serum albumin. So if the patient had low serum albumin their clearance was higher. And so, how do you adjust for that if you have a narrow therapeutic index monoclonal antibody? We were fortunate in that we

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feel that we were significantly overdosing the patients, so that that didn't impact our efficacy, but if you've got a monoclonal where, you know, this example is 4 grams, that's a lot of monoclonal antibody. The cost of goods for 4 grams is quite high, so you really want to make sure you've got your dose right and you don't want to under dose. So it's important to understand the impact, for example, of co-morbidities on the PK before you embark upon your Phase III trial.
We also saw that sample size is important, so if your sample size is too small and you've designed a superiority trial, you can fail even if you've shown a difference that's clinically meaningful. So it's really important to consider what things are going to impact your endpoints and to, you know, is there a valuable population as opposed to the mITT population, what things are going to impact that? So for many of these anti-bacterial trials, you've got patients with co-infections, you know, you've got patients getting antibiotics that could target the same bacteria for other infections, and then how do you handle that

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patient's data? You really wouldn't want to include that patient, because it's confounded. So you need to consider those things as you design your endpoints.

And then the other thing is the fact that serious infections occur in patients with co-morbidities who are at high risk for adverse outcomes, that aren't related to the infection, leads to multiple early discontinuations. And how do you count those early discontinuations in your endpoint estimation? It doesn't seem fair to the product to count them as -- to impute those as failures. So you need to have some way of adjusting for those early dropouts. And in part, you need to over enroll to account for that.

And then in terms of safety, fortunately, if your target is a protein that isn't found in the human body then there is less potential for off target effects. So that is one advantage of studying monoclonal antibodies. But as has been mentioned, you do need to be concerned about anti drug antibodies being formed. So it's really important early on to understand the potential for anti drug antibodies and

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what can cause those. So this example here was humanized versus a fully human that could have potentially caused this. Formulation is important too because a propensity to cause aggregates can increase the chance for acute hypersensitivity reactions. And also if you're going to give a single dose for an acute infection versus you're going to give multiple doses for, you know, long-term prevention, multiple dose will increase the risk of immunogenicity, so you need to take all that into consideration.

Then the other question that came up was about imbalances in adverse effects that you see -- a serious adverse effect in this situation mortality, there was an imbalance that was seen. So these patients are really sick, how do you know that it wasn't just by chance versus something that was caused by the therapeutic? And you know, one way to look at this is if you have information based upon large database trials of how many -- what is the incidence in that population. If you can get that information, so if you know that the death rate is 20 percent and you know, you found 20 percent in the intervention arm

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versus in the comparator arm, you know, 15 percent then it could just be by chance that the rate was lower in that comparator arm. But if you don't have any idea, you know, what the rate is in the general population it's really hard to be able to understand if it's the drug that caused it or if it's just by chance. So that's my comments, thank you.

MR. IARIKOV: And now, Dr. Ghosh.

MS. GHOSH: Thank you for your comments, Mary Beth. I will make some general comments in this context and I share similar concerns as reflected in Mary Beth's comments. In terms of trial design, if a product is being developed for -- as an adjunctive treatment of standard of care anti-bacterials, then generally need to demonstrate superiority over standard of care and placebo. In terms of sample size for diseases with low incidence, a large sample size will be necessary to show the treatment effect of the product for prevention of disease. A small reduction in the incidence of the disease could have an impact on the sample size and the potential for benefit of the treatment is also a critical factor. In terms of

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selection of endpoint, for treatment trials choosing an endpoint which has a large treatment effect would provide the strongest evidence of efficacy, but just as Mary Beth said, clearly defining the disease itself would also help in selection of the endpoint. If the product is being developed for a reduction in recurrence of the disease, one needs to consider not only the reduction of recurrence of the disease as a primary endpoint, but also the cure of the initial index infection. As we have seen with basil toxin MAb, (ph) an imbalance in the initial cure rate could result in the treatment groups being not comparable and then the effect of the study drug on the recurrence of -- reduction in recurrence of infection would be difficult to interpret. One option could be potentially treating the index infection and then randomizing, so the cure of the initial episode could be with a different product.

One other scenario that comes up is, let's say, an antibody targets a specific pathogen like Staph aureus, with reduction in incidence of Staph aureus pneumonia. However, the subject then develops

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Pseudomonas aeruginosa pneumonia, then consideration should be given as to how to address this problem and how to address this analysis. What would be clinically relevant would be if the subject is alive and free of pneumonia overall.

In terms of VAP prevention trials, sometimes it's difficult for diagnostic confirmation of the disease, for example, if a sputum culture is positive for a pathogen in the absence of clinical signs and symptoms, it may just reflect a prior colonization of the disease and in this situation clearly defining the infection would help.

In terms of safety, sometimes assessing off target actions of the product could be difficult when there is a high mortality due to the disease itself and a separating out of the treatment effect in such situations is also challenging. One should also consider what would be the size of the safety database in such prevention trials when you're using the product to, let's say, treat a large population of uninfected population and would that tip the risk benefit ratio?

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In terms of adjunctive treatment, like Mary Beth said, when monoclonal antibodies can be administered, let's say, with standard of care; pre-clinical animal efficacy studies could be considered. However, as mentioned in Doctor Suvarna's talk earlier this morning, these models may not be predictive of human efficacy.

Lastly, a combination of antibody cocktails; when an antibody is being developed as a combination of antibody cocktails, one has to show the contribution of each component. And a study with a factorial design may be helpful in such situations to assess the contribution of the component, and sometimes in vitro and animal studies may be helpful. However, we have seen in the case of basil toxin MAb (ph), the animal studies predicted that the combination to Antitoxin-A and Antitoxin-B may be beneficial. However, as the clinical development program progressed and Mary Beth can chime in, the -- showed that be basil toxin MAb (ph) was, if more effective. Sometimes the studies with the factorial design can also inform -- the -- more that there is

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less toxicity of the combination as compared to the individual components, and that's all I have.

MR. IARIKOV: Thank you very much, it was very informative, and now we open the floor to discussion. But before we proceed, we have a question from our web audience that very relevant to our current session, so I'm going to read it and I will ask, actually my co-chair, to address it.

The question is MedImmune. If we are targeting several virulence factors with the combination monoclonal antibodies, how do we overcome regulatory challenge to this several single mono therapy arms versus a multi combination arm in a first in human study?

MR. DUBOVSKY: Right, so I think we just two sentences ago heard opinion about combination approaches and how -- and there are reasons to rip them apart and test each individually. But I think we need to weigh this against what's actually practical. So, if you're doing a study to prevent C. diff that's one population. If you're doing it to prevent VAP that's completely different and I would propose that

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if you're going with a combination of four -- three, four, five monoclonals it's not feasible to do five arm study to look at clinical endpoint in this indication. And that's why earlier I proposed that perhaps a complete different approach would be required, one that would push the risk into different directions than it is now and perhaps to push the risk more into the sponsor side, where they would take the risk of being accountable for the product in general benefit risk. But they would also take an additional risk, a more nimble product could take them over in the marketplace.

MR. PEREZ: As soon as I got the case and when I review all the safety profile, the clinical and non-clinical and the clinical results, being honest with you all I was asking myself, does it make sense to keep developing this drug based on these results enable us to know what is the opinion of the audience because if we were in some of these meetings in a company these results at least for my taste not really worrisome. I've never seen a monoclonal with this preclinical safety profile, I've never seen a

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monoclonal in clinical with this clinical profile that is just an question.

MR. COX: I might make a comment on the combination issue. So yeah, we do see combinations of drugs whether they be small molecules or whether they be monoclonal antibodies and, you know, in this instance, you know, folks of Merck have described the factorial design that they used to help them sort of dissect this. There are various different ways that we look at combinations -- combination products and the type of information that we get to justify, you know, that the product has more than one component. You know in some instances you don't do monotherapy studies, you don't do a factorial clinical trial because of concerns that if you went in with one agent you would lead to resistance that would lose the one agent that you got and then you ended up with so -- and then there's also a difference of if all of the components of the drug are targeting, you know, the same organism as compared to having multiple different components that are each targeting different organisms. So there's a lot of different questions

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here and I think, you know, the bottom line is, is that we do look at it from the standpoint of, how do you justify each of the components, what's the role for each of the components, and how can you show that?

The answer is not always a factorial clinical trial design, it is sometimes. In other instances there may be other information based on the science that helps up to understand the role for each of the components within an overall combination product.

MR. AMBROSE: So, maybe it's to Mary or the antibody experts around the table, but is the failure of -- you know you predicted in the preclinical model that antibody or Toxin A was a potential target for your drug. Is there a way to know before you move into man or propose to move into man how much of that toxin is produced in the rabbit or grasshopper, whatever your model is relative to what's produced in a person. So is it a chance that yeah, it was produced, that toxin was produced in your preclinical species whatever that was but it wasn't produced in people and that's why the FDA found that, that toxin was important. So it's not just as a toxin, right?

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Are they produced in the same sorts of magnitudes in the two different species?

MR. BLACK: The standard diagnostics for toxin do measure toxin levels as Mary Beth said, that was kind of our early assay. So you know, Toxin A is certainly produced in the situation. We could have looked at strain epidemiology if you had trusted that because you will almost always see Toxin B or A and B coproduced but you, I think, on very rare occasions might see an A only strain from a clinical lysis. So that was very rare and so there seemed to be some implications there that B might be the appropriate toxin in that. So yeah, we do think that, you know, toxin is produced it's not that it wasn't present.

Now, in terms of translatability of animal study, so after we had licensed in the product we did support a study at Tufts with (Inaudible) during the gnotobiotic piglet model and that model actually did recapitulate the human data both with the monoclonal or with polyclonal antibodies that neutralizing Toxin A had no effect in his model, either only Toxin B seemed to be impactful in that. So if we have the

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foresight to know that, that was going to be the translatable model we might have been able to preclinically make that prediction. But years of, you know, of lore was that we had both toxins to address.

MR. COX: I think one of the fascinating things is that -- I mean how much we learned from that, when it really did call into question some of what we had thought we knew before.

MR. BLACK: Well, I mean the fascinating thing is I think people are still having difficulty accepting that Toxin A isn't doing anything and, you know, we can't definitely argue that it's still isn't, that something else clinically happened but, you know, this was the first clinical result and I think it addresses kind of what Ann's saying too that we have so much comfort in the way that we do small molecule development and how translatable and predictable and, you know, probably people like William and Paul have modified these but we have a lot of confidence if we know the drug is there that we're going to have an effect. But with these new therapies, our animal models, you know, just may not be telling us what we

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want to know.
We know in vaccine's side, we know, you know, we say mice lie, you know, monkeys fib and humans tell the truth. So as you're trying to sort these out it is very difficult to get, you know, high confidence in the translatability until you start to get some clinical experience that replicates what you're observing in these models.
MR. REX: I just -- I want to -- go ahead.
MR. KALEKO: Actually just to confound -- confound things further. If I remember the 1980s mouse data, all the data with pure toxin was very different than those with knockout bacteria, but that's not my question. And I may have missed it, I'm sorry, I was more concerned with getting my lunch, I apologize. But why is this Staph protocol designed as a prophylactic protocol as opposed to a therapeutic one, where you know that certain strains tend to cause certain diseases. Maybe you have a strain that causes endocarditis. Why not take endocarditis patients treat them then you'll also have time to do your diagnostic and you could stop the antibody if it turns

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out to not be useful; seems to me that would be an easier trial design. Am I missing something?
MS. NAMBIAR: No, this is really just meant to be an example for us to have a discussion around how one might develop a product for prevention of disease. You are right just if, you know, this antibody could potentially have been used for the treatment of Staph aureus pneumonia.
MR. KALEKO: Okay.
MS. NAMBIAR: This is really just meant to be a hypothetical case. To stir a discussion and raise some of the points that one would encounter when you develop a product for prevention, that's the intent here.
MR. KALEKO: Okay. My apologies.
MS. NAMBIAR: No problem. Just to clarify.
MR. DUBOVSKY: So --
MR. DANKER: I think the discussion points of the questions are all the ones that normally would come up in trying to think about a prevention study such as this but what seems to have been missing is how do you get the data to make these decisions? And

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it seems like the ability to tap into what's now called big data and start looking at incidents of disease, what are some that are going to be the confounding factors to do the natural history is going to better set the company that may be developing a product such as this or other products in a state where they actually can make the best decision of whether it's even worthwhile to pursue a prevention study in this type of a setting.
MR. DUBOVSKY: So, in this particular case the attack rate and the placebo rate was quite high, right? I mean we could all hope to be doing studies in this kind of situation where it could be easily powered, our colleagues from (Inaudible) were facing a different situation completely. So when you think about prevention and the size of this H (ph) database I think you need to think a little bit more granularly and what's the attack rate. How much were you able to enrich the population before you did this study and that should perhaps inform the size of this H database and not strictly whether your prevention versus treatment.

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MR. HOPE: So some of us in the room grew up in the anti-fungal era when there were no animal models or experimental models and it took a large amount of funding from NIH to make new experimental models especially even basic mold infections and that unlocked a huge amount of ability to make new anti-fungal agents. So my question is strategically -- so I've heard continuously that there's a failure of translatable experimental models but what's the community's, I guess, strategy given that there were a whole lots of dots up in the right hand side of the CARB-X compound library about who's going to fund all of those experimental models so we could get better predictability for disease because it seems that's difficult just to put that onus on to sponsor alone.
MR. REX: So if you pick up that question and come back to the story that we heard a minute ago about the Merck compound where presumably Toxin A does something in some models, right? And is it the case that in general neutralizing Toxin A in human beings isn't necessary, is it hurtful? And before you jump into that, the next place I'm going with it is, what

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if the products that have gotten registered was Antitoxin A plus Antitoxin B and we kind of left somewhat undefined the question of which one mattered the most. And I know it sounds unscientific not to know okay, because I am here -- I'm extending a little bit of Filip's question. What if there were five toxins that you were interested in neutralizing? And you had -- you can put in five monoclonals and so -- and I can't swear to you that neutralizing Toxin 3 is all that important but I've chosen to stick it in and I do the study with my mixture of my five monoclonals and it does something that seems to be broadly useful to the human beings who get it but you can't swear that neutralizing 3 mattered. Do I care?

MS. DORR: So very good question. So Merck actually had proposed to just develop the combination and the only reason why we didn't was because the FDA insisted. So again, you know, congratulations to the FDA for having a very precise crystal ball. But you're right, I think that was our argument. So what, you know, if the combination is safe and effective what does it matter. I mean in the end it was a

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benefit to us because monoclonal antibodies are very expensive so our cost of goods is half but I mean you -- one can't necessarily argue against what you're suggesting. If you show the combination is safe that would be my feeling but, you know, our situation -- we're glad that we have that information. So, it's a balance.

MR. IARIKOV: If you don't mind me please. Was Toxin A arm performing worse in the Phase II study?

MS. DORR: So -- no. So in Phase -- so there were two phase, two studies.

MR. IARIKOV: Right.

MS. DORR: One was only Toxin A antibody. And that study was stopped early because animal studies showed that you needed to neutralize both toxins. So then the companies that we end licensed the monoclonal antibody firm decided to do the combination and the Phase II-B study was only with a combination. They never did anything with Toxin B antibody alone, so they only had a very small study with Toxin A alone and there were five recurrences in

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each arm. So you couldn't -- there was no difference between the two. But you could say well, it was a really small study, it's inconclusive, maybe it was just by chance. But it was enough for Merck to feel that A alone -- the A lone antibody would not work but we had no information about the B alone antibody. So in our first study we included each one of the antibodies alone, a combination and then placebo and everyone got standard of care antibiotic, so nobody got only placebo. Everybody got standard of care plus one of these four treatments. And then we had an interim analysis after 40 percent of the patients were enrolled.

What we saw at the time of the interim analysis is that the combination separated from placebo. The B antibody separated from placebo. The A alone did not separate at all, and not only that there were more SAEs than deaths in the A alone arm. Now again, these are really sick people. Is that due to chance or is it due to, you know, what you suggested, John, is that perhaps giving A alone actually without also neutralizing B is a problem. We

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don't know, we may never know the answer to that question.

MR. REX: So just to be clear the combination if A is toxic then A plus B should -- might also be toxic. But you are then saying if you compared A plus B to B alone there wasn't a corresponding shift.

MS. DORR: No, no. So, if you look at B alone plus A plus B there was no difference in safety. And so -- so, you know, we have spoken with people who do preclinical research specifically on the roles of the toxin and their concern is, if you only neutralize A it could be helping B to be more virulent. So there is some kind of interplay.

MR. DUBOVSKY: I'd like to pick up on a thread that we heard both from the FDA as well as from Merck and that's about endpoints and how to deal with them. And I'd like to bring it back to the case we talked about because in this case there was a clinical case definition, which didn't meet significance but it depends a lot on how you count that. We also saw there was, in this case there were a large number of deaths. And back to the point on how do you deal with

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those because it's essentially missing data. It's missing data if they die before you reached the window, it's missing data if you don't get a bacteriological diagnosis, or even if you get an alternative pathogen, but you can't be sure that Staph wasn't in the case.

So one option is to dump them all as failures and though obviously decrease your point estimate of efficacy. The other option is to examine them, a, either through sensitivity analysis or as a safety finding and the let the global benefit risk drive whether it's a real product or not. So I'd be curious to see if people have opinions on this and I have to say from a product development perspective when you count those as failures -- and these drugs shouldn't impact death directly and they shouldn't impact other pathogens. So the assumption is that these would fall out equally in the placebo and the active group and therefore just dilute your effect and that has real implications for the value ascribed to the product both from the payer as well as the practitioner's perspective and its ultimate use.

