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U.S. FOOD AND DRUG ADMINISTRATION

IMMUNOMODULATOR/ENHANCERS PRODUCT DEVELOPMENT

10903 New Hampshire Ave.,  
Silver Spring, MD 20993

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Reported by: KeVon Congo  
Capital Reporting Company

<p style="text-align: right;">Page 2</p> <p style="text-align: center;">A P P E A R A N C E S</p> <p>1 Dan Rubin  2 Edward Weinstein  3 Cara Cassino  4 Michael Kaleko  5 William Hope  6 Helen Boucher  7 Todd Black  8 Mary Shatzoff  9 Filip Dubovsky  10 Sumati Nambiar  11 Filip Dubovsky  12 John Rex  13 Michael Bevilacqua  14 Shampa Das  15 Edward Cox  16 Edward Burd  17 Ann Eakin  18 Brian Tse  19 Kevin Outterson  20 Paul Ambrose  21 Wes Kim  22</p>	<p style="text-align: right;">Page 4</p> <p style="text-align: center;">P R O C E E D I N G S</p> <p>1 MR. RUBIN: (In progress) the nontraditional  2 therapies workshop. We'd like to get started, if you  3 could please take your seats. Today I don't think  4 we're going to be going around the table and doing the  5 introductions again. We'd like to move into the last  6 case study of the workshop which is on lysin product  7 development. And for this I'd like to turn it over to  8 my colleague, Dr. Ed Weinstein.  9  10 MR. WEINSTEIN: Hi. Good morning. Ed  11 Weinstein. I'm a clinical reviewer in the division of  12 anti-infective products, CDER, FDA. And I'm pleased to  13 present the last case study which is a hypothetical  14 case of a chimeric bacteriophage endolysin called drug  15 Z-4.  16 So this drug is a recombinant chimeric protein  17 of 30 kD in size that's composed of an ectolysin domain  18 from a bacteriophage enzyme fused to a staphylococcus  19 binding domain of bacterial origin. The development  20 program is intended to treat staphylococcus aureus skin  21 infections via topical administration and endocarditis  22 via intravenous infusion. There's no activity against</p>
<p style="text-align: right;">Page 3</p> <p style="text-align: center;">A P P E A R A N C E S (Continued)</p> <p>1 Vu Truong  2 Mary Beth Dorr  3 Wayne Danker  4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21  22</p>	<p style="text-align: right;">Page 5</p> <p>1 gram-positive or gram-negative bacterial species.  2 The nonclinical safety data profile includes  3 rats and mini-pigs. Intravenous administration was  4 tolerated at doses up to five times the proposed human  5 equivalent when administered daily for 2 consecutive  6 weeks. There was no dose limiting toxicity. Transient  7 fevers of less than 24 hours duration were noted in  8 some animals. This was suspected to be due to  9 endotoxin, the drug substances produced by batch  10 fermentation of E coli cultures.  11 Anti-drug antibodies were identified in rats  12 at day 28. Perivascular neutrophilic infiltrates were  13 noted at the injection site. Significant toxicity in  14 related ectolysins include severe, irreversible  15 vasculitis due to off-target activity. In mice and  16 rabbits, the topical solution at the proposed clinical  17 dose was applied to abraded skin daily for 14 days  18 without significant toxicity.  19 The nonclinical microbiology program revealed  20 that drug Z-4 is only active versus staphylococcal  21 species and this includes staph aureus and coagulase-  22 negative species. The MICs follow the normal</p>

<p style="text-align: right;">Page 6</p> <p>1 distribution for staph aureus with an MIC range from  2 0.03 to 16 mg/L; MIC 90 8 mg/L. There was no overdose  3 resistance noted in the screening panel. Time-kill  4 study revealed a 4-log reduction in MRSA USA300 counts  5 following 15 minutes exposure at four times the MIC  6 concentration in vitro. There were insufficient data  7 to establish a pharmacodynamic model.</p> <p>8 The nonclinical microbiology and PK/PD program  9 revealed that the predicted PK/PD properties associated  10 with bacterial killing revealed a linear relationship  11 between killing and drug concentration, with the mode  12 of action characterized by irreversible binding to the  13 target consistent with protein-protein interaction.