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MR. DANKER: There's the other problem of the fact that in the United States there's a whole aversion to calling anybody as having VAP because it impacts negatively upon your CMS standing and so they called them VAEs, did a VAP study this was a real issue in the US. So less of an issue in Europe, they don't seem to have as a big a deal about it but in the US people avoided calling things VAPs.

So number one that starts to -- automatically start to impact your endpoint, it then would be useful to have an adjudication panel that could look at all the events, not just the ones that are called VAP but then -- and then this way it relieves the hospital of calling something VAP and they're not caught up in it.

But the deaths are also, I think, an important issue of how you look at the deaths, you know. The FDA for years moved away from attributable mortality because attribution is sort of like beauty is in the eye of the beholder and it gets very complicated to try to sort those out. I'm not sure what you do with the deaths unless you make it a composite endpoint or you do what this winner take all

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concept where you match on whether they had VAP and then you match whether they had death and then you basically form some kind of statistical analysis based upon the matching and see how that pans out.

And then obviously the other thing that would be a concern in this particular scenario was we saw the data from the Merck vaccine trial for Staph aureus and we saw more deaths in those individuals who eventually got the vaccine and had Staph, we don't know why. But now you have a monoclonal antibody that's directed against some virulence factor in Staph and interestingly there's more deaths in the arm who had gotten the monoclonal antibody.

MR. DUBOVSKY: I guess I wasn't suggesting we ignore the data. I just think that looking at it as a safety finding may be one, an alternate approach. And if you do count this as failures do you actually get a label claim that you stop all-cause pneumonia or all-cause mortality as part of it? Seems like a pretty broad claim.

MR. COX: So let me throw some numbers out to this because I think, you know, these are good

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questions. And the other -- so if we think about the pathophysiology of you know nosocomial pneumonia, you've got something somewhere in your mouth and you're fearing something and then you're aspirating and that stuff is getting down there. What's in your mouth, what is in your pharynx maybe influenced by whatever treatment or preventative that you're getting because if it's only active against one or a couple of bacteria those may disappear and then there's always this question of replacement colonization. So let me throw out one for you there -- and this scenario is not unfamiliar I'll say. So the test drug is active against Staph aureus so it's one of the examples that we saw. The rate of Staph aureus pneumonia in the test drug arm is 20 percent. The rate of Staph aureus pneumonia in the placebo arm is 25 percent. We'd just assume this is statistically significant; we won't bother getting too hung up on the numbers. But then if we look at all-cause pneumonia the test drug is 40 percent and the placebo arm is 30 percent. So, I'll give you those numbers again. So test drug Staph aureus pneumonia 20 percent, all-cause pneumonia 40

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percent, and then placebo Staph aureus pneumonia 25 percent, all-cause pneumonia is 30 percent. And obviously I've picked these numbers for the purposes of discussion and I've made this a difficult case. I mean if the all-cause pneumonia was, you know, I mean you'd hope to see some decrement but -- so, you know, this is the question I'm trying to get --

MR. REX: It was protective against Staph aureus --

MR. COX: Oh, so there was something going on with shifting the flora and you can always make an explanation of you shifted the flora to something that's more likely to cause pneumonia when aspirated. So the Staph aureus is still a problem but whatever replaced it is in fact, you know, a lower innoculum when it gets down into the lung it's more likely to cause pneumonia. That's the post-hoc explanation.

So what do people think about that? So this therapeutic only goes after Staph aureus, what's the right endpoint? Is it the Staph aureus pneumonia? Is it the all-cause pneumonia? Should we be looking at both? What do we do with that?

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MR. REX: Well, you don't want to take away from the fact that the drug or the monoclonal did the job it was supposed to do. So this gets into this concept of process versus outcomes. I mean you look at just pure outcomes, you can basically throw the baby out with the bathwater sometimes. So I would say if I were that company I would hook up with somebody that had monoclonal against the other pathogens so that I can get the all-cause mortality lower but the drug did what it was supposed to do. The issue is if it's causing replacement pathogens that may be an issue that has to be looked at more from a, I guess, a societal perspective and are you causing more serious pneumonias than you had before.

MR. COX: But could you argue too from a patient perspective, not even a societal perspective. The patient essential is not better off in this instance because you're getting 40 percent of patient getting pneumonia with the test and 30 percent with the placebo.

MR. REX: So effectively what you got I'm call it for a second an off-target toxicity. Yeah, in

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a sense because, you know, what you've just argued is the monoclonal prevented pneumonia, the Staph aureus, it did that part of the box. But as a consequence of that there was an off target toxicity, which was that the elimination of the Staph aureus from your trachea caused E. coli to overgrow -- I am making all this up -- E. coli to overgrow, which caused you to get more E. coli pneumonia. So you're right, it did stop the Staph aureus but it triggered an off target consequence. And, you know, I think we do pay attention to those, and so -- and argue that this, you know, that in fact this product reduces Staph aureus but increases something else and it's not a use so I wouldn't want that personally.

So, I mean that is a very interesting way to describe the importance of measuring this. But what if -- we've drift a little way from the question of the combination bit and I do -- I wish I had a better understanding of that, you know, this idea of what if there were multiple components in there and you didn't care what each one of them did so much as the product as a whole. And Ed made the comment that in fact

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that's what polyclonal is. It's -- when we don't insist on the polyclonal, what if I invented rather than a single monoclonal to Filip's five toxins I have a polyclonal. Do I have to study each of the components of the polyclonal, which I don't -- maybe I have to purify them out as antibodies against the individual antigens and re-administer them as a combination or separate components. You know it's interesting that we choose to study the individual components because we can, but do we have to?

MR. OUTTERSON: John, before we let Ed answer that I want to pile on just a little bit, okay? And because I was thinking about microbiome, I mean what is the unit of analysis for the monoclonal antibody? We understand what the unit of analysis is. But if you have, you know FMT you know, how many species are in that? You know do we extend this analysis in the microbiome and what is the unit? Is it every species, is it, you know, you can go on forever, right? And so, you know, this question of combination becomes more acute in the next case, is that where we're about to go to?

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MR. REX: And there is no one single answer to the combination question. And, you know, the combination rule talks about, you know, you can use a variety of different ways to try to understand the contribution of each of the components within the combination product. So it really becomes, I think, a scientific question and yes, issues of feasibility come in there too. There are certain things that are doable and other things that are not. And yeah, as the number of components starts to increase it becomes exceedingly difficult and the question is are they even separable or, you know, are they yeah, depending upon how they're made and such so, you know, it would be -- I mean there's no way that I can answer the question as to what the one answer is as to how you address the combination, you know, the combination rule but I can tell you that, you know, when you're thinking about it you got to think about, you know, how can you demonstrate the component and each component is adding something, what are the various different ways to do that, you know, thinking of preclinical and clinical and all the way through.

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And, you know, how much data we need really becomes a scientific question which depends a little bit on what we understand from the pathophysiology of the disease. So if that is something that you're thinking about doing come in and visit us. You know the anti-infective division, that's certainly a question that we're more than happy to entertain and recognize that it is an important part of product development.

And I think -- Kevin I think your question is sort of falling in the same sort of area, you know. You're putting out the example where, you know, maybe there's many, many different components and the question is how do you try and figure out that you need each of these many different components. And I think again, you know, that's something -- yeah, we probably, you know, work to try and figure out what the answer is to that question, when somebody's got such a development program and come up with something that is scientifically doable that, you know, helps to address this question about the role of each of the various different, you know, parts of what's in an overall mixture of stuff.

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MS. BOUCHER: Thanks. I just wanted to come back to the endpoint discussion and see if we could push out a little further. So, from what a patient wants I think and from the discussion earlier this morning of getting to products that people want to pay for, thinking about maybe more of a continuum of priorities. You know everybody wants to survive. You want to survive without an infection. You want to survive without an infection and toxicity, and this kind of gets to DOOR. And, you know, just want to tip it over to Scott to talk a little bit because I think as we think about these products that kind of an assessment is even more important because you're talking about in large part adding two drugs that we're already giving patients who are very complicated in the hospital getting a lot of therapies and having a value around that just seems even more important. So I just want to raise that and see if maybe we can hear more from Scott.

MR. EVANS: In statistics we have a saying that there are lies, damned lies, and antibiotics. I think one of the issues is you mentioned this issue

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around death for example, is a missing data problem, but it's not really a missing data problem. We know exactly what happened to the patient, it's not missing. We know their outcome. It's a competing risk problem. And so one possibility in going back to this example, what could be done. What happened in this example study was that, you know, we did a primary -- there was a primary analysis on Staph aureus pneumonia, seemed to a trend going in one direction but wasn't significant. There was some trend in mortality although again not a big enough sample size to really distinguish very much. But one way you can think about this is instead of using the patients in the trial to analyze the outcomes, you use the outcomes in the trial to analyze what happened to the patient and by doing that you eliminate your competing risk problem that you just brought up.

So what you have is a scenario of a drug that appears to have some effect on preventing Staph aureus pneumonia, it may even have some -- but it wasn't significant. But if I just look at Staph aureus pneumonia by itself, I don't recognize that some of

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that prevention is actually of mortality. I don't pick up this sort of this extra signal that I'm getting in mortality. And by looking at mortality by itself I am unable to pick up the signal that I get by preventing Staph aureus pneumonia particularly in those that survived.

So suppose, in this particular trial that I create an outcome, let's consider three levels, ordinal levels. The most desirable level is the patient survives and they avoid Staph aureus pneumonia, or any pneumonia, even all-cause.

Second, the bottom category is the patient dies, in the middle, so the most desirable category survival without any pneumonia, least desirable the patient dies. But then there's this middle category where the patient survives but gets pneumonia, has a pneumonia diagnosis. So with placebo the patients are going to fall into these three categories wherever they happen to fall and you had a certain percentage that died, you had a certain percentage that got pneumonia. And what's you're hoping for is that with preventative treatment that you can get patients to

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migrate to more desirable categories, this notion of desirability.

And because you've got finer gradations of these outcomes your sample size problem and your significance problem is going to begin to diminish. You're picking up signals, gradations of outcomes. And if you think about what this was, the purpose of thinking of things this way is actually much more pragmatic. You know we created this DOOR outcome and many people use it to think about this sort of sample size problem that you get perhaps more sensitivity in the outcome. And that can be true in some cases, and in this particular case may indeed be true.

But the real reason that DOOR was created had a much more pragmatic purpose that this is the outcome that the patient experiences. You're using the outcomes again to analyze what happens to the patient rather than the other way around. And this is important because if you analyze each endpoint by itself you can get very distorted -- you have this distortion problem, you know, maybe I am measuring duration of hospitalization. And I think that

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duration of hospitalization, the shorter the duration the better off I am. But the patient, the faster the patient dies, the shorter the duration. So when you give me any summary statistic of duration of hospitalization, I don't even know how to understand it. But if you tell me whether the patient survived or not, now I understand but we keep separating them.

Or even if I analyze efficacy in ITT population safety, and some safety population, you say well, I do some benefit risk and put them together. I don't even know how to interpret it. I'm analyzing different outcomes in different populations. How do I even generalize what's happening? Somehow I have to sort this out in a more comprehensive way. So you may be able to improve on your sensitivity issue in terms of sample size problems by thinking about these finer gradations which are also a more complete characterization of what's happening to the patient than trying to think about how to chop it up into different pieces.

And the last sort of thing I would say about, you know, this particular example is a prevention

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trial. And so the other thing you may even have to think about factoring in is you've got 70 percent of the patients in this particular trial that never get the infection even without any preventative treatment. So you're going to have to treat a lot of patients, a fair number of patients in order to prevent a few, few events.

So with preventative treatment the toxicities have to be either one, very rare or two, very manageable. So whether you're able to manage or resolve any sort of adverse events is really the key about whether you're going to be able to think about whether this is going to be a reasonable thing to apply. So, I'll stop there. Thanks.

MR. MELNICK: So Scott, you beat me -- you beat me to the punch here. You know the hypothetical case addresses preventative therapy. One wonders whether the endpoint, you know, the sort of ordinal endpoint that you're describing would work better in a setting where we were looking at adjunctive therapy for established infection. You know on the face of it you think; well, it's very difficult to show

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superiority versus antibiotics that work pretty well. On the other hand if you use the appropriate endpoint could we in treatment of established infection show, you know, an adjunctive effect from the antibiotic plus antibody.

MR. DUBOVSKY: I guess I'd like to maybe shift the discussion a bit and that's to alternate endpoints completely, nontraditional endpoints. So with a monoclonal antibody you could well anticipate maybe having data or even a label claim around preservation of microbiome, perhaps about doing resistance versus nonresistant organisms, perhaps something around AMR in general, or use of antibiotic which you could possibly measure but maybe not in a sick ICU setting. The question is more global and we're going to get this in some of the discussions later, in the next day and a half. Is there actually a way to capture that because I think that has true societal value and one that at least from a sponsor's perspective could be useful in helping the medicine we use. I mean how do you get label claim for microbiome preservation?

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MR. COX: Would anyone else like to answer that one? So Filip, I think what you're talking about is do you want something in the label that talks about the patient's microbiome?

MR. DUBOVSKY: Or the greater public health societal benefits we think the nontraditional antibacterials bring to the hospital setting.

MR. COX: And so, what is that benefit and how is it shown?

MR. DUBOVSKY: Well, that's the question, isn't it? So you know, maybe the microbiome is more -- it's a harder task. Perhaps something around does not promote antimicrobial resistance and that could be one just based on the mechanism of action of the drug.

MR. COX: Right.

MR. DUBOVSKY: Or perhaps it's something even softer, but one which I think as a society we all crave and would be useful in the greater public health perspective.

MR. COX: Right. So -- I mean, you know, if there is a benefit, then the question, I think, is more -- it's more how do you demonstrate it? How do

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you show it? And if there is something that can be given that will reduce the rate of development of resistance and rate of resistant infections that patients experience, and then showing that in a clinical trial I think is really the answer to the question about how you would, you know, essentially show that the product does such a thing. What gets to be a little bit tougher is if you're just showing an alteration in the bacteria that you culture from somebody's GI tract, there become, I think, significant questions about, you know, what's the right mix, what does this mean, is this going to persist, is this is going to go way on its own a day or two later anyways and the patient will experience no clinical consequences? So, you know, oftentimes the way I think about this is, is to think about, you know, if you had a person how would you explain to them in lay person languages what benefit you've conveyed to them. And if you can do that you can say, you know, Mr. Jones, if I give you this therapy you're less likely to get a pneumonia that's caused by resistant organism. I think Mr. Jones can understand

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that. If you say Mr. Smith, I'm going to alter the distribution of the different bacteria that are in your GI tract. If I were Mr. Smith I'd say, so? What's that going to do for me as patient? So I think a lot of this comes back to what is the clinical benefit. And for some of these scenarios it can be quite challenging to actually design a study. If the effect size is small, if the event that you're trying to capture occurs only rarely, then that is, you know, unfortunately a difficult trial to do even though the product may have that mechanism, and that's one of the -- you know, we didn't create that challenge, that's actually the biology of the disease that we're learning and understanding and that's what makes it difficult. But I'll stop there and welcome comments from other folks on that very topic or things that are related.

MR. BLACK: So maybe, if I can look at it a little bit different way. So, Helen commented how important prevention is and I think we see that over and over again. If you can prevent the infection, you know, that is really the best outcome for that

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patient. So we have a situation where they're using, you know, a diagnostic for colonization and I was just looking at guidelines and we have guidelines for empiric use but none of these have incorporated PCR tests or colonization tests into risk factors for potential to progress to pneumonia in these ventilated patients. So I guess does this approach kind of lower our hurdle for a therapeutic intervention at something as, you know, maybe benign as colonization because we think we could prevent that progression, whereas we certainly are trying to discourage utilization of antibiotics in that type of situations to prevent resistance development. So is it through, you know, preventing use of treating an infection because we actually are intervening earlier with a therapeutic, which should not be driving drug resistance, is that the type of benefit that we could, you know, really enumerate?

MR. COX: So what you're describing sounds enumerable, but if the antibiotic usage is appropriate and what patients need, it seems that the reason that they would not get them was because they did not have

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an infection. So it sounds like at the core of your argument is a reduction in clinical infections --

MR. DUBOVSKY: I think at the core what is the value of that diagnostic for risk factor for progression to ventilated pneumonia, I guess. And at this point we don't think that colonization is sufficient to prescribe antibiotics. But if that patient population is in fact at a higher risk to progression, do they still benefit, then if you could prevent that with a nonantibiotic therapeutic.

MR. COX: So I think I'm understanding what you're saying, which is you're trying to identify a higher-risk patient population and going with some nonantibacterial agent and show a reduction in infection. And that sounds like a very doable trial. With the one caveat being that the size of the trial will be somewhat dependent upon how high risky this -- how high the risk is for this patient population to progress to the disease. In this case I think it was pneumonia, yeah. But that sounds like a doable trial and one that would show clinical benefit to patients.

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MR. DUBOVSKY: And they ask about the prophylactic study because I do think this gives you an opportunity to show superiority towards no treatment or placebo in this case as opposed to a treatment regimen, do we have the confidence that this would be a monotherapy or you do have to show actually benefit above standard of care which I think that is then a superiority design, that's going to be very challenging.

MR. COX: So that one is a little more complicated.

MR. DUBOVSKY: Right.

MR. COX: Because if you're adding in additional therapy, but showing no added benefit for that additional therapy because you're arguing that you can't show it above the standard of care, then I think there are some primary questions about what the role of that therapy is. Unless what you're talking about is, you know, there is some noninferiority margin that you can develop for what the standard of care is and you're trying to replace that and show that the effect size of this new thing, you know,

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absent the standard of care in the one arm is essentially coming out the same as the people who get the standard of care. That's just the way I'm thinking if I'm understanding your question correctly.

MR. REX: Kevin and I had a jovial debate about this one day. When I -- we're talking about the spread, and I proposed I'm going to register sterile water as my add-on, sterile water plus antibiotic is not inferior to antibiotic but being hydrated is good. So it's -- I think that, you know, when we started to think about it that way, you know, this notion that there might be some secondary benefit being hydrated by the sterile water is a good thing. But it is not enough really to compel me to buy that at an interesting rate of return.

MR. IARIKOV: We're approaching lunch time which is sacred since -- and we have one question from our web audience, I'm not sure who is going to address it, maybe -- we'll see it, maybe Collins. For the staph or this antibody example, will you look to see how much of the toxin is neutralized from patient samples? Is it better to select patients based on

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toxin detection rather than staph aureus colonization status? And --

MR. DUBOVSKY: I'm not sure it would be practical to select on a serum biomarker versus dominic (ph) PCR at with the current tests that are available.

MR. IARIKOV: Right, because antibody might reflect prior colonization infection and that would be very hard to put the patient at risk for development of infection based on serological markers, right?

MR. DUBOVSKY: I would think.

MR. IARIKOV: All right. And after we dealt with such a difficult question I think it's time to summarize our session.

MR. DUBOVSKY: Are they -- right. So we, just at a high level we talked a lot about combinations which vaguely surprised me since this case does not contain any combinations. But I think we got some pretty decent guidance about the flexibility of approach depending on what the specific product is. There was also lot of discussion about the endpoints with some cautionary tales about using

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PCR that can lead to false positive endpoints and having to deal with comorbidities and -- either compounding or missing data for that endpoint.

I guess we also had some discussion about how PKP can be different in patient populations with whom we are -- healthy normal volunteers to your sick populations. Then we did talk about the utility of animal models and the trickiness of them being actually relevant and not knowing that until you do the experiment in people to validate them. And I guess, yes, I think those were the major themes I captured.

MR. IARIKOV: Right, and I don't have much to add. I think we talked about the importance of -- also talked about the importance of sample size. We talked about the importance of the sample size and the study that dovetails with the importance of appropriate endpoints and maybe to all enrolled subjects and account for early discontinuations which could be critical in these trials and the importance about natural history data to inform us on the trial designs and help maybe to interpret data mortality

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imbalances. And yeah, I think it covers. All right, so we're adjourned for lunch. And from 12:35 exactly to 1:35, we'll have a hour. And we'll open our next session with public comments at 1:35 sharp.

(Recess)

MS. NAMBIAR: Speaker at the public comments is Dr. Grint from AmpliPhi Biosciences.

MR. GRINT: Thank you very much. Good afternoon, everybody. My name is Paul Grint. I'm CEO of AmpliPhi Biosciences. We're a company focused on bacteriophage development based in San Diego. Very much enjoyed this morning's discussions. It's been very, very interesting. But I'm going to just have a couple of slides in a few minutes to add a slightly different layer of complexity, I think above and beyond what we've already talked about this morning as we consider natural bacteriophage development.

So by background I'm actually an infectious disease physician, but have been in the industry a very long time, privileged to have worked on a number of products in antibacterial, antifungal, antiviral space. But I've now been involved for last 3 years

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with bacteriophage development which I must say certainly has been a real education for me.

So just to remind you, bacteriophages were actually discovered just over a 100 years ago. So we've known about them for a long time. But it's really only more recently that we've really tried to develop them as proper therapeutics. Having said that, many people were really not aware that they were actually sold as therapeutic products back in the 1930s by some of the larger pharmaceutical companies both in Europe and the U.S. at that time but really disappeared from the scene as antibiotics became -- penicillin in particular became more broadly available in the 1940s.

So just quickly about bacteriophage biology, if you're not aware of it. Of course this is a natural virus, the so-called predator of a bacteria. It infects the bacteria. We're talking about lytic bacteriophage here now. Infects the bacteria, binds to a very, very specific binding site on that bacteria, so phages are very specific, which is good news in some ways. But obviously a challenge when it

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comes to drug development. Obviously DNA is injected, there is replication that goes on and the bacteriophage lysis the bacterial, releases progeny virus that go on to infect other bacteria in the vicinity. So that's a bit of basic history, so a basic lifecycle.

So if you think about it, these are very, very interesting organisms. So the question is how do we harness them and use them as potential therapeutics. So our approach has been to build bacteriophage libraries, screen these and select a limited number of products that actually have broad spectrum across the specific bacteria strain that we're interested in. And currently we actually have a staph aureus product and pseudomonas product, a pseudomonas aeruginosa product in the clinic soon be entering Phase II clinical trials. But what I wanted to do today was just to highlight some of the difficulties or differences that we think about and face when it comes to administering, in essence a live virus which when it gets to where you want it to get to, which is a pathogenic bacteria will in fact

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replicate, create more of itself, obviously locally in that environment. But once that infection is cleared it is then naturally cleared by the body.

So we had an interesting discussion this morning, obviously, you know, talking about potential dose selection for antibodies. So think about a dose selection for a bacteriophage. This is not very easy as you can think about it because clearly the dose you administer doesn't necessarily affect the dose or concentration of bacteriophage you're going to end up with at the site of infection.

Persistence in unaffected animals really is unrelated to what you see in infected animals. And we have done bacteriophage kinetics in humans, limited amount of work, but if you inject these IV and that's how we generally treat, within an hour or 90 minutes they're actually cleared from the bloodstream. So it doesn't really tell you very much. But clearly that's as much information we have.

Moving on to PKPD. So obviously as long as sufficient dose is reached at the site, then we -- and replication is initiated, then obviously as I just

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said, serum concentration really is not relevant in terms of predicting what we're doing. So I'm not going to go in too much the detail, but I'm trying to give you some ideas.

And preclinical toxicity, so studies in unaffected animals may obviously show you some toxicity of the manufactured product, but obviously don't really reflect phage exposure locally in a given organ or tissue that happens in an infected animal.

So I just very simply put a table together again just to drill into a bit more detail to highlight some of the differences and maybe just to help you understand some of the things we think about every day as we take what is known about the bacteriophage science and we try and translate that obviously into the clinical setting.

Sensitivity testing. Yes absolutely, you can test the sensitivity to bacteriophages and we do that. And clearly that's -- we do that on the samples before we treat patients and then subsequently as patients are going through patient treatment. But it's not what we used to, it's more molecule antibiotics being

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MIC based. So we're still really trying to understand what that means, you know, what does an intermediate sensitivity look like for bacteriophage.

PKPD models. Again, we've done some work in the space. We'll continue to do some. But the real question is how relevant are these given some of the bacteriophage biology that I just briefly discussed. That's a very, very interesting question.

Proof of concept animal models. Yes, we have conducted some of these in some of the classic models, let's say, of, you know, pseudomonas pneumonia or other ones we can demonstrate that bacteriophage dosing is similar to -- has similar effects to in terms of efficacy to some antibiotics. But again how far do we take this. We had this interesting discussion this morning that really one needs to get into the clinic, I think, to understand more before you can really understand how useful some of these translational models are and do they really translate.

So our idea is move forward to the clinic as much as we can and then try and take that information

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back and refine the models by the predictors of what we might see clinically.

Toxicology. Again we've done limited work. But the question is when you think about a lot of the conventional toxicology that's required, the small molecules, how much of that is really relevant for what we're trying to do. And again, we're trying to work that out as we go along.

And finally, clinical experience. You know, many, many tens of thousands of patients have been treated with bacteriophages over the decades. That information is really very sparse and not very helpful as one thinks about a more conventional sort of regulatory package. You may have seen that there are now a growing number of case reports that are coming out on an individual patient basis. We're actually publishing some of these right now ourselves.

We've been working very closely with CDER on the expanded -- single patient expanded access program under the emergency INDs where we have been able to treat quite a number of folks now at a limited number of institutions in the U.S. and in Australia and

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capturing that data. And that's useful and it helps guide perhaps narrowing some degrees of dose selection and duration of therapy and the types of patients that we may treat in the future.

But really for us to really understand the potential of bacteriophage therapeutics, we do need to move forward into randomized clinical trials. And we are heading towards that in the early part of next year and I really look forward to try to being able to investigate bacteriophage therapeutics as an adjunct to antibiotics in some of the real multi-drug resistant infection settings. So thank you for your attention.

MS. NAMBIAR: Thank you, Dr. Grint. Our next speaker is Dr. Wagner from EnBiotix.

MR. WAGNER: Good afternoon, everyone. So EnBiotix is an engineered antibiotics company founded on the synthetic biology and artificial intelligence platforms of the Collins Laboratory at MIT. Jim Collins is a noted researcher in this area and has licensed to us a number of exciting platforms shown here, ranging from engineered bacteriophage just

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following on to Paul's stimulating presentation to Tunable Target Degradation where we can tag any bacterial gene of interest and whether that's nonessential or essential and then selectively degrade the protein product of that gene. A very powerful tool for target identification, target validation, pathway elucidation.

Anti-persister where we use artificial intelligence to elucidate bacterial physiology in order to develop potentiators of existing antibiotics. We've tackled the aminoglycosides first, we have potentiators of both tobramycin and amikacin in development, but we've extended that now to fluoroquinolones as well. And then we acquired the LPA platform, seem down at around 6:00 p.m. here, as initially a payload for engineered phage. However the profile that's emerging with these LPAs as standalone therapeutics is very exciting. This is our portfolio. Generally speaking, a mixture of both in-licensed and in-house developed products.

With respect to LPAs, as you all know, some of today's most successful antibiotics are peptides.

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We acquired this actually from a laboratory in Germany that had been funded by both Boehringer Ingelheim Venture and Novartis Ventures. So far the profile is very unique, very novel mechanism of action, very good potency, broad spectrum gram-positive, gram-negative activity. Very low mammalian cell toxicity as well. And we've demonstrated this both in vitro and in several animal models so far.

You see here that the difference between these LPAs and traditional antimicrobial peptides is, as you know, the previous generations of these types of molecules have shown high mammalian cell tox because they have been primarily membrane disruptors. And that's the mechanism by which they call -- cause cell lysis. In our case we're actually targeting the ribosome. I will get into that in a moment.

The two classes of these that we're developing, they're both insect-derived, one from the honeybee, another from the milkweed bug. We have extensively derivatized them from the starting peptides, not only to be more prolene rich which confers some of this antiribosomal activity, but there

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is a number of other properties that we've been able to design into the molecules as well.

There are specific transporters in the inner membrane that are very, very redundant for both classes of LPAs that we are developing. We've done some fairly extensive resistance development studies that show that the redundancy here is thought to confer a strong resistance to resistance development, so we're quite encouraged by that so far.

There is a few mechanisms of action that are involved in terms of being antiribosomal. First with respect to the Apidaecin class. We have two that we're investing, one is ribosome subunit assembly. Thus far by a unknown mechanism of ribosomal assembly inhibition we are investigating that. We're still -- it's too early to publish on that yet.

The other mechanism which we have published on, not shown here, is whereby release factors in the ribosome are inhibited which then prevent the elongated peptide from the ribosome from being released.

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In the Oncocin class we actually blocked the entire exit tunnel of the intact ribosome. This is actually we think quite significant for a number of reasons. We think that the mechanism by this blockage is really steric hindrance along the entire exit tunnel. And because it overlaps several known binding sites to other antibiotics, again resistance development is very slow.

We have good in vivo efficacy thus far for both the Oncocins and the Apidaecins. Here is an IP model on the left and showing both very good survival data in E. coli and Kpn. Thigh Burden Model for both Oncocins and Apidaecins. Here showing Oncocins with a 4 logger, so a reduction in CFU recovery in Thigh Infection Model. Apidaecin, similar types of reductions and similar types of survival curves in the IP model as well.

We are continuing to derivatize both classes in order to expand spectrum to both gram-positives and gram-negatives. That's shown on the bottom particularly. Potency is quite good, especially when viewed from a molar level. Very comparable to other

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agents that are out there obviously because these are peptides molar comparability in terms of MICs does amount to a slightly higher dose, but still something that is administrable. With that, happy to take any questions if that's allowed. If not, thank you.

MS. NAMBIAR: Thank you very much. So our next speaker is Dr. Lajaunias from Combioxin.

MS. AZEREDO: Thank you for the opportunity to say a few words about our efforts to move forward with a nontraditional agent named CAL02. Combioxin is a very small Swiss company and we develop liposomes as anti-infectives. Since 1995 more than 10 liposomal formulations have been approved for human use. All of them have been used as vehicles for an active drug. None of them have been described with a pharmacological activity of their own. These are biologically neutral compounds.

And we've been working on liposomes in a very novel manner. We engineered specific mixture of anti-liposomes that can mimic cell lipid microdomains used as docking stations by numerous bacterial toxins. Preclinical studies have shown that when given the

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choice to target cells or these anti-liposomes, toxins fully bound to CAL02 irreversibly. So the mode of action of CAL02 is to act as a winning decoy in order to entrap and neutralize a large panel of toxins. Here the liposomes are the active agent.

As you all know, toxins are bacteria's most deadly weapons. They play a key role in a number of components of severity that may lead to long-term or even fatal complications. CAL02's activity is complementary to that of antibiotics which effectively kill the bacteria, but fail to neutralize these toxic missiles. It is however independent from antibiotic's MIC or class.

It has a unique broad-spectrum activity against both gram-positive and gram-negative bacteria including some escape pathogens regardless of the resistance profile, and it does not prompt any resistance on its own. And because it entraps these toxic components that play an important and upstream role CAL02 is expected to have a wide therapeutic impact including an organ dysfunction or inflammation.

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Preclinical studies were carried out against a number of toxins and bacterial strains. Toxins neutralized by CAL02 include pneumolysin or streptolysin, alpha-hemolysin or PVL. And in vivo studies were performed with a view to translating at best the clinical situation. So pneumonia and bacteremia models CAL02 are systematically used hours after an infectious challenge. And in some cases hours after the start of antibiotics. And infections were caused by strep pneumoniae or pseudomonas or staph aureus including some MRSA strains such as USA300.

And overall, results highlighted that adding CAL02 to antibiotics improved outcome. I'm not giving much details about the preclinical studies, but we also observed that CAL02 alone as a monotherapy could provide full protection. We met -- we had a scientific advice with the U.K. agency to discuss the preclinical package and a first-in-human trial directly in patients and we used the VHP to launch the trail in France and Belgium. And this first-in-human trial was recently completed.

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It was a randomized double-blind placebo controlled study that was composed of three arms, CAL02 -- namely CAL02 low dose, high dose or placebo in addition to standard of care. And the primary objective was of course safety and tolerability. Now for this first assessment in human we decided to focus on a specific population, severe pneumococcal community-acquired pneumonia for a number of reasons. Importantly, it still addresses a huge medical need since considerable percentage of patients still developed complications, need to be admitted to the ICU where they spent about 2 weeks and where mortality rates still surpasses 30 percent despite best available care.

CAL02 was administered intravenously twice within 24 hours and after first group of patients were treated with either CAL02 low dose or placebo and IDMC reviewed safety, dose was escalated to the high dose and this IDMC reviewed safety once again after first group of patient was treated with CAL02 high dose or placebo to allow continuation.

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The severity of the 19 patients that were finally recruited was as expected by the protocol. More than half of the patients were in septic shock at baseline and more than 40 percent under invasive mechanical ventilation. Overall, placebo patients were less severe than those randomized to the CAL02 treatment arms with a mean APACHE II of 17.4, for example, as compared to 25.3 or 22.1 in the CAL02 treatment arms.

And also all bacteremic patients were in the CAL02 treatment arms. The primary objective was safety and tolerability. All AEs were in line with the profile of the study population. There was no concern raised regarding safety. And regarding exploratory efficacy, there was one death in each arm and all surviving patients were cured at TOC. However, at early TOC on day 8 which was set 1 to 2 weeks earlier than TOC, more patients in the CAL02 high dose arm were cured, 56 percent versus 20 in the placebo arm, and this translated into a shorter time to cure. This arm also presented a shorter duration of invasive mechanical ventilation.

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Now for both the CAL02 low dose and CAL02 high dose arm we observed faster improvements of organ dysfunction with a 50 percent decrease in the SOFA score by day 5 versus 12.5 in the placebo arm. We observed a protection and full stabilization of the hemodynamic parameters versus no improvement or even worsening for some placebo patients and a faster normalization in inflammatory biomarkers.

So all this is in line with the mechanism of action of CAL02 and was translated in a shorter ICU stay, length of stay of 5 days for the CAL02 high dose arm versus 12 for the placebo arm. By the way, this length of stay for the placebo arm is in line with that described for patients under standard of care in similar populations in recent trials.

So overall, no parameter got worse with CAL02 high dose enough to plan another larger trial. And our priority now is to meet with the FDA and help authorities to discuss the next step.

We are here with a broad-spectrum agent, quite different from other antitoxins in development. It has the potential to be used on top of any

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antibiotic standard of care treatment to improve standard of care for severely infected patients. We will have to show superiority, we need to decide on the study populations and the endpoints. And we certainly want to address the full potential of CAL02 and expand to other pathogens including MDR strains. Thank you.

MS. NAMBIAR: Thank you and our next speaker is Dr. Mannino from Matinas BioPharma.

MR. MANNINO: Thank you very much for giving me the opportunity to speak to you today. What I'd like to do is to tell you about a process that we have, a little lipid nanocrystal that allows us to take traditional pharmaceuticals, antimicrobials and deliver them by a very nontraditional process.