</p> <p>14 In animal infection models, drug Z-4 was  15 effective in treating staphylococcus aureus infections  16 in two different animal models. This was judged by a  17 reduction in CFU/g and thigh infection in peritonitis  18 models. There was a survival benefit that was seen in  19 the peritonitis model.</p> <p>20 There are two clinical studies that were  21 completed. There was a Phase 1A, 24 healthy  22 volunteers, single and multiple dose nasal ointment at</p>	<p style="text-align: right;">Page 8</p> <p>1 subject. No other areas of AEs of concern were  2 observed. The drug was not detected systemically, but  3 one subject was positive for anti Z-4 antibodies at day  4 20.</p> <p>5 This raises a bunch of interesting questions  6 for the panel to consider. The first is the clinical  7 trial design, which indications in patient populations  8 should be recommended for a clinical trial involving a  9 single-course, single-genus therapy, where a trial be  10 feasible if enrollment is limited to the pathogens of  11 interest and outcomes are confounded by the  12 administration and effective empiric therapy?</p> <p>13 And secondly, considerations of safety. Given  14 the potential immunogenicity of a drug derived from  15 foreign proteins, how would you ensure that a patient  16 would receive a limited exposure when you screen for  17 the presence of anti-drug antibodies? Thanks.</p> <p>18 MR. RUBIN: Thank You, Ed. We'll now have an  19 industry perspective from Dr. Cassino from ContraFect.</p> <p>20 MS. CASSINO: Good morning. And thank you for  21 including us. Thanks for the opportunity to speak with  22 you about our experience with our lead lysin candidate</p>
<p style="text-align: right;">Page 7</p> <p>1 the proposed dose of 1% by weight. In general, drug Z-  2 4 was well tolerated, there were no discontinuations or  3 serious adverse events reported. One subject with  4 transient fevers 4 hours after administration was  5 noted.</p> <p>6 There was a Phase 1B proof of concept study  7 that was involved in nasal decolonization. This open  8 label study conducted in 20 healthy patients with MRSA  9 nasal colonization, the drug Z-4 ointment was given  10 topically three times daily at several doses for five  11 days. The study endpoint was daily quantitation of  12 MRSA by lavage from the nares 3 minutes before  13 administration, 30 minutes after drug administration  14 and 4 hours following the evening application.</p> <p>15 The only efficacy analysis that displayed a  16 significant difference between drug and placebo in  17 staph aureus clearance was the highest dose group, 30  18 minutes after drug administration, but the difference  19 appeared at the 4-hour time point. This was only seen  20 on the first day.</p> <p>21 One adverse event, a fever and leukocytosis, 4  22 hours post administration was noted on day 5 in one</p>	<p style="text-align: right;">Page 9</p> <p>1 CF-301. I'm Cara Casino. I'm the chief medical  2 officer and the head of R&amp;D at ContraFect. So just a  3 word on lysin technology just so in case everybody is -  4 - everybody's familiar. Lysins are bacteriophage-  5 derived cell wall hydrolase enzymes. In nature phage  6 secrete the lysin in order to release progeny phage.  7 The cell wall hydrolase breaks through this  8 peptidoglycan cell wall from the inside out, releases  9 the progeny phage. And what we're looking at doing  10 then is to harness that ability to break through the  11 peptidoglycan cell wall associated with rapid  12 bacteriolysis and turn that into a medicine,  13 medicinalize it so to speak.</p> <p>14 And so our approach has been to follow the  15 science to where we are now. Currently CF-301, which  16 is an anti-staphylococcal lysin, is in Phase 2 clinical  17 study which is evaluating a single dose of CF-301  18 administered intravenously for the treatment of known  19 or suspected staph aureus bacteremia and/or  20 endocarditis.</p> <p>21 So a few things that led us to this Phase 2  22 study. First of all I would comment, the company did a</p>