This is just a way of pointing out that along with the physiology that bacteria change enzymes, ways of rejecting drugs from the cell, a lot of microbial pathogens find a way to get into the cell and to take over the animal cell physiology, for example preventing destruction by macrophage. And they use the interior of the cell in two ways; one to grow and

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multiply, but the other way to avoid the ability of very potent antimicrobial drugs such as aminoglycosides, for example, to get through the membrane and attack them. So they hide from the drug there.

What I'd like to show you today is a little lipid nanocrystal that we are using which enables us to deliver very, very safely and in a very targeted fashion the antimicrobial drugs into the interior of the cell. This lipid crystal is formed simply and we have this now at GMP scale so we're making 100 liter batches of this. So it's a little nanocrystal which forms from the addition of calcium, and this is very unique to calcium to a lipid cell made of phosphatidylserine.

So the process is you take your liposome, you add your API to it, you drip in calcium and the liposome changes. It goes from a fluid structure, sort of like water changing to ice. The lipid structure of the bilayer turns into a crystal and it rolls up. So the process you see here is the little nanocrystal, multilayered, highly stable. As long as

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there is enough calcium and enough is only about 0.5 millimolar, this crystal with the drug on the inside can be boiled in detergent and it won't open.

That provides high stability in two ways. Number one, because this is an anhydrous process unlike a liposome or a lipid nanoparticle, which has a fluid bilayer and some sort of water associated with this. As this crystal forms, it ejects the water. So it's an anhydrous process, so it eliminates hydrolysis and the material on the inside is not susceptible to oxidation. So we stabilize it on the shelf, that's number one.

But number two, because physiological calcium on the outside of cells is between about 1.5 and 4 millimolar, when you introduce these particles into an animal, either through IV, IM, or through oral or intranasal delivery because there is enough calcium in gastrointestinal secretions for example, the crystal does not open.

These crystals then enter the gastrointestinal tract and the pharmacokinetics suggest that it goes across the GI tracts through the

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lymphatics at which point you still have the drug in the crystal. And I think this is a very unique phenomenon because we are hiding the drug from the body and you'll see the toxicity effects. The reduction of toxicity is a consequence of this.

So we've shown it reduces environmental attack and it reduces attack by the body. So now, how does this crystal with the drug inside actually deliver anything that can have an effect? Well, it turns out this calcium and the lipid we're using is a negatively charged lipid called phosphatidylserine. This is a process that is used for example for the secretion of neurotransmitters and synapses or the secretion of adrenaline in the adrenal cortex.

The calcium channel opens the intracellular calcium is about 1,000 to 10,000 times lower than extracellular and that's to prevent membrane fusion on the inside of the cell which would destroy the integrity of the cell. So what happens is if you want the release of adrenaline, the body sends a signal to the plasma membrane, the calcium channel opens, calcium goes in, binds negatively charged lipid and it

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makes membrane fusion, and the adrenaline is released.
This natural membrane fusion process, it has no positively charged lipids, it has no proteins. So we reduce toxicity, we reduce inflammation, we reduce any immune response to these crystals and you can see here in the picture we have a fluorescent dye in the little aggregative crystals interacting with spleenocytes and you can see how the fusion of the crystal membrane, because this is an intermediated membrane fusion with the target cell now allows the delivery of the drug into the cell. So it's naturally taken up by cells, it is taken up by activated cells such as activated macrophage neutrophils. We've also delivered it to virally infected cells.
In healthy animals you see very little targeted distribution. In infected animals you see highly targeted to the site of infection and you also see very, very low blood levels. I'll show you some of the tox studies that we've got. So we're fundamentally changing the pharmacokinetic dogma. We're saying that we get very low blood levels, which gives us low toxicity and very high targeting to the

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target tissue and very good efficacy.
So I just gave you some examples of the three of the drugs that we are using. Our lead product is Amphotericin B. We are in Phase II clinical trial, I'll show you some data of that, at the NIH Clinical Center right now. But you can see in animal studies it's worked against Candida, Aspergillus, Cryptococcus which are both intracellular and extracellular, but it's worked against Leishmaniasis in an in vitro model, which is just intracellular.
The Amikacin data, and I'll show you one slide of that, against mycobacteria, we have that in Phase I and for Francisella we've show in an in vitro model. And with Atovaquone, we've shown that in an animal model of Pneumocystis that again we have very low blood levels, we have oral delivery, we have systemic bioavailability and high efficacy. So let me show you three examples.
This is a study being run at the clinical center at the NIH by Dr. Alexander Freeman, the patients are born with immunodeficiency diseases which make them highly susceptible to mucocutaneous

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candidiasis. Because they were treated with azoles for long periods of time, they're azole resistant.
Amphotericin, you know, has been around for a long time. If you give any of the IV formulations, more than 2 or 3 weeks you begin the kill the kidneys. The literature tells you that giving a human being more than 3 grams of Amphotericin in your life will cause kidney damage. You can see the patients that we have here, we've had two of our patients on the drug for over 545 days at the same doses. The clinical symptoms have been reduced. The study protocol is 50 percent. Most of these women now are living clinically free of the disease and there are no kidney problems, and they've all signed up to maintain a longer term on the protocol because if they come off the drug because they don't have an immune system, the Candidiasis comes back.
I'm going to show you some data that we're doing. Dr. Peter Williamson at the NIH with his mouse model of cryptococcal meningoencephalitis. And I don't have any of the efficacy data but Dr. Williamson has shown that the oral Amphotericin in this model is

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as effective as injectable Fungizone. But what he wanted to do is see actually can you give this crystal orally and have it appear in the brain, going across the blood-brain barrier.
And so we gave him rhodamine-labeled Amphotericin crystal that he gave in his mouse model and you can see the top two panels that we were not treated, so there's no rhodamine in the brain. In the bottom one, they're infected with crypto, but they were not given any drug, but in the third panel down you can see in the infected treated animal there are high levels of the Amphotericin rhodamine particle in the brain at the site right by where the crypto -- the yeast is.
Finally, with Amikacin, this is a cystic fibrosis mouse model that we are in collaboration with Dr. Diane Ordway of Colorado State. And in cystic fibrosis you have two levels of barrier to get through to treat mycobacterium. One is the intense mucus that you have in the lung which prevents material from getting down into the lung and then the second one is again the cell membrane. How do you get a highly

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charged water-soluble aminoglycoside like Amphotericin into these sites?

Our hypothesis for how these lipid nanocrystals target and deliver suggested that rather than trying to get through the mucus into the infected tissue we would give this orally and macrophage which originate in the bone marrow as monocytes, as they evolve. That the macrophage which are activated because of inflammation would pick up the crystals, the Amikacin would be released as the macrophage travel into the infected lung. And you can see here that we have very strong efficacy in all lung, spleen and liver. And Dr. Ordway did the Pathology and you can see both in the low dose and the high dose of the Amikacin and the lipid crystal the lesions in the lung are essentially gone after long-term treatment.

So basically what we say we have is a very nontraditional way of being able to deliver highly potent and well-understood antimicrobials. We can increase the oral bioavailability of injectable drugs. Both Amphotericin and Amikacin are only available by injection at this point. We use a natural targeting

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to get the drug to the site of the infection or the inflammation. We have very low blood levels, which is a wonderful blessing because we have very low toxicity, but it's kind of a curse when you're trying to figure out how do you bring a drug forward when the plasma PK does not tell you anything about the efficacy, okay.

This material right now we are making again routinely 100 liter batch, the particle size is highly reproducible. The encapsulation of the drug is highly reproducible and it's made from a soybean lipid. So the matrix again is simply soybean, phosphatidylserine and calcium, very safe, very nontoxic. Because there is no water in it you can either save it and deliver it as a crystal suspension or you can spray dry it, laphalyze (ph) it, we've done all of those things and it works.

Again we're in human clinical trials and for those of you who are interested also in the nucleic acid polymer world, we're using this now to try to achieve intracellular delivery of nucleic acid polymers as well. So thank you very much for letting

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me speak today.

MS. NAMBIAR: Thank you, Dr. Mannino.

Our last speaker in this session is Dr. Leininger from Aridis Pharmaceuticals.

MS. LEININGER: Good afternoon, I'm Lizzy Leininger with Aridis Pharmaceuticals.

Like to talk a little bit about the products we are developing at Aridis Pharmaceuticals and some of the challenges that we are facing. We actually have a repertoire of like three or more antibodies, antibacterial human monoclonal antibodies that are under clinical development for acute pneumonia.

I'll talk about AR-301 which is against staph aureus alpha-toxin, AR-105 which is against Pseudomonas aeruginosa alginate, and AR-105 which is against Pseudomonas aeruginosa LPS. So all of these are targeted against the bacteria. These are fully human monoclonal antibodies that have been made by Ardis' proprietary technology where we are able to make them from the B-cell repertoire of convalescent patients. They're fully human to start with.

We are in different phases of development

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ready for Phase III with our Pseudomonas aeruginosa antibody and going on we are in Phase II with AR-105. We are looking at these antibodies as adjunctive treatment with -- to standard of care of antibiotics. And the reason we're looking at it as an adjunctive therapy is really to avoid commercialization risks that were discussed earlier today, which is associated also with the prevention in the low attack rate and we're looking at a preventive mode. So we are in the therapeutic mode here.

We are also looking at clinical superiority, since we're in an adjunctive therapy to standard of care and we are looking at superiority based on clinical cure, which I'll talk a little bit more about that. And we are in VAP patients, so in ventilator-associated pneumonia and hospitalized patients.

So I'd like to discuss just a little bit, present some of the development challenges that we have been facing, developing these therapeutic monoclonal antibodies. And as we had discussed this morning and it was presented, of course we are facing challenges with the study design. And this is really

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based on the patient population that we are dealing with.

Here we are hospitalized patients that are ventilated, so that whole setting is a little complicated. We are also looking at pathogen-specific infections in these patients in addition to other associated infections that they may have. And we are also giving it as an adjunct therapy to the standard of care of antibiotics. So just standardizing standard of care is another challenge itself in these trial designs.

So in addition to the trial design setting itself, we are challenged with the definition of our clinical endpoint. We've been challenged all cause mortality as a clinical primary endpoint and we have also brought into the discussion and have agreement with the agencies to use clinical cure as a primary endpoint.

The problem with clinical cure as your primary endpoint that's not a standard definition, so we have been negotiating the clinical cure definition based on clinical meaningful parameters and also

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parameters that are measurable. So we have been in consultation with FDA, with the EMA, with key opinion leaders to come up with a consensus on our definition of clinical cure for this specific setting of our pathogen-specific pneumonia in the VAP population.

In addition, we have also -- have challenges along the size of the safety database and trying to understand what is the minimum safety base that would be required to be able to bring this product to the market. In many of our discussions, the database suggested has been larger than maybe what required to demonstrate efficacy and based on that this is a limited population.

So in addition to having hospitalized VAP patient in a ICU setting, we are also dealing with these are unmet medical needs and we're dealing with in some of our indications with orphan drugs, so there's a very limited population. And so trying to define what that minimum safety database is, sometimes the magic number of 300 shows up. But we would like to challenge and understand more based on the product safety profile and the patient population and the

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indication that we're dealing with.

We also have challenges in our development program with the CMC area. I'm not going to go into detail. These are monoclonal antibodies that as we start early on in development and then move forward there's always going to be optimization to outline changes, manufacturing changes, so we have to deal with those comparability issues independent of treating antibacterials.

And finally, I'd like to talk a little bit about the challenges and the need for effective communication with the FDA and with regulatory agencies in general. As I mentioned, not only are we in these new therapy approaches for bacterial therapies, infections, we're also in orphan drug setting and we're also in unmet medical need. So there is an urgency to get these products out there and to demonstrate they are effective and safe and get them out there to the population.

And having an effective way of communicating with the agency is really critical. And we believe that we want to pave the path together because we

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don't have that regulatory precedence of other therapeutic products to understand what needs to be done and what's required. We are paving a new path here and we really want to partner with the regulatory agencies in doing so.

There is a big need for the timing of these communications and we are very thankful that we have very good relationship with the agency in communication and their doors have been open to us with all the standard PDUFA meeting settings and we have set fast track designation et cetera. But sometimes I like to challenge a little bit more what is the optimal timing besides the PDUFA standard meeting and questions.

If we have additional pre-IND meetings or questions or during the IND review or prior, post IND meeting, pre IND meeting and before filing your IND mechanisms to communicate in an efficient manner. And I asked the agency what are the best mechanisms to do that for us to provide them adequate information and get a speedier feedback.

Normally we get 4 to 6 weeks when we have

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submissions and request for consult offline from the PDUFA meetings. And then finally we're also in a global development, so in order -- we're looking for mechanisms. And one of our challenges is to expedite how we get global consensus, because we're going to the FDA, we're going to the EMA, we're with key opinion leaders to really understand the practice of medicine and how to expedite our drug development for these novel therapies.

I would like to encourage to have additional workshops like these and maybe even more focus, like clinical cure definitions where we can bring all those key opinions leaders and experts in a room and define these kind of endpoints that are critical in these novel therapies. And maybe I'd like to propose if there was a mechanism with the agency just to have brief pause with them. You know we're using e-mails and everything and we have our conference calls with, again, preset conference with PDUFA meetings, but is there a mechanism to have "informal" communications orally with the agency in addition to written? Thank you.

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MS. NAMBIAR: Thank you, Dr. Leininger. Should we take a couple of minutes break --

So Kevin's recommendation is that we all take a 1-minute stretch break. I think it looks like post lunch people are tired and --

MR. OUTTERSON: One minute.

MS. NAMBIAR: One minute.

(Recess)

MS. NAMBIAR: So let's move into session 3 that Kevin and I will be co-chairing. So this is a little different from the previous session. This is a two-part session. We will have two case studies. A panel discussion after the first case study. We'll take a short break and then discuss the next case and have a final discussion for that case as well.

So just to give you a little bit of background about the intent of this session. The first case will be presented by Ramya Gopinath, who is a Medical Officer in the Division of Anti-infective Products. Ramya will discuss a hypothetical case of a drug that minimizes the effect on the gut microbiota following exposure to antibacterial drugs. The

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emphasis of this case is on the outcome that can be evaluated if such a product were to be developed, where clinical benefit can be demonstrated in a patient who is receiving such treatment. And Dr. Kaleko from Synthetic Biologics will give his perspective on the case, and followed by some comments from Ramya on the case.

The second case will be presented by Dr. Rex. This case, the attempt is to highlight a different aspect on the effect on gut microbiota where a hypothetical case of a drug that reduces the prevalence of MBL producing organisms in the gut of an individual who has received this drug will be discussed. The intent in presenting this case is really to have a discussion about the scientific challenges that one might encounter in developing such a product where the benefit to the patient might be difficult to demonstrate. However, there is a potential for such a product to have an impact on the community. And so we have sort of two slightly different cases. We're discussing very similar effects on the gut.

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So with that Ramya, we'll have you present the first case. Thank you.

MS. GOPINATH: Good afternoon everyone. Seems very appropriate to be talking about the gut microbiome as our own gut microbiomes are digesting lunch. So I'll start by presenting the first case study. So this is drug Z2 for prevention of C. difficile infection by minimizing disruption of the gut microbiome.

So to begin with just let's consider the principles of therapy here. Antibacterial use disrupts the gut microbiome, reduces alpha diversity and is known to reduce colonization resistance of two antibacterial resistant bacteria. The extent of disruption is dependent on the concentrations of antibacterial drugs achieved in the gut, the degree of local inactivation of these drugs, and the duration of therapy.

Selective pressure from antibacterial drugs inhibits susceptible members of indigenous flora and facilitates overgrowth of antibacterial resistant flora which includes C. difficile. Drug Z-2 reduces

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the concentration of beta-lactam drugs in the gut, thereby potentially decreasing the incidence of C. difficile infection which are referred to as CDI and potentially decreasing the disruption of the gut microbiome.

So known clinical studies in vitro rapid and complete dissolution and release of drug Z2 from an oral delayed release formulation to be used in clinical and pharmacological studies was evaluated. Stability of drug Z2 at different levels of the gut environment, that is at the action site in intestinal chyme and with intestinal contents has been evaluated.

In vivo studies include a 28-day dog safety study with placebo versus varying doses of Z-2, that is 15, 30, and 60 mg/kg/dose, administered three times daily, so a maximum of 180 mg/kg/day. And in these studies drugs Z-2 was well tolerated. There was also a 14-day dog study with drug Z-2 and administered in conjunction with beta-lactam drugs and no interaction between the two was demonstrated with no significant effect on the plasma PK of the beta-lactam drugs.

Once again drugs Z-2 was well tolerated. So

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if we move onto the Phase 1 studies in healthy volunteers, they were both single and multiple ascending dose PK studies. So single oral doses of 10 milligrams to a 1,000 milligrams and multiple oral doses of 10 to 200 milligrams administered every 6 hours for a week were evaluated.

Drug Z-2 was found not to be systemically bioavailable except at the highest dose, that is 1,000 milligrams where systemic concentrations of 6 to 8 nanograms/mL could be detected. However, most plasma concentrations were below the lower limit of quantitation for the assay which was 1.5 nanograms/mL.

In the Phase Ib and IIa studies, clinical studies were done to confirm the mechanism of action in the human intestine. So in these studies healthy subjects with functioning ileostomies were administered drug Z-2 with serial sampling of intestinal chyme to ascertain levels of drug Z-2 and a variety of beta-lactam drugs. In these studies plasma PK or beta-lactam drugs was found to be unchanged. However, intestinal concentration of these drugs decreased significantly with the action of drug Z2.

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In addition, drug-drug interaction studies were done with compounds that alter the PH of the gut, such as proton pump inhibitors or the composition of the gut microbiome, i.e., probiotics.

So for the Phase II study it was necessary to have an endpoint that could be measurable. And prevention of CDI was used as such an easily measurable clinical endpoint. So in this study design it was a parallel group double-blind placebo-controlled multicenter trial conducted to evaluate the effectiveness of drug Z-2 versus placebo for prevention of CDI in hospitalized patients receiving beta-lactam drugs for various non-GI infections.

So, in other words, it was used in conjunction with beta-lactams. The duration of treatment with drug Z-2 administered three times daily was concomitant with and for 72 hours after the course of therapy with beta-lactams and patients were followed for about 6 to 8 weeks.

The efficacy endpoint was prevention of CDI for 4 weeks following the start of treatment with beta-lactam drugs. In this study 300 patients were

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enrolled per study arm, 55 percent were male and the mean age was 67 years.

The following results were observed in the drug Z-2 versus placebo arms. There was lower incidence of CDI in the drug Z-2 arm 3 percent versus 5 percent in the placebo arm, reduction of colonization with C. difficile as well as Vancomycin-resistant Enterococci, 5 versus 9 percent at 72 hours when we looked -- when they looked at C. difficile. And in addition colonization with extended spectrum beta-lactamase producing gram-negative bacteria was found to be similar between the groups and no different from baseline.

Further there was no effect on the incidence of antibiotic associated diarrhea, which was not associated with CDI. So the questions for the panel that arise from this case study are the following, what are some important clinical trial considerations for these kinds of products with respect to trial design and endpoints? How does the expected higher mortality in the population that might be at greater risk for CDI factor into the endpoint?

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Is being alive and free of CDI the only appropriate endpoint? Besides reduction in CDI are there other endpoints that we could consider as clinically appropriate? What -- are there other measurable benefits of such products and if so what are they? And our study results from these trials generalizable to populations beyond those evaluated in clinical trials. So for example, to individuals who receive other antibacterial drugs. Thank you.

MS. NAMBIAR: Thanks Ramya. Dr. Kaleko --

MR. KALEKO: Thank you very much. By way of disclosure I am an employee of Synthetic Biologics and I am familiar with the development of products similar to Z-2. Z-2 is designed to be used prophylactically to degrade beta-lactam antibiotics in the small intestine to protect the downstream colonic microbiota and could have potential benefits at three levels.

At the level of the patient it could diminish the risk of CDI, prevent colonization of the colon by multidrug-resistant pathogens and prevent secondary infections caused by these pathogens. At the level of the hospital it could diminish the spread of CDI and

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of multidrug-resistant pathogens. And at the level of the population it could generally diminish the delivery of antibiotics to the colon as if the antibiotics were being used less frequently, like a form of antibiotic stewardship.

However since it's intended for prophylaxis Z-2 faces hurdles in clinical development. First and foremost, the primary efficacy endpoint CDI is a rare event with an incidence less -- less than 5 percent in the placebo group. Thus to convincingly demonstrate the Z-2 diminishes the incidence of CDI may require prohibitively large phase three studies and that's the crux of the problem, how do we diminish the cohort sizes?

Second, patients who are at greatest risk for CDI are those who are most debilitated and have a mortality rate that greatly exceeds the CDI rate, thus it is necessary to separate the safety and efficacy endpoints so that the high mortality rate does not obscure a reduction in CDI. If for example CDI goes from 5 percent to 2 percent, that's measurable. If you roll in a 10 percent mortality and it goes from 15

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to 12, that's less measurable.

Finally, even studies with large cohorts run the risk of low numbers for the primary efficacy endpoint. Thus if patients lost a follow-up or consider drug failures cases of CDI, this could quickly bias the efficacy analyses. So I'd like to suggest a strategy to deal with these limitations specifically when considering the balance of risk and benefit for Z-2 shift the emphasis to establishing appropriate safety then bolster the efficacy outcomes with ancillary information to establish a reasonable expectation of clinical success.

The basis for this proposal is that the demonstration of safety is key especially for prophylaxis. And due to the high mortality rate in the target patient population should be achievable with small cohorts. In contrast it's the efficacy endpoint that's the one that requires the large cohorts. So what ancillary data could be considered to shore up the clinical efficacy data? Well let's start with the microbiome. First, the bad news. To the best of my knowledge there's no definitive

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microbiome or metabolome changes that predict impending CDI in patients exposed to C.diff. So I actually support the conclusion that the microbiome does not yet provide a surrogate endpoint for clinical disease.

However, in Phase IIb Z-2 diminished new colonization of VRE and C. diff. These endpoints could be more predictive than microbiome analyses for clinical outcomes. Since the 1950s we've known that seeding from the gut can cause secondary infections, more recently a 2012 paper from Eric Pamer's Group at Sloan-Kettering showed that in bone marrow transplant patients antibiotic mediated mono-dominance with enterococci increased the rate of VRE bacteremia nine fold and mono-dominance proteobacteria increase the rate of gram-negative rods in the blood by fivefold.

Additionally, four recent papers show that colonization of the GI tract with multidrug-resistant organisms and in particular new colonization was associated with increased morbidity and mortality. Taken in reverse, we can be confident that patients who do not experience new colonization with VRE and

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CDI are not likely to suffer infections with these bacteria. So perhaps a diminution of such colonization could be considered ancillary data to support the clinical CDI results.

Alternatively, could we bolster the efficacy data with mechanism data, that is microbiome protection. For example, for a product like Z-2, one with which I'm familiar, protection from antibiotics was first demonstrated with dog chyme and pig microbiome studies. The same findings were then reproduced in human chyme and human microbiome studies. Thus the translational data across two animal models and into humans support the mechanism of microbiome protection and suggest that the CDI efficacy data albeit with small numbers are in line with what we predicted.

So what I'm proposing is that with an emphasis on safety perhaps we could use these ancillary strategies to achieve sufficient comfort with efficacy to circumvent the need for prohibitively large Phase III studies.

Of course the sponsor would need to provide a

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commitment and plan for Phase IV studies to nail down any efficacy questions and of course obtain additional safety data. And then -- so I'd like to conclude by thanking the FDA for convening this workshop to explore ways of building flexibility into the strategies to advance these potentially valuable nontraditional therapies.

MS. NAMBIAR: Thank you Dr. Kaleko. Ramya.

MS. GOPINATH: Thank you for your comments. I'll try to present a little bit of the FDA perspective on these types of products. So certainly as we all know, and I think we got a taste of that in the morning session, there is increased and rigorous focus on the role of a balanced gut microbiome in maintaining health. And conversely on potential disruption -- disruptions or disbiosis that may contribute to disease causation.

From a regulatory perspective, the evaluation of a new product such as drug Z-2 intended to minimize disruption of the gut microbiome poses challenges. Most importantly, one has to identify a clinically meaningful endpoint as change in the microbiome in and

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of itself is difficult to interpret. However, identification of this clinically relevant endpoint related to the gut microbiome is problematic because the exact definition of a healthy microbiome and its variations is still unclear.

The specific relationship between the gut microbiome and disease, for example CDI but even other conditions such as obesity, et cetera is undefined. The measurable clinical significance of a quantitative change in a particular bacterial species such as VRE is still uncertain. The exact effect of antibacterial drugs on the microbiome either as a class or individually is unknown and therefore designing a study or a clinically significant endpoint directly addressing these issues is currently very challenging and almost impossible.

However, one might be able to infer the potential for drug Z-2 to preserve the gut microbiome at least partially by evaluating its ability to prevent or reduce occurrence of CDI when drug Z-2 is administered along with bacteria -- antibacterial therapy.

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CDI is known to be associated with overgrowth of C. difficile bacteria and administration of antibacterial agents especially the quinolones, beta-lactam's and clindamycin and particularly for prolonged durations is a major risk factor for occurrence of C. difficile infection.

We also know that older adults are at greater risk for development to CDI and following resolution of the first episode CDI may recur in as many as 15 to 40 percent of patients. A product that in some way reduces the concentration of systemically administered antibacterial drugs secreted into the gut may therefore aid in prevention of CDI.

However, designing such a trial presents several challenges including the need to define an appropriate study population in terms of age, comorbidities, concomitant medications and previous history of CDI, potential exposure to hypervirulent C. difficile strains, the baseline rate of CDI in these study populations, appropriate sample size and appropriate endpoints.

It may be challenging while it is a goal to

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achieve a balance between trying to enroll the at-risk population with those who have many comorbidities. As my colleague, Dr. Kaleko, alluded to, if the baseline incidence or prevalence or incidence of CDI in a population is low it becomes difficult, so then you -- one has to think of ways to potentially enrich a population.

Trials for prevention of CDI by itself would ideally be defined as placebo or active control -- controlled superiority trials with the primary efficacy endpoint being absence of CDI within a predefined study period. However, the anticipated increased mortality in hospitalized older adults receiving systemic antibacterials who are also the population most at risk for CDI needs to be considered, i.e. if a patient dies during the study period it is impossible to ascertain whether CDI was successfully prevented in that individual.

In addition, a potentially small treatment effect of drug Z-2 may be obscured by the background rate of death or may necessitate a prohibitively large sample size. Important PK considerations would

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include identification of an appropriate nonclinical model for prevention and very importantly evaluation of systemic absorption of the product from both normal as well as diseased gut.

In nonclinical Phase I as well as Phase II studies evaluation of administration with food and drug-drug interactions with agents that alter either the pH of the gut such as PPIs or those that alter the got microbiome such as probiotics. In such a scenario evaluation of the gut microbiome could be included in some predefined way as an exploratory endpoint. Thank you.

MR. OUTTERSON: So I wonder if -- thank you for that -- if I could push back a little bit, trying to find the places where those last two presentations disagree. Because it seems like there's a lot of agreement between the two, you know and we could run through them, but I am -- I am more interested in the gaps where there's not clarity between the two and so for example, you know, how would the FDA view the question of -- you know, he mentioned colonization as being an intermediate, you know, additional endpoint

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in addition to CDI. And the other one that I thought that it wasn't clear to me whether you were on the same point together was, you know, the issue of just the methodological questions of patients' lost to follow-up. You know, maybe I misunderstood, but it seems like the rest of it, you know, you were both ticking very similar boxes to me, which I find to be encouraging. So help clarify if I'm confused please.

MS. GOPINATH: Thank you. So I think in terms of the bacterial colonization, I mean, this is something that really gets at the heart of the discussions that we've been having, what is the benefit. And currently I think you can approach it from a clinical standpoint versus a regulatory standpoint and I think that currently the FDA's thinking on this is that we would approach it as a exploratory endpoint because for the reasons that I outlined in my remarks, it's a little unclear how changes in the microbiome, although they can be documented, what impact it has both to the individual and beyond the individual.

MR. OUTTERSON: And on the methodology of

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patients lost to follow-up and I don't know if, Michael, if you have any comments either.

MS. GOPINATH: So I'll start. And so I think that, you know, again this is -- I think it was alluded to in one of the previous talks as well. This is a difficult problem because the population that's most at risk for CDI is also the population in who, you know, if they're hospitalized for pneumonias or they're hospitalized for some other infection, the death rate is higher in this population and so as was mentioned by Dr. Kaleko, I think if the treatment effect is small, then we really struggle with this because then in order to show that a preventive therapy is working, you need a really large sample size. So I think that's a topic that we're struggling with and that it would be good to get people's thoughts on.

MR. KALEKO: I actually agree that the microbiome is not a primary endpoint. I think some day when we have drugs that work in the microbiome, we'll be able to look back and find those correlates that provide predictive value that doesn't exist at

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the moment. I feel a little differently though about VRE and C. diff colonization because there really is a wealth of literature that show that when you have new colonization, you are likely to have a -- you're more likely to have an infection, you're more likely to have greater morbidity and mortality and that's even as I said, I particularly pulled out Eric Paymer's (ph) work because it's actually quantitative.

So I disagree a little bit about -- in that regard. The way I look at this is mechanistically. Now I used an example of another drug that's little less hypothetical than this one where in dogs, the Z-2 like drug removed an antibiotic from chyme; and then in pigs it protected the microbiome from loss of diversity, overgrowth by expansion of antibiotic resistance genes and then exactly the same thing happened in humans, okay? The antibiotics removed from the chyme in ileostomy patients and then the microbiome is protected from loss of diversity and there is less overgrowth of antibiotic resistance genes.

So the mechanism is consistent all the way

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through, so when you do see a drop in CDI, albeit with small numbers, you can say, you know, this is via a mechanism that we would have predicted. Therefore, it's possible, highly likely -- not highly, let's say likely, I mean I overstated, likely that it's true. On the other hand when patients die, the 10 percent mortality rate, they're also dying by a known mechanism. They have infection. They have COPD. They have high blood sugars. They have high BUNs (ph). And those mechanisms are separate. So if each -- the incidence of CDI and the deaths are taken in the context of their mechanisms, we can actually keep them somewhat separate.

Now that said, that's all hypothetical and therefore, there is no doubt that one needs a large definitive clinical trial to prove this, but whether or not that clinical trial needs to be right up front isn't clear to me as long as the drug really demonstrates an appropriate level of safety. So those are my thoughts. I hope that's in line.

MS. BOUCHER: Thanks. So I just wanted to maybe push back a little bit on the comments about

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this being almost impossible and the need to enrich. I mean this is a very common infection; 500,000 cases per year and that's probably an underestimate and I think I just don't want us to get confused about risk factors. You know, there are risk factors for relapse that we talked about this morning being old or being immunocompromised, but we have young healthy people who get one dose of antibiotic for dental work. Young healthy man who gets one dose of antibiotic for prostrate biopsy. A lot of people get C. diff. This is a common infection and I think that preventing in those individuals is just as important as preventing it in the people with the risk factors.

So I think one should consider even studies in the so-called low-risk group, if that would ease some of -- mitigate some of these concerns. The cost in thinking about this at both the individual patient and in the hospital and the population level is really important and I think harkening back to some of our discussion this morning, you know, the regulatory issues are the regulatory issues right there. You have to have -- you have to meet the standards, but I

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think from a patient care pharmacy P&T approval standpoint and getting uptake for a therapy like this, addressing issues like decreasing resistance and positive impact on the microbiome, whatever that is, however we define it, I think those things are important and the science is advancing so rapidly that including that to the extent feasible would be desirable in this kind of a study.

MR. RUBIN: The comment on the question about lost to follow-up, I think these patients would probably be censored and so not counted as a CDI event, but I also think that it would be important for the protocol to distinguish lost to follow-up from death, lost to follow-up means you don't know if the patient is alive and you don't know whether they have CDI. Also, if you're dealing with the trial with a very low background rate, then it's unavoidable that if you have a nontrivial rate of lost to follow-up, then that study is going to be very difficult to interpret, so you'd probably need some kind of streamlined outcome collection where for almost everyone in the trial, you are able to determine

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whether they had CDI or not. I don't think it's that different from what you see in these large cardiovascular outcome studies where it's known going end of the study that if you have a lot of people where you don't know whether they have the event that it's going to be hard to interpret when you finish.

I agree with the comment, there was a comment earlier in the day about big data and I think this could be an area where it could be useful to try to enrich for patients who are at low or high risk for CDI to make -- possibly make the trial more feasible possibly by including patients who've had CDI before and for whom you're looking at recurrence. And then also this is an area where there have actually been a few very large vaccine studies, I think Pfizer and Sanofi, someone correct me if I'm wrong, over 10,000 patients for preventing CDI. And ideally you'd like some of these studies to be done to validate some of these surrogates that we're talking about like colonization or changes to the microbiome to show that a treatment effect on an endpoint like this will actually translate into an effect on -- of clinical

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outcomes.

MR. KALEKO: Can I add briefly that I actually dropped my little spiel on enrichment that I had here and the reason is because it's -- the way I view it, it's a curve that goes up, has a maximum and then comes down. As you enrich with sicker and sicker and sicker patients, yes, you'll have more CDI, you probably also start diminishing your effect-size after a while and you'll be increasing your mortality rate. So the two things that confound the data actually increase while you're enriching. So I think there probably is a maximum, but mathematically I don't know where it is.

MR. RUBIN: Wayne will take it.

UNIDENTIFIED SPEAKER: Can we get a value?

UNIDENTIFIED SPEAKER: Okay.

MR. DANKER: So I have a bit of experience with this from a closed door session years ago, so I can't talk about that, but there was a discussion when I was with another company looking at the use of a drug to reduce the colonization for ephesia (ph) which in cancer patients and if I remember the discussion

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that went on behind closed doors was the whole issue about surrogate markers and how the colonization was still just a surrogate for the prevention of more serious bacteremia disease associated with ifesium (ph).

So the question would be, there is a mechanism within the FDA for approving drugs based upon a surrogate with the ability then to do a subsequent definitive trial and I think that's sort of -- in some ways there was some of that discussion of committing the company to doing that. So -- and then as pointed out, there was that pretty large trial with a C. diff vaccine that you could look at what the colonization rates and so on if they did those studies properly, but I'm just wondering if there is an opportunity in this regard with a drug that may have some real benefit for society to look at the surrogate marker concept. I recognize that it was a difficult discussion back then. I don't expect that it would be any easier than it was previously.

MS. NAMBIAR: So thank you for your comments. I mean I'm sure you know where we had a discussion on

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microbiology as a surrogate endpoint just last week at an advisory committee meeting. And so I think it really depends on what data one has for a particular organism and a clinical outcome for that particular condition. So I think last week's discussion was around nontuberculous mycobacteria and whether or not sputum culture conversion correlates or it is likely to predict clinical benefit. And you know, there was a lot of assumption that it might, but when you actually look at the data more closely, you realize the shortcomings of the data and even though in that instance, you know, it's become part of clinical practice, the data that support a correlation between microbiologic surrogate and the clinical outcome for that particular clinical entity are pretty weak.