<p style="text-align: right;">Page 10</p> <p>1 lot of upfront work and took a while taking a brand new  2 concept, taking the concept of harnessing one of the  3 killing elements from the phage and turning it into a  4 recombinantly administered medicine free of phage  5 remnants. It took the company a while to get through  6 the upfront processes, be able to file the IND and move  7 on into clinic, but through that process learned a lot.  8 CF-301 has some hallmark features. Rapid  9 potent targeted bacteriolysis, active against all  10 staphylococcal specie and a few strep, not surprising  11 actually given the specificity of phage. Strikingly  12 rapid biofilm eradication both in vivo, in vitro and  13 more recently in biofilms formed in the setting of  14 human infection, synergy with conventional antibiotics  15 in vivo and in vitro. And in vivo again and again  16 replicatively shown in the rabbit infective  17 endocarditis model and the rat infective endocarditis  18 model, thanks to Arnie Bayer at UCLA who performed  19 those models for us.  20 And to give you an idea of what that looked  21 like, that was a single dose of 301 administered in  22 addition to human therapeutic equivalent doses of</p>	<p style="text-align: right;">Page 12</p> <p>1 Phase 2.  2 Animal studies did show the potential for  3 anti-drug antibody development, that's not surprising.  4 And in the animals, those ADA's were non-neutralizing.  5 I'll tell you what happened in Phase 1. We conducted a  6 Phase 1 trial of 20 patients. Four doses of 301 and  7 placebo taken in, in a single escalating dose Phase 1  8 study. And in that study, it was a very quiet Phase 1  9 study. No serious adverse events. This was healthy  10 volunteer study. No adverse events of hypersensitivity  11 reported and overall generally well tolerated. PK  12 profile linear and we're grateful for that because that  13 allowed us to use popPK from Phase 1 and our animal PK  14 to estimate our dose for Phase 2.  15 And in the arena of antidrug antibodies and  16 immunogenicity, ADA's were present and emerged 14 to 28  17 days post dose in healthy volunteers. The ADA's waned  18 or were completely gone by 180 days. And the  19 interesting thing we noted was that ADA's were not  20 associated with IgE or basophil activation, so not  21 associated with typical markers of allergic type 1  22 hypersensitivity.</p>
<p style="text-align: right;">Page 11</p> <p>1 daptomycin in rats and subsequently in rabbits, with  2 induced infective endocarditis, wherein 4 days of  3 daptomycin resulted in a three log drop in CFU's and  4 the addition of 301 resulted in an additional three log  5 drop in CFU's.  6 Those features we believe may be the core of  7 this new class of lysins because we're observing very  8 similar collection of features in our antipseudomonal  9 lysin discovery program which, thanks to CARB-X, we are  10 working on. Thank you very much. And we have now got  11 15 leads that we're going to be bringing into in vivo  12 studies.  13 A couple of other things about 301. One of  14 the things we're fortunate with is because of that  15 potent killing, we're also able to actually leverage  16 traditional antimicrobial susceptibility testing.  17 We've been able to develop an MIC methodology for use  18 in clinic that has been validated, CLSI approved. And  19 we've also been able to develop a PK assay and  20 therefore leverage relatively standard PK/PD approach  21 to determining dose, to determining PK driver of  22 efficacy, and to determine the dose to take through in</p>	<p style="text-align: right;">Page 13</p> <p>1 So we moved on, and so currently we're  2 conducting a randomized double-blind placebo-controlled  3 study in, as I said, bacteremia endocarditis. We went  4 in this direction. There are a couple of directions we  5 could have gone in. I think there was an extensive  6 discussion yesterday about the directions you can take,  7 a non-traditional therapy.  8 We had a number of options at our disposal.  9 We thought the high unmet medical need for new  10 treatments to address biofilm associated staph  11 infections and the fact that our animal data  12 repetitively showed us from the infective endocarditis  13 models, the potential for efficacy in this clinical  14 setting and the fact that the last drug approved, the  15 last small molecule, the last approved drug for  16 endocarditis bacteremia due to staph was Dapto back in,  17 I'd say, over a decade ago. We leveraged the Dapto  18 Phase 3 study.  19 We worked with folks like Helen who was on our  20 first clinical advisory board. We worked really  21 closely with Vance Fowler, he still is working with us  22 in the -- as our lead PI. And so we've been able to --</p>