So I cannot comment on the adequacy of the data for this particular instance, but you know, we would have to take a look at the literature very closely and see if in fact there is support. I mean we've used microbiologic surrogate endpoint for tuberculosis, the approval of Bedaquiline a few years ago was based on a surrogate endpoint, but a lot of it

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really depends on how reasonably likely it is to predict clinical benefit, and if the treatment benefit on that surrogate endpoint will hopefully translate into clinical benefit or not, so. I wasn't part of those closed door discussions, but I think I know what you're talking about and --

MR. KALEKO: May I add one other quick point? And maybe somebody could help me figure out how to do this. I suspect that a drug like Z 2 at the hospital level actually diminishes CDI very much the way vaccines work mathematically with herd mathematics. If you -- every time you get rid of a case of CDI, you diminish diarrhea, you diminish the spread of spores and then you diminish other cases of CDI. So how can you -- normally in your clinical trials, you look at the effects in the patient. How do you look at the effects in the hospital which might be amplified?

MR. COX: So maybe I'll just start and I'm thinking maybe Dan and Scott have additions to this one, but -- so it sounds like what you're looking for is -- it feels like the way you'd try and answer this question would be like a cluster randomized trial and

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you'd randomize healthcare institutions, that would be your unit of analysis and you would give -- some healthcare institutions, you know, would have access to the product that you're talking about. And then you would look for, you know, lower levels of cases of C. difficile infection in the hospitals that receive the experimental therapy compared to the hospitals that did not have a therapy available. Does that sound right or no?

MS. BOUCHER: I guess the question is do you need to do that? I mean the data exist that decreasing rates of C. diff decrease rates of C. diff, right? That data exist. There's no -- every hospital epidemiologist knows this, that's why they push like they push. So the question is do you need to do that? That's almost like an epidemiology study you're describing or would -- showing that this drug decreases C. diff in individual patients, would that be enough to make other more general conclusions?

MR. COX: Yeah. No, I mean, there are times when you can make general conclusions based upon the data from other studies. And you know, there's always

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questions about what actually did it, and you know, would the drug do it or was it, you know, room cleaning and other things and so all these other factors are always sort of part of it. So it can be hard to attribute what actually the cause is, but usually for a drug claim, I mean you want the evidence-base that supports that the drug actually did it, so -- but you know, I mean we can always look and see what somebody's got, but it's at least one way to think about it.

And it's hard, you know, for some of these conditions where there are multiple different things that are impacting upon, you know, why a C. diff rate is going down, it's always hard to dissect what was responsible for why that rate went down.

MS. NAMBIAR: Yes, Mary Beth.

MS. DORR: So I wanted to comment about the impact on the hospital. I mean it makes a lot of sense. The same thing with quality of life. If you can prevent C. diff, then you should be able to improve the quality of life of the patient if you're preventing recurrences for example. But in the

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hospital environment, payers don't want to pay for prevention. So you can show that your drug prevents something, but how are you going to get that reimbursed? So we can't forget about at least in the United States how we're reimbursed for our drugs. So it's something that we all need to consider when we're developing drugs.

The other thing I wanted to talk about is the impact of this enriched population. Your population is already enriched because they're getting a high-risk antibiotic. What we saw in a subgroup analysis for the modified trials, in those patients who were getting a high-risk antibiotic, their mortality rate within 90 days, which was our follow-up period, was 10 to 15 percent, so that's high. So I really do agree that you need to consider that because your population is already enriched even if you're enrolling those younger people who had clindamycin after a dental procedure, that's an enriched population who has a high mortality rate.

MR. KALEKO: Can I quickly ask a question about the payer issue? It was my understanding, and

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please educate me if I'm wrong, that in the U.S. hospital-acquired CDI is paid for by the hospital. So as long as the total cost of diminishing CDI is lower, I'm getting this straight, than the actual cost of the drug; did I get that right or did I get it backwards; the hospital should be interested in it and that's even without bringing in the quality of life and the liability and all the other things that hospitals have to suffer when patients get CDI. So -- but I think your point is well-taken. The issue of payers is one that needs to be addressed.

MR. EVANS: I think a couple of points, and I think it's very admirable to the forward thinking about future patients and you know, very thoughtful to be thinking ahead that way. I think we need to marriage it or think about what that means to today's patients, in particular patients that come into trials. So the surrogacy we're talking about that may have effects on future patients or the rest of the population ecologically is different from the surrogacy we traditionally talk about in trials where you're talking about something you can measure on me

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today that may tell you about a clinical event that happened somewhere down the road that's too far down the road for you to measure today. And that's a little bit different than the surrogacy of preventing something for -- not necessarily for me, but for somebody else and what that means to the patient coming into the study when you're consenting them that you're talking about a benefit that may not benefit them, but may benefit somebody else, and how that might affect how they look at things.

I don't think the -- in many ways, I think we're turning to this door discussion this morning is a discussion about the mortality and so forth. Causality is measured by a contrast of randomized regimens. It's not measured by adjudication of what somebody believes is the reason for something. You measure causality by contrast of randomized regimens. So you can set up an ordinal level endpoint where you've got death on the bottom and levels above it are, you know, survivors that either have CDI or not and that helps to deal -- that's the way you deal with the competing risk of death. And I don't think that

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necessarily you have to study more healthy patients in order to see those effects. We've -- there are at least some studies we've done in which for many of these diseases, the sensitivity occurs in the most sick patients. That's where you find -- if your drugs have an effect, that's where you find the effects.

Now so -- and in a very pragmatic setting, if that's where the drug is going to be used, that's where you want to know what the -- what your effect is in those populations. So you know, I think there are ways to deal with the mortality issue is, you know, that's a -- you have a randomized study, you cannot do any better than that. You're going to compare how patients end up on a randomized study in that fashion and I'll stop there, thanks.

MS. EAKIN: All right, thanks. I think William made a point earlier this morning about possibly there being a need for new animal model development. And you know, one of the things that we're interested in at NIH and I know also colleagues at FDA and BARDA, we're interested in trying to make investments in the spaces to, you know, meet where

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there are gaps in the science with new animal models for instance. And one of -- this is one of the areas we've at least been talking about internally and I'd just be interested to hear more whether people think there is a need for more animal model work to try to, you know, recapitulate what's seen in say Eric Paymer's studies and clinically in an animal model setting that might be used to strengthen some of these new products.

You know, particularly I know there are animal models looking at, you know, colonization and microbiome diversity et cetera, but really taking those models forward to look at, you know, gut-derived, you know, bacteremia and things like that to actually strengthen some of these arguments and of course I can't imagine it ever replacing the clinical evidence, but if it would strengthen that, I'd be interested just to hear what people think about the value either in discussion today or as follow-up discussions.

MR. TRUONG: Yeah, I just want to make a comment about prevention versus treatment in some of

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these nontraditional, you know, we are developing as pseudo-monoclonal antibodies and when we take a look at the -- whether we should be developing these clinically to prevent or to treat, we gravitated to treatment primarily because in some of these indications such as pneumonia, we don't have good command on what is the attack rate. So for example, if we're trying to develop these monoclonal to prevent pneumonia episodes in colonized but asymptomatic patient, we actually don't have a good feel for what is the prevalence of progressing to pneumonia of a staph aureus pneumonia at-risk patient or pseudomonas pneumonia at-risk patient because the -- some of the data we're seeing is for either one of these bugs which represent the most prevalent gram-negative and most prevalent gram-positive in nosocomial pneumonia, you're looking at somewhere between 20 to 30 percent attack rate.

So if that's the case, we have to set at effect sizes very large. Let's say you set a 50 percent effect size, would a 25 percent attack rate means that for every 8 patient or 10 patient that one

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treat, only one would benefit and so from the payer's perspective, you have very difficult commercialization risk. Conversely, in the treatment mode, which is what we're developing, we're using the adjunctive therapeutic treatment modality as a way to develop these drugs. There the risk is different. There the risk is to show that incremental benefit, right, what is the effect-size over, above what the standard of care antibiotics could afford. So there we -- you know, when you ask, you know, the physician, what's the effect-size as clinically meaningful to you, there is a significant difference if you're doing prevention because if you ask physician if I have a drug that I could prevent X percentage from relapse in pneumonia, what is clinically meaningful to you? If you ask that same question to the payer, the response is actually very different.

From the clinician's perspective, you tend to hear about 10 to 20 percent prevention, meaning effect-size would be clinically meaningful and valuable. If you ask the payer based on the attack rate, they're going to tell you somewhere between 50

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to 100 percent. And so I think as we decide whether or not develop these drugs for prevention or for treatment, I think some of the epidemiological data is going to be very important to make that decision.

MS. NAMBIAR: Are there any questions from the audience? No, all right, I tried.

MR. REX: A comment and then a question. So the comment is that I think we're hearing a number of times a statement about the effect is really small, it's going to be hard to show where a large trial and I think we need to think carefully about what does it mean to say that an effect -- if the effect is really small, then who cares, right? You can make the argument that there's -- there can be small effects that you may -- maybe you do a study of 100,000 people and you show you -- the number needed to treat is 50,000 to produce some benefit. Is that actually something that you want to chase.

Now -- but small -- preventing one case of Ebola however may have a different consequence than preventing one case of C. diff. One case of Ebola would set off a global panic if it were to occur in

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this room whereas one case of CDI would -- you know, it would have a different consequence. So this notion of small effect-size, I think it is important for developers to stay focused on things that have reasonable effect-size, but you can keep in mind the severity of the thing you're chasing. So the question I want to get at though is this, we've beat around the microbiome a lot and what evidence would we need to show that microbiome pattern 1, whatever you want to define that to be, is in some ways safer or better than microbiome pattern 2. Have we ever debated that question? Another -- to turn it around another way is to say under what circumstances is detectable carriage of organism X, fill in the blank, an infection in and of itself that merits either treatment or prevention, under what circumstances for example would -- is carriage of VRE something that I should treat as an infection that I should seek to treat or prevent?

And some other thoughts for you would be, for example, group A strep and a surgeon who is not sick, but is carrying group A strep, that's actually a problem if he or she is shedding the organism into his

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or her patients. Group B strep and a pregnant lady, I suggested that one to third trimester, that's not an infection of her so to speak, yet it is an infection we actually actively seek to treat that. Carriage of neisseria meningitidis in the nose is considered to be a thing that you want to prevent. It's not an infection, but it's bad news when it occurs. So is there a way to use those models as some sort of a tool that would let you get at this broader question of when is your microbiome -- when should you say out to your microbiome and what is the metric for that that would be useful to us as a community so that when Michael is developing his next product, he actually -- he has a tool already qualified that defines the definition of the point at which the microbiome is painful. How about that one? And have, you know, worked on that? Any work on that? I mean I --

MS. EAKIN: We work on just about anything, so in some fashion.

MR. BURD: We've been working on recurrent C-diff. And as part of our data gathering on our patient populations, we've been looking at what's

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their microbiome constituents when they walk in the clinic and then what happens to them after treatment. And we're seeing some very profound patterns that arise out of that that are predictive of success. And I heard earlier that they are not measures that we could use, but the work that we're -- body of work we're gathering, which will be published soon, really does suggest that there are ways to look at the baseline of your patient population coming into the clinic, and then the effects upon the microbiome following your treatment. And these are predictive of both short-term efficacy as well as long term.

And so we talked earlier about how you would go about validating those surrogates and that's sort of the problem that everyone's going to have. Until we get a validated surrogate, we have a chicken and egg problem. So for our company at least, we're thinking about this prospectively with the idea that eventually we will have to develop this as a surrogate and validate it in randomized controlled studies. But there are ways to do this and there is a body of data being developed.

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MR. KALEKO: Can I ask you a question? First of all, I should mention that's why I said to the best of my knowledge. Are these profound changes? There are ones that your -- that your therapeutics are creating. If you were to look at just the general population who haven't been on antibiotics, and who would not be at risk for CDI, do they come in with those change, with those profound improvements and then lose them with antibiotics and then you bring them back?

MR. BURD: But -- so we have not done those studies.

MR. KALEKO: Or those profound changes specific to your therapeutic?

MR. BURD: So what we've done is that we have a cohort of healthy individuals that we look at. And this cohorts being compared to larger bodies of work that's been done I think in part by the NIH. And you get a population distribution of a variety of groups of bacteria. When you look at those groups and you look at them in the context of recurrent CDI, you see a profound inversion of the predominant species in

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normal or healthy individuals versus in those who are having recurrent CDI. We can talk about the specifics of the data offline.

MR. KALEKO: So is that a legitimate now secondary endpoint for a Z 2 trial?

MR. BURD: It very well could be. I mean one of the questions is how do you enrich your patient population when you have these low rates? This is one way to think about it. Patients that are coming in the door that are very near normal in terms of the distribution of these families of microorganisms aren't much -- are potentially at much lower risk of -- of having an infection.

So if you want to enrich for patients that are on that sort of, steady slope of losing normal control of their microbiota and moving into dysbiosis, this would be a way of enriching for them reducing the number of patients I think for some indications, but not all.

MR. KALEKO: Yeah, I think it makes for a -- for a really interesting endpoint. The problem with the Z 2-like trial is patients come in, they're

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infected, the emergency room docs got to get them on their antibiotics immediately. The clinical trial doesn't really have time to enroll.

MR. BURD: Right.

MR. KALEKO: But for an endpoint, I think that would be very interesting.

MR. BURD: Right. So one way to think about it is, if you're able to get a sample at the time the -- they start treatment, the question is have you made them worse at the end of it. So you don't have to look at from normal to total dysbiosis, but you could look at stability of that profile over time because if it's still degrading, then you have -- then you know that they're worse off than they were.

MR. DUBOVSKY: So I thought it was very interesting that this competing risk of death was as troublesome for the CDI-enriched population as it was for the back population this morning. And it occurs to me that it's going to be same for any product you're testing in patients of high acuity, that if you count those as failures, it's going to drive down your point estimate of efficacy. I'm still not sure I've

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heard a really good argument why you can't look at that as a safety feature. In other words, if he is able -- if product Z is able to prevent CDI infection and doesn't increase death, it still seems like that's a clinical benefit. Whether -- but if it were flipped and you had increased mortality in the active group, it seems like that would not be licensable. So is there a downside to looking at it that way?

MR. KALEKO: I think that's reasonable.

MS. DORR: I wanted to make another comment about the enrichment. Like the example that we had this morning where for the VAPP study, they were only enrolling patients who were colonized with staph aureus. Have you thought for Z 2 just in randomizing patients who were colonized with C. diff at the time that they start their antibiotic or X number of days after they start the antibiotic?

MR. KALEKO: I can't speak for Z 2 per se hypothetically. But the way similar studies are run is patients come into the emergency room and they're enrolled as quickly as possible and so you don't have time to figure out if they are colonized. Clearly C.

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diff pressure as it's called is a tremendous risk factor. And the -- I think the way that one gets at that and this is going to sound terrible, but you find hospitals that are having breakouts or have actually a long historic -- long history of breakouts as you know. The problem is those are the hospitals that are likely to actually have cleaned up by the time you actually get going with your clinical trial.

MS. DORR: Right. Long-term care facility patients, you know, they're going to have an increased risk of being colonized and a PCR (ph) test to show a patient's colonized is pretty rapid and most hospitals can perform those studies within a 24-hour period. The test takes an hour, but if they batch it, you know, could take as much as 24 hours to get the result back.

MR. KALEKO: Agreed. Thank you.

MR. OUTTERSON: All right. We're almost -- we're at the end of the time I think for this session. I was going to give a 60-second summary of just some of the things that we talked about. We talked a lot about surrogate markers and I think, you know, the FDA

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it seemed to me was saying that, you know, we're open to surrogate markers. Show us the scientific evidence of clinical, you know, connection or clinical benefit on that. We had a I thought a interesting back and forth on what if there's an Epi benefit in the hospital and then the response was close to -- close to randomization.

And then the response from Dr. Boucher was why bother, we know it's right. We know this is how it works. But I like the thought of this is one way for us to think about how to measure the positive externality of the treatment of this patient, is one way to measure value beyond the individual person, right? And so that's a good thought. I love to -- first question I always ask is how is it going to get paid for, right? It goes back to my training. And so all of these discussions, you know, one question I would leave out there is how is this study that we're designing any better than the study that was done for deficit which sells about $7 million per month in the United States? You know, so we have to do better than that, right?

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And so John needs to pull the magic -- pull incentive out of his hat. He doesn't have a hat. Bad example. I liked what Scott had to say about -- Scott Evans on the surrogacy that we're talking about is really surrogacy for other patients, right, as opposed, you know, this is a different type of surrogacy. It's not the patient X and then at time, you know, plus 6 months we are doing a surrogate marker of how this individual will be in 6 months. We're really talking about surrogacy in some fashion about other patients, right? And that has ethical implications and other, you know, we need to have that mindful.

And there was a discussion as well about the who is going to -- what the payers and the providers, you know, or, you know, the payers -- providers are okay with a 10 to 20 percent, you know, Delta whereas the payers want -- a 100 percent, you know. And those are very interesting, you know, differences there. Thank you for your attention. We have a break of a few minutes, much longer than the last break.

MS. NAMBIAR: Fifteen.

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MR. OUTTERSON: Fifteen minutes. Enjoy your time and come back for case study 3.