<p style="text-align: right;">Page 14</p> <p>1 we opened the study last year, enrolled our first  2 patient in May. We are now beyond or thereabouts  3 around 75% enrolled. Our target enrollment is 115  4 patients randomized 3 to 2.</p> <p>5 This is a single dose of 301 administered in  6 addition to conventional standard of care antibiotics,  7 IV administration. And our primary endpoint is  8 clinical response at day 14. We're also looking at  9 response at end of treatment and test of cure, the  10 traditional endpoints. Again leveraged a lot from  11 Dapto study, definitions, endpoints, some features of  12 the study design. We have a data safety monitoring  13 board in place. They met last week. They told us to  14 continue the study as planned.</p> <p>15 We are of course still blinded as the sponsor.  16 But as I stand here today, we've had no SUSAR's, no  17 adverse events of hypersensitivity considered related  18 to study drug. And we are quite encouraged by our  19 progress to date. We're tracking towards a goal of  20 having data by the end of this year, top line results.</p> <p>21 And, you know, all I can say is we're pleased  22 by our progress. We continue to learn from 301 and we</p>	<p style="text-align: right;">Page 16</p> <p>1 design, we're doing a superiority comparison of 301 in  2 addition to standard of care, compared to standard of  3 care alone.</p> <p>4 So the question is what percentage of clinical  5 betterness, clinical response will constitute what's  6 considered a substantial evidence of efficacy. And I'm  7 looking forward to hearing what the panel thinks. So  8 thank you.</p> <p>9 MR. RUBIN: Thank you. We'll now have  10 additional FDA comments from Dr. Weinstein.</p> <p>11 MR. WEINSTEIN: Thank you. Thank you, Dr.  12 Cassino, for your comments. I just have some brief  13 points I'd like to add. The first is that the case I  14 presented was a hypothetical case. It's not an actual  15 product. You know, lysins in general, they're familiar  16 in the sense that they have a direct killing mechanism.  17 But they have two areas of development challenge that  18 make them non-traditional.</p> <p>19 You know, the first is that these are narrow  20 spectrum agents. In this case, it targets a single  21 genus and that creates difficulties with clinical trial  22 design that John Rex had described on day one.</p>
<p style="text-align: right;">Page 15</p> <p>1 continue to learn from what we're doing. Recent  2 observations, some things we're going to be presenting.  3 We have a upcoming presentation in Lisbon. As we've  4 observed that in vitro 301 appears to have the ability  5 to re-sensitize MRSA to penicillin derivatives in vitro  6 and in vivo from the infective endocarditis study.  7 We're planning to follow that up, but we're starting to  8 talk about that.</p> <p>9 We've also observed low propensity for  10 resistance with 301 in vitro, and we've also observed  11 this very interesting thing that if you administer 301  12 together with conventional antibiotic in 26 days serial  13 passage studies, not only does 301 not manifest  14 resistance to itself, it suppresses the emergence of  15 resistance to the conventional antibiotics.</p> <p>16 So we think there's more to learn about the  17 potential use of lysins, but as I said, we're  18 encouraged by our progress and we're happy to be here  19 to share this story. And I guess to discuss, we look  20 forward to the discussion around the future, where we  21 go from here and perhaps how we think about  22 augmentation because of course based on the trial</p>	<p style="text-align: right;">Page 17</p> <p>1 Second, they are foreign proteins and they may  2 induce host-immune responses. This was less of a  3 concern yesterday when we were talking about humanized  4 monoclonals, but lysins are fully foreign proteins. So  5 the range of host-immune responses may not only include  6 IgE mediated hypersensitivity reactions, but also more  7 subtle complications.