(Recess)

MR. REX: Okay. Boys and girls, ladies and gentlemen, I think we're going to get started. Kevin is waving at me saying it's time to rock and roll and -- okay. So for the final act on this rainy slightly sleepy afternoon, let's look at this case, case Z-3, a case that looks at the idea of reducing risk of infection due to a metallo-beta-lactamase producing organism by preventing the acquisition of said organism. And I'm going to acknowledge Patty Bradford is not here today, but who helped me a lot with trying to make this into actually a credible concept.

So two bits of background. The first is that travelers are at risk for becoming colonized by resistant gram-negative bacteria, and in particular you can demonstrate that you can get colonized by ESBLs and CRE by traveling. So look at two bits of data. First is a paper by Tang et al from 2010 where they looked at a 100 travelers from Sweden who were setting off to travel outside of Sweden, mostly to

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Asia, but not exclusively. And they screened them all before they went on their travels and they screened them again, screened their stool when they came back. And what they found was that of a 100 people who set out, 24 came back carrying an extended spectrum beta-lactamase in their stool. And then they followed them a little bit longer. And of those 25 percent, 25 percent of them were still carrying ESBLs 6 months later. So I'd like you to remember those numbers. A fourth of them came back carrying a more difficult to treat gram-negative and 6 months later a fourth of a fourth were still carrying that organism.

And another one where I think the title says it all, included it just for another demonstration, this -- the ECDC carbapenem producing OXA-48, Klebsiella pneumoniae in travelers previously hospitalized in Gran Canaria, Spain. So, you know, we wind up in the hospital there, the organism is present locally. You can come back to your home based in Europe carrying the organism that you picked up.

In high prevalence areas, a high fraction of the CRE, so here I stepped up from ESBLs to

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carbapenemase-resistant Enterobacteriaceae, so that's a variation on ESBL. High fraction CREs are metallo-beta-lactamase producers. And here are the data, I have one paper, I was looking for nice surveys of this and the best one I found 2017 Mohanty et al looked at carbapenemase production in Enterobacteriaceae bloodstream isolates. And two-thirds of the CRE were metallo-beta-lactamase producers NDM-1, that's a very high prevalence.

And then 2011, an earlier paper, one of the papers that has almost started it all, New Delhi metallo-beta-lactamase from a travel returning to Canada. So, you know, makes sense. The organism is out there. If you eat the wrong thing, you can pick it up. Nothing magic about that. So this leads us to product Z-3 which is a hypothetical non-absorbable prodrug that doesn't do anything in its prodrug state. The prodrug conjugate however can be hydrolyzed by a metallo-beta-lactamase and this interaction is specific to the beta lactamase activity of bacteria. It's not affected by human-derived metalloproteases.

Upon cleavage by the metallo-beta-lactamase

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in the periplasm, a peptide is released that kills the metallo-beta-lactamase expressing bacterium. Z-3 has been studied pre-clinically and in phase I data and we have the information required to permit daily dosing for up to 3 months in human beings. So with this in hand, we set out to do a phase II study of travelers from Northern Europe to Southeast Asia or India, and we enrolled 200 healthy adults, half men and half women from Northern Europe who have travel plans to go to Southeast Asia or India for 4 to 8 weeks.

They are all screened prior to travel and found in there's -- that their stool is free of ESBL and MBL-producing strains of Enterobacteriaceae by culture on selective media and by next-generation metagenomic sequencing. They are randomized one-to-one to begin daily oral dosing with Z-3 versus an identical placebo beginning at the time of travel and to continue this for 2 weeks after their return.

One month after return, that is 2 weeks after stopping Z-3, rectal swabs are again tested. And lo and behold 24 percent, exactly like tanged in 2010, are found to be carrying CRE in their stool. And this

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is true for both groups, both the placebo and the Z-3 treated. They have CRE. Of those CRE, 8 percent which is a fictitious number taken as one-third of the number I found in India just sort of reflect a rate of travelers of the study -- of the subjects in the placebo group and 0 percent in the Z-3 arm are found to be carrying an MBL.

So you've got a fraction of them who come back colonized with an MBL. And that's chosen because it's an irritatingly close p-value to 0.05, but one you might choose to disbelieve. P equals 0.04. Six months later, again just like tanged in, a quarter of those who were colonized are still colonized, and they're still carrying it in proportion. So there are six people still carrying an ESBL and two still carrying an MBL. So the persistent MBL rate is 2 percent.

Two infections occurred during this 6-month period, one in each study arm, both were uncomplicated UTIs in women. Both were due to a -- an ordinary Enterobacteriaceae, not a CRE, just what these women were carrying. Hence 1 in 50 women in this traveling

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group developed urinary tract infection during a 6-month observation. I had a hard time getting a really strong number for this, and the 1 in 50 could be a overestimate of the frequency of this in these otherwise healthy female travelers.

So this leads us to the questions to debate. Z-3 is not going to keep you from getting an infection, but the infection that you do get cannot possibly due to an MBL if you're not carrying one. It's gravity. Can or how can these data be translated into a large-scale demonstration of utility? And specifically is demonstration of reduced rates of infection due to an MBL producer required for proof that not being colonized prevents you from being infected with an MBL, do I have to prove it? If I do, why do I have to prove it? Okay. If I -- it's almost like one of those jumping out of the airplane parachute questions, right? You know, I don't really feel like I have to test the importance of wearing a parachute when I jump out of an airplane.

On the other hand, if it's not required to prove clinical efficacy, why is that not true?

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Because, you know, this is a product with a potential side effect, and you know, it feels like we ought to do the -- ought to study it. And so one way I thought about this was, well, the number needed -- maybe I can do this based on urinary tract infections. So if you do the math, the number needed to treat for women is 1,250. If 1 in 50 develop a urinary tract infection and the proportion due to an MBL is the mean of the 8 percent rate when they came back right at the end of their trip, and the 2 percent rate they have 6 months later. So it's sort of picking a midpoint. I have no idea if that's right or not, but 50 over 0.04 is 1,250.

So if I want to show that I reduce the rate from 1 in 1,250 to a smaller number that is statistically meaningful, my very crude sample-size calculation was I needed to have 30,000 people, 15,000 in each arm to produce the -- to prove a reduced rate of urinary tract infection in women. Men aren't going to get it at that rate. So it's only in women. So if I do this study and it's positive, is Z-3 now indicated for preventing acquisition of MBLs in women,

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but not in men?
Finally would you pay for this if it was available for $500 at CVS and you're about to go to someplace where you could pick up an MBL? Would you -- would you be willing to buy it? If so, which of these data sets would you require before you would put your $500 on the table? That's it. Ed is shaking his head at me. I don't know why.
MR. OUTTERSON: Can we buy it for $50?
MR. REX: No, because the plant that manufactures it, you know, I have to run that darn thing and you know, and it's -- you know, these things aren't entirely free to make. So I guess I'll add that we invented this case to be as clean as possible a question about a community-level benefit. I mean, there are lots of ways you try to get at the question, but this one was meant to try to take away everything but the community-level benefit. I'm seeing stunned silence here. But good for you.
UNIDENTIFIED SPEAKER: But doesn't it then --
MR. COX: Too though, right?
MR. REX: Well, so --

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MR. COX: Yeah, so what I was -- I was asking John about was this, doesn't it benefit the patient some too? What do you think?
MR. REX: Well, yeah, you know, I guess and what I thought about this, you know, why would I be willing to buy this before I take my trip? And the reason is that I'd rather not be colonized with the metallo. You know, I think my chance personally of getting, you know, sick with infection in the next 6 months are relatively small, but if I'm -- don't have a metallo, I won't have a problem with it and I won't spread it to anybody else. I mean I think those are the two things that seem straightforward to me about it. But I think the likelihood that I personally would benefit is going to be really small because my chance of an infection in the next 6 months is really small.
MR. DUBOVSKY: Is there anything to learn from other decontamination things like chlorhexidine or mupirocin?
MR. REX: So Helen's going to have to help me a little bit on this in terms of hospital or infection

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prevention. We do have some data there.
MS. BOUCHER: Yeah, no, we have some data for surgery for example with chlorhexidine bathing and mupirocin for 5 days before open-heart surgery that it's beneficial.
MR. DUBOVSKY: Right. But my guess is those weren't a licensing phenomenon.
MS. BOUCHER: Right. I don't believe that's a licensed indication, but I defer --
MR. REX: But is my use of -- is chlorhexidine a drug? I mean is it --
MS. BOUCHER: Yes.
MR. REX: -- do I have to have somebody --
MS. BOUCHER: Mupirocin is a drug. Mupirocin is a drug.
MR. REX: Mupirocin, but --
MS. BOUCHER: So we use mupirocin.
MR. REX: But to use the chlorhexidine bath, that's not a --
MS. BOUCHER: That's not a drug, but the mupirocin is, that's a prescription.
MR. COX: Yeah, I think -- I think it is. I

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think it's handled by our nonprescription products group, yeah, and it's -- I don't know the division between what's handled under monograph and what they handle under an NDA, but it -- it is a drug from what I recall. But I think what you're talking about are probably studies that are done, you know, by the academic community for at least some of these studies. And they are using approved products and they're using them, you know, perhaps as combinations or mixtures to look at, you know, in various different infection control measures.
And they're in the published literature, but they may not be done by, you know, the pharmaceutical company. They may not be something that's connected with the pharmaceutical company. So they may not lead to supplements that would come in to us that would lead to changes in the product label. But they could.
MR. REX: I mean I don't -- I may not be looking it up correctly, but I just found there's a chlorhexidine oral rinse that seems to have a -- some sort of an FDA label. But I didn't find one for skin prep.

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MR. HOPE: So John, isn't there a literature on invasive procedures in men after they come back traveling? So there's -- I think there's literature published on prostatic biopsies for example, where -- that's the first point I just want to make. And then the second is I just want to say something about precision of language, which I know that you're very interested. And it goes right through this afternoon's discussion about the distinction between infection and disease.

And so that the -- those terms are being used interchangeably where I don't think that you -- I mean, so VRE infection, we're all infected with VRE in the sense that we -- it's present, but it's not causing disease. And that is just -- well, maybe semantics, but an important distinction here sorting out because we're really interested in clinical endpoints in disease rather than in infection. So -- and you know, it's the same in fungal diseases as well because we're all infected with aspergillus right here and now, but we don't have aspergillus disease.

MR. REX: So if I may pick up on both of

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those. First, earlier when I used -- when I asked the question, is there some definition of microbiome that you should treat as if it were an infection, I meant it deliberately in that sense, that -- and I meant I should -- maybe I should have said disease and it's -- Neisseria meningitidis in my nose is probably something I would treat as a threat to me that I would like to do something about, even though at this moment it's not replicating in my CNS.

So I -- to my mind, that's -- it's not -- I can't feel it, but it's certainly scary and I suppose a correlate would be you can't feel colon cancer for a long time, and yet when you discover that you have a polyp, you get it taken out. So I think there is a sliding scale here for some of these things that have a long period -- a long runtime before they eat you kind of a question. And your comment about men and prostatitis and gram-negatives, absolutely there is a relationship there. Jason Gale wrote a series of articles about how the use of antibiotics and shrimp farming has led to carriage in shrimp of multi-drug resistant E. coli which led to a pretty clearly linked

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series of outbreaks of prostatitis in Southeast Asia.

And so it's possible for that sort of thing to occur. And the link here I -- I was trying to come up with a way to do this that didn't require anything special to happen. I was looking for a very -- something that I could imagine doing. I mean I can, you know, I could see that, you know, all -- everything about this case was something that, you know, I'm having trouble seeing that you could actually do it if you really wanted to.

MR. HOPE: So maybe I'll just comment a little bit. So I mean, if we think about, you know, the surgeon who has group A strep, I mean, you know, it's been a while since I've done the infection control sort of stuff. But you know, maybe you have three or four patients with post-operative infections with group A strep and that sends you looking for the source. And if you find out that they all had the same surgeon or the same surgical team, then you start to culture. So I think what you have there is a, you know, a fairly strong epidemiologic connection between, you know, an event and then an actual

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infection in patients.

So I think John's on to something when you started to talk about, you know, how close is the connection because as that connection starts to become closer between the clinical event and the state of carriage, then I, you know, then I think you're in a better position to understand, you know, if you alter the state of carriage that you may reduce infections. And you know, same thing if, you know, the -- somebody comes in with a Neisseria meningitidis infection and the person who intubated them has been, you know, exposed to secretions and all that is a presumably a high risk.

I mean, I haven't looked back at the primary literature there, but presumably is it sufficiently high enough risk of infection that it's worth prophylaxing those folks, so that -- I mean, so it does seem, you know, what is the information that connects the event to that -- either that at-risk exposure state or that carriage state leading to a clinical infection? And to the extent that you can figure that out, it certainly helps to understand, you

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know, what an intervention might do as far as altering, you know, state of what may be carriage or colonization and as far as actually leading to the reduction of a clinical infection.

MR. REX: So I can't -- I'm not going to back the slides up, but you've got slide 6 in front of you. Set it up so that there actually was a p less than 0.05 for our demonstration that you prevented acquisition of metallo-beta-lactamase producers. Can I bring you a dataset on the real version of Z-3 and get an indication for Z-3 is indicated for the prevention of acquisition of metallo-beta-lactamase-producing organisms while traveling to Southeast Asia?

MR. COX: So it's always hard to talk about the approvability of a hypothetical NDA (ph) in the spot, but he's done a series of slides. But --

MR. REX: Do you mean yes?

MR. COX: Well, it's a maybe. Would you take a maybe?

MR. REX: Yes, okay.

MR. COX: So it sounds like what you're telling me and I'm not entirely clear on this, but if

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you actually have a clinical trial and it sounds like it's a lot of patients that you actually show reduction of, you know, the event of clinical urinary tract infection with MBL organisms, then you might have something there, so. But there's always the -- oh, you don't have that.

MR. REX: No. I personally -- well --

MR. COX: Okay.

MR. REX: -- I'm asking you, yeah, this right here. So this is as far as I've gotten. I haven't -- I've done a 200-patient trial and I come back with this, okay? And maybe I do a 2,000-subject trial, but basically you -- this is all you've got and nobody -- and I don't go to the trouble of doing a 30,000-subject trial. It's, you know, it's -- all I really ever show in real time with this is that it keeps you from -- it keeps you from coming back with an MBL that I can detect in your stool.

MR. COX: Right. So again, I mean -- you can come up with a gazillion different hypotheticals. So I can then postulate that these people were all cultured 3 weeks later and they all -- all their MBLs

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where everybody was going. And then nobody had a clinical event. So I think you really have to -- you have to be able to tie what's going on here to the clinical event in a very sort of solid way. That's the hard part. Because, you know, if you're treating something, it's going to go away 2 weeks later on its own anyways, and you're going to have no clinical events, I think you have to start to ask the question of what am I doing.

MR. REX: Yeah.

MR. COX: If you -- if the carrier state persists and you have clinical events, then I think you've got a connection with, you know, preventing a clinical event. And this is what's so difficult and so challenging about, you know, these issues of carriage. And so that's just sort of the hypothetical talked about at the high sort of theoretical level to make it even -- you know, which makes it even more complicated that's why it's very helpful to have the clinical events to help sort this all out. You know, how often do you culture, what's your level of detection with the culture, you know, are people

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transiently positive and transiently negative?

I mean there's just a lot of questions that come up and these are all -- I mean if you can get to the actual clinical event and show the reduction in the clinical event, then some of these difficult questions in essence are eclipsed by the benefit that you've shown to the patient.

MR. REX: So that I -- you know, I put you on the spot, but it's -- actually it's not a regulatory issue in a sense. I mean if I -- even if it were approved, would you pay for it? You know, I'm looking at Kevin Outterson as our -- as a patient rep in effect.

MR. OUTTERSON: With a preventative care taskforce.

MR. REX: With a preventative --

MR. OUTTERSON: Care would be.

MR. REX: Right, yeah. Say that again?

MR. OUTTERSON: But would the prevention care taskforce give it an A or B rating and therefore --

MR. REX: Yeah.

MR. OUTTERSON: -- require, you know, U.S.

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insurance policies to cover it.
MR. REX: Right.
MR. OUTTERSON: Yeah.
MR. COX: And then let's add in that it has some adverse effects.
MR. REX: No. No, no.
MR. COX: So then -- you know, then the benefit risk gets a little complicated too so --
MR. OUTTERSON: No. That's not on the hypo.
MR. COX: Pardon?
MR. OUTTERSON: That wasn't on the --
MR. COX: But it wasn't on the slide.
MR. REX: Yeah. But you know, I made it as -- I made it very clean. But nothing is ever that clean.
MR. OUTTERSON: Right.
MR. REX: You know, there would be something that it does though occasionally and so you might feel like you wanted to see the next level of proof, but the next level of proof is a big study.
MR. COX: But there are -- people travel a lot. There's no reason why, you know, 30,000 people

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could be accrued.
MR. BLACK: So taking this comment, John, because I meant the study that you described, you say you want to focus on the community benefit. The component that you haven't really addressed here is what then is the transmission rate of these people? So is it really just local cluster that's at-risk or have you prevented further environmental dissemination and then it becomes more like, you know, a vaccine herd assessment of how many people do I need to treat to really prevent enough carriage to then have an impact on a cluster analysis-type of study I think on progression of disease. And that's not necessarily captured here if it's going to be kind of treatment as prevention.
MS. DORR: I was just going to comment from the perspective of if it wasn't paid for by my insurer or by my company if I was traveling on business, would I pay for it. If I was paying out of my pocket to go to Southeast Asia, I'm probably spending $10,000 or more dollars to go on vacation and if I'm educated and I know this is a bad thing, I personally would spend

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$500. But how many people are you going to have that would personally spend $500 because how many people go to Southeast Asia? So I think, you know, it does come down to economics and whether or not it's worthwhile to even bring such a drug to the market.
MR. KALEKO: At the risk of violating again the constraints of hypothetical scenario, wouldn't this particular therapeutic be useful? It seems that the greatest issue with MBLs is that they will expand under selective pressure from antibiotics. So wouldn't the best use of this be to give it to everybody who comes into a hospital knowing that 50 percent of them by the time they leave the hospital will have been on antibiotics. Or someday have it in -- on a formulary at your local drug store so that everybody who gets an antibiotic gets it. So that eventually you stop the expansion of MBLs and then they will by their very nature drift away.
MR. COX: So that may be a studiable question.
MR. KALEKO: Yeah. It might be.
MR. COX: You know, you could try and figure

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out if the effect that you're postulating the drug has can be demonstrated in a clinical trial and that is in fact the effect that the drug has.
MR. REX: You know, I guess I was thinking this was -- in this case it's going to be food-borne acquisition of organisms in a healthy traveler. And in a nosocomial setting, hospital setting, you've got other ways of acquiring pathogens who -- so that is you took the stuff by mouth and it works in your gut to keep the colonization recurring seem to me to be part of the storyline. But the notion of a prevention -- well, but that actually is like a -- that's a standard infection prevention question, isn't it? I mean, it's the -- you know, what kind of hand-washing and gloves and carrying on prevents you from acquiring a difficult organism.
I didn't -- you know, this one isn't set up to -- if you've gotten -- if you've already gotten an infection due to an MBL, it's not going to help you at all because this only works -- this made-up thing only works in the gut. But it's really we're back into a very standard infection prevention question there.

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MR. DUBOVSKY: But John, in this case people who go to hospital could be screened, know they have it, they could be decolonized, right?

MR. REX: Well, I guess that's true. This is a -- you know, in theory if it -- you know, the way it's invented, if you're carrying this in your stool and you took some of this in theory it would -- it might clear you I guess and no reason why not.

MR. KALEKO: What percentage of people who have it in their stool also have it in their nasopharynx or someplace else?

MR. REX: I don't -- I didn't really dig deep there, but the main place where you carry the gram-negatives -- well, you could certainly carry them in your mouth and your dentition, you can if you've got bad teeth. No question the way to get and the way I -- - the way this one was invented, unless you did a swish and swallow, I mean, I -- you know, we're kind of -- we're getting very inventive with it here. But the notion here was about the reason the pay-in I thought maybe you could make this work was, acquisition is going to be oral, this got to stuff in

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your gut at the time that you are exposed to organisms and they just can't stay if you've got this in your gut.

MR. MELNICK: But John, once you've established that a carriage state is associated with infection downstream, you know, and it could be this trial or another, the cost benefit of using it in patients who are known to be colonized becomes very different. So the scenario of somebody coming into the hospital, getting screened and then found to be a carrier and treated, that's a different cost-benefit equation.

MR. REX: Can't argue with that. It -- here this is -- I was trying to create something or to create a storyline that was about a question that was as close as possible to I as an individual can get almost no benefit from this. The benefit -- yeah, there might be some and I -- sorry, I didn't throw in something about transmission because you can certainly look at your family, partners, and see if it had little bit of spread locally because, you know, that's how these things get around, right? It certainly is

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known to occur.

MS. DAS: I can't -- I keep thinking about the synergies as an anti-malarial here and can't you think about development on those terms? And you know, if you are developing it, is it of greater use in the countries where you have more MBLs prevalent, you start to decrease the instance of MBLs?

MR. REX: Well, I mean that's why I had the travelers go from Northern Europe to Southeast Asia we've discussed at the low because I knew the rates were higher there. You know, that's the -- there was -- it wouldn't be a point doing it from Sweden to Norway.

MS. DAS: No, but I guess my point is that was why you're developing an anti-malarial because, you know, I take anti-malarials when I go to a foreign country, but I'm not the person that primarily developed for and I'm not the cost-benefit argument I guess. So could you develop this drug actually for use -- for greater use in the countries where you have higher rate of MBLs and added advantage of it is that the new travelers can use it?

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MR. REX: Oh, oh, oh. So the primary market for this is people who are living in a high-risk area and in that group you would have -- they would be at risk for all the things that happen to human beings in ordinary course and that would give you potentially a larger pool of things, it wouldn't be as hard to find the people -- you know, finding the subjects actually would be a more straight -- it would be a simpler trial to do in many ways, wouldn't it?

MR. OUTTERSON: Yeah, but you make most of your money on the travelers' market.

MR. REX: Presumably.

MS. NAMBIAR: So --

MR. REX: Because I better get busy and invent this stuff.

MS. NAMBIAR: So I think if it draws a similarity with malaria, I mean that's how malaria studies are done, right? Very often we would study it in semi-immune population, people who live in endemic areas. We try to study it also in a non-immune population, which really would be the travelers. But the use is really for -- for the vast majority will be

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people who are traveling from non-endemic areas to endemic areas.

MR. BLACK: So just ask another hypothetical around this, so let's say my Merck chemist make a nice safe prodrug version of this and it becomes the best therapy for treating, you know, expressing pseudomonas. Would you want to continue using your drug in this manner? Because this is an antibiotic, right, and it has the same potential risks of being an antibiotic and can be developed into a more therapeutic version.

MR. REX: Well, the way that this one was invented, it's limited to the gut. I did -- where there's a way to give it systemically, I -- you know, maybe there is. But in order to use it as a therapeutic, you would have to deliver it systemically, right? And I didn't think -- well, maybe it could.

MR. BLACK: I'm just saying -- I'm just commenting, it is a novel antibiotic that you've discovered and described and if we could progress that, would you still want to use it in this way, is

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what I'm asking? And so --

MR. OUTTERSON: Yeah, I feel the room is -- John, you've beat them into stupor or something with the type of it. You have a future in law school teaching if that's -- what you're doing now doesn't work out for you. So I want to press -- I want to put my good friends to the right of me here on a little more pressure. So looking at this study that John is recording 30,000 people and really if you want to power it for men, you know, and get things other than UTI, you know, there might be 50 or 100, you know, there's going to be a lot of people in the study. The previous slide showed a much smaller study, say 200 or 2,000 people. So my question, you know, pushing back what John said earlier, what other evidence would it take for you to approve it based on slide 7? And so I'm assuming that if there was, you know, a good study, various studies out there saying that MBL carriage results in 1 out of 1,000 or 1 out of 500 with X and 1 out of 500 with Y, and X and Y are bad things; you know, would just the fact that it's 100 percent efficacious in eliminating MBL, would that be

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sufficient? And the analogy, one analogy could be HPV which, you know, it wasn't shown to reduce cervical cancers, to reduce, you know, carriage of the subtypes plus pre-cancerous lesions. Could you accept a smaller study with and what would you want the other thing that was done by somebody else to say?

MR. COX: Yes. So I mean, I think again it gets back to these issues of, you know, limits of detection, when are you looking, you know, have you actually shown that, you know, treating will actually reduce the infection? If you don't have direct evidence of that, how good is the other evidence that you have that you're relying on? In essence you're looking at a surrogate. I mean there's just a lot of questions here that are very difficult to answer in a very hypothetical way and it wouldn't, you know, if I say "Yeah, yeah, sure we can do that," I haven't done anyone any favors because we haven't really thought through the issues. And I think, you know, one of the things that this case brings up to me is that whenever we talk about idealized situations and then you move into the real world, there's a lot of things that pop

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up that maybe you thought about, maybe you haven't thought about, that are really important in understanding the connection between, you know the disease state, the intervention, and the clinical outcome that you're trying to figure out.

So I mean you can see what we're trying to get at is, is the patient better off or not and some way to really figure that out. And you know, usually that's in bacterial diseases where the outcomes happen in a relatively short term in most of the situations, usually we're trying to get direct evidence of that. You know, if there is really, really strong evidence and you've shown that, you know, that reduction of a carrier state is associated with reduction in disease and that should happen with agent A, agent B, agent C, and you can, you know, demonstrate that that surrogacy is in essence, you know, valid, you know, then that can be helpful.

But you know, that's why we're really sort of interested in trying to see that we're really impacting patients with a clinical outcome. And you know, the discussion has been interesting here

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because, you know, as this case was developed, it went towards a low-frequency event and then we also heard some comments from Shampa saying, you know, is there a possibility of using this in a scenario where, you know, this event maybe something more frequent.

So again it gets to the idea of enrichment and we've heard several people talk about, so is there another way to look at this, that's another thing to think about when you're -- when you're trying to show a clinical effect for a drug, is there a population, is there a circumstance and I credit the folks that have come up with this idea of, you know, maybe there's a more frequently, you know, a population in which the infection will occur more frequently. So enrichment is always something to think about and maybe I'll just stop there, let's see.

MS. NAMBIAR: If I can make a comment. I think we've seen the same discussions happen, not just in the context of decolonizing the gut. You know, you can -- you know, we've seen products come through and there is interest in seeing -- applying it in the nares and having some degree of decolonization in the

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nose, is that good enough? And what is the benefit to the patient and I know Helen mentioned in practice mupirocin is used, but you know, prior to cardiothoracic surgery. But in some of the clinical studies, the treatment benefit, which is a clinically meaningful benefit, I think wasn't that clear-cut in those studies that were done. I mean it was a certain subgroup in which you actually demonstrated a benefit.

So I think this issue goes beyond just say decolonizing the gut for a travel, but it can be an effect on a bacterium that is just part of your flora for the most part and whether or not that offers a benefit to the patient.

MS. BOUCHER: So John's question, part of it was about the benefit to the population, right? And so as we think about things like decolonization and procedures that we do before big surgeries, that's for the patient undergoing surgery, but it's also for every other patient in that unit because we know that if patient A gets a staph infection, the patient next door is likely to get it from my hands, you know. So those decisions that are made on less-than-perfect

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data, right, those -- the infection prevention teams analyze the data, they come up with the best strategy that we can feasibly implement in our institution. And my institution is different than yours and the next one.

I think the question that's here that I'm hearing is do we know with certainty even the period of risk. So if we could surmise that this product decreased colonization sufficiently or made it go away, whatever we agreed upon, for 30 days, 60 days, you know, what's the period of greatest risk to that individual for getting infected and potentially passing it around? And some of that is knowable, right, because we know about the cases that have come here that have been imported and we know when they were, wherever they were, that where they presumably acquired the organism. But then maybe some of that is what needs to be known. But it -- is it enough -- could it be enough, that's the question back to you. Could it be enough to know that? Yeah, you could only decrease colonization or make it go away for 60 days or 30 days. You know, is that enough if it was

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knowable that that was the period of greatest risk.

MR. REX: Well, I obviously don't have any data to show you the -- I was keying off the idea that the time (ph) and data suggests that you could acquire certain organisms when you lost them over time for whatever reason. And so presumably there is some period of, you know, some people go persistent and others get rid of it. And that there is a finite risk of an infection during the period when you are colonized. And that is one going to prevent you from getting an infection, it was just going to prevent you from having an infection due to something that was harder to treat and that was the only -- that was the only value. If you have a UTI, it won't be due to an MBL if you're not carrying one.

And that -- and I did think a little bit at the time, but I obviously didn't write it down about the fact that also your spouse, your child can't have that organism as well obviously if you didn't bring it back from your travels. So this -- that's as far as I could make it go.

UNIDENTIFIED SPEAKER: Can we --

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MR. REX: But that felt to me like that was potentially an interesting benefit for a community as a whole and if what that did over time was -- you know, right now we're seeing these rates of -- and I chose the MBL because certainly we've seen how ESBLs crept into the rest of the world and as ever reasonably that MBLs are just as pathogenic, there's no obvious loss of that, so will we see a time 20 years from now when MBLs are meaningfully more common because they have continued to live around the world. You know, maybe the WHO global action plans will slow that down.

But you know, the odds aren't bacteria smart and they have lots of chances to replicate and move around the globe and so you'd think you'd begin to see little bits, you know, more and more of this. And the idea that you might do something that would slow it down struck me as attractive. But it just -- it seemed to ask an interesting question that made me not sure what the right answer was. So before -- I think we're getting close to quitting time as they say. I've been trying to come up with a list of strong

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factors that it will cut points if you will in terms of the non-traditional, what are the things that need to be debated and how would you divide it.

And I'm just going to read off the list I've got right now and if you think of something else, let me know because it feels to me like one of the real valuable outcomes from today would be if we identify some subset of the concept of non-traditional that we can articulate is a place where a good, in-depth conversation would be instructive, that would be a useful output from this. And so the list that I've got right now has four things on it. One is the difference between it works for the host versus working at a non-host level. So that could be immune, but you know, broadly it works on you rather than on the pathogen.

The second one is that it's a combination of things versus being a single thing. And we talked about that in terms of monoclonals versus polyclonals, but also the idea of, you know, FMT (ph), is it a thing, is it a single organism or is it something that you -- is it 19 organisms that you choose to pull

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together or is it mixed human stool and does that change your strategy whether it's a single thing or a combination of things. The third one I almost wrote down biology versus not, but I ended up concluding that wasn't right. I looked for it. So it's immunogenic versus not. And maybe even that's not right, I don't know.

But things that are immunogenic seemed to have a set of toxicology issues and possibly short -- maybe the product itself can be -- it gets neutralized in some fashion, I don't know whether that's right or not. And then the fourth one is the one we've just now been debating, which is direct clinical benefit versus not. And those categories seemed -- so host versus non-host; combination versus single thing; immunogenic versus not; and direct clinical benefit versus indirect clinical benefit seem to me to be boxes that might enable you to have specific conversations where you try to sort stuff out about how you might take a product forward.

So those were the thoughts that I had and I -- and if people have stuff to add to that, this -- now

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or later or tomorrow if you think of something, I would be very interested in trying to make a better version of that list with the thought that that might identify buckets of things that would be worth more detailed debate.

MR. KALEKO: It might be too late in the day for me at this point, but can you clarify the difference in 1 and 4 on your point list?

MR. REX: Well, my list number 1 was host versus non-host, that is it's working. You know, something that it works at the host level would be activating my immune system to throw off to -- as opposed to something that kills the bacteria directly. And maybe variance factors probably fall into that category as well. That's -- that would be host -- if it doesn't kill the bacteria, just somehow slows it down or -- and then my list number 4 was direct clinical benefit versus not. And so Z-3, a lot of its benefit presumably is an indirect benefit as opposed to the monoclonal prevent staph aureus pneumonia. If I'm at risk for staph aureus pneumonia, I can get it -- I personally can get a benefit directly from that.

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And here with Z-3 maybe I can -- there's a little bit of possibility that I get a benefit, but not a lot. And so that was the pole I was thinking about.

MR. OUTTERSON: We've had a lot of comments up here, but is there anyone in the audience who wants to step up to that microphone and boldly ask a question or make a comment?

MS. NAMBIAR: Okay. I think I got somebody.

UNIDENTIFIED SPEAKER: Dr. Dan --

UNIDENTIFIED SPEAKER: So John -- is that working? Yeah. So John, the other area is which I thought you were talking about in number 4 is, that's come through a lot of these surrogates as well, so that's K1 (ph) that seems to be running through nearly everything is a way of doing that to make it useful.

MR. REX: Yeah, so it's hard to hear a little bit, but you're saying that you could extend the concept of direct versus indirect benefit to talk about surrogates for subsequent presumably direct benefit. But where you actually though -- as you well hear and see --

UNIDENTIFIED SPEAKER: And if you could get

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direct benefit as a surrogate that for a longer term -

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MR. REX: Right. Here in Z-3, you could say that the surrogate is absence of colonization with an MBL for the long-term benefit of no infections due to an MBL, right.

MR. EVANS: Yeah, my comment on that was when you talk about direct clinical benefit, I think there's really two pieces of that puzzle, when you -- direct clinical benefit is really two pieces of the puzzle, part number 1, for whom? And whether that's the person who is being randomized and treated or whether that's beyond that. And how do you interpret the beyond that stuff? The second thing is the surrogacy and in some ways it's connected to the first one because if you're going to talk about surrogacy, am I talking about surrogacy for the patient in the trial or am I talking about surrogacy for a population level outcome that's happening, and what level of validation of that surrogacy has to happen in order for, you know, feel comfortable to move forward?

MR. OUTTERSON: So my 30-second summary is

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that the FDA is willing to entertain stories about surrogacy and about, you know, complex stories, but they need to be things that are routed in actual hard science, not just fanciful leaps of logic that and -- but you know, we were open -- you know, there's an openness to at least exploring some of these ideas of a population-level benefit of surrogacy in both of the ways that has been expressed and just opening the boundary of what -- you know, John frequently talks about, you know, is it going to benefit this patient and we're broadening that discussion, is it benefiting this patient now versus later in this patient versus the population as long as the clinical evidence of that or the science evidence of that is robust. But that's my summary, not the FDA's summary, so I'll let -- if you want to say anything to close up today?

MS. NAMBIAR: No, it's -- I know when we started talking about this hypothetical case, we did think it was going to be difficult. But honestly I didn't think it would be so difficult. I think you've really got the panel members and most of the audience fairly perplexed and thinking and I think this is --

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it's a particularly hard one to address. But having said that, I think there's no harm to wrapping up the day a little sooner than we had planned. Many thanks to everybody who participated today, presented discussions, and we start tomorrow at 9:00 as well. I think registration is prior to that, but the first session which will be the last case study for this workshop will be tomorrow morning, we'll talk about the lysin products, I mean other interesting discussion. So thank you everybody for joining us today and we'll see you all tomorrow. Thank you.

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September 4, 2018
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