</p> <p>8 So there's the potential for host mediated  9 resistance to therapy in the form of anti-drug  10 antibodies. We don't often think about host  11 resistance, but in other areas where host resistance  12 has occurred such as rheumatology, it's in the context  13 of a chronic non-life threatening disease. So this  14 creates challenges for appropriate dosing and  15 therapeutic monitoring.</p> <p>16 In terms of this case, it's not uncommon to  17 have a dataset such as this in the early phases of  18 clinical development. Consider this an advertisement  19 for early engagement with the agency. You know, we're  20 open to pre-IND discussions regarding development  21 plans. Proof of concept study linked to changes in  22 CFU. In this case it's interesting, but it's not</p>

<p style="text-align: right;">Page 18</p> <p>1 valuable without a link to a clinical outcome.</p> <p>2       So, for example, if the outcome or a reduction</p> <p>3 in surgical site infections, then that's a tangible</p> <p>4 benefit to the patients, that could be readily</p> <p>5 understood. So the study reflects some of the</p> <p>6 conundrums that we wrestled with on day one.</p> <p>7       In this case, as a summary, the study was</p> <p>8 highly feasible. It's estimated that 20% to 30% of</p> <p>9 people have staph aureus in their nose. But the</p> <p>10 endpoint was without clinical meaning. The results</p> <p>11 could not be interpreted. The treatment effect was</p> <p>12 only one point in time and appeared to be transient. A</p> <p>13 durable treatment effect is important.</p> <p>14       The generalizability was unclear. It's</p> <p>15 unknown which patient population would benefit.</p> <p>16 Defining a patient population likely to benefit from a</p> <p>17 treatment has been a recurring theme in this workshop.</p> <p>18 So I'll stop there with those comments and turn it back</p> <p>19 to the panel.</p> <p>20       MR. RUBIN: Thank you, Ed. We'll now move to</p> <p>21 the moderated discussion starting with the panel and</p> <p>22 then allowing questions from the audience or from WebEx</p>	<p style="text-align: right;">Page 20</p> <p>1 vegetations in the heart and potentially saving heart</p> <p>2 valves?</p> <p>3       On the other hand, could this be a problem in</p> <p>4 lysing vegetations in the heart and potentially</p> <p>5 releasing emboli? So I was -- well, that seems to me</p> <p>6 to be a great indication though, it was getting rid of</p> <p>7 the biofilm short term so that you can then blast away</p> <p>8 with your antibiotics. I'm sorry for that longwinded</p> <p>9 statement.</p> <p>10       MR. WEINSTEIN: So thank you for the question,</p> <p>11 and it seemed that there were a few components to it.</p> <p>12 The first part was the potential role of neutralizing</p> <p>13 antibodies and the spirit of the hypothetical case was</p> <p>14 to address that. Saying that if there are drug</p> <p>15 neutralizing antibodies, is this a consideration and</p> <p>16 what would be the appropriate steps to address it.</p> <p>17       In terms of your very insightful second</p> <p>18 question, in terms of the effect upon biofilm and the</p> <p>19 potential for the release of vegetations as emboli, we</p> <p>20 don't know. We'll have to see what the data ends up</p> <p>21 showing us.</p> <p>22       MS. CASSINO: Yeah. So we weren't able to</p>
<p style="text-align: right;">Page 19</p> <p>1 if you could just get my attention by turning your</p> <p>2 nametag up or otherwise getting my attention or that of</p> <p>3 Dr. Hope, and I'll start right there.</p> <p>4       MR. KALEKO: I'm not sure if I should comment</p> <p>5 on the hypothetical or the real at this point. But</p> <p>6 when I look at immunogenicity, yes, it's a safety issue</p> <p>7 and I agree with you. It's probably more an -- as much</p> <p>8 an efficacy issue as a safety issue. I heard that the</p> <p>9 antibodies in the animals were not neutralizing, that's</p> <p>10 a little surprising to me. I come from gene therapy</p> <p>11 and vectors get wiped out by antibodies.</p> <p>12       I didn't hear whether or not they were</p> <p>13 neutralizing in the humans. But in either case, it</p> <p>14 would suggest to me that if this is going to be used</p> <p>15 systemically, it would have a short timeframe for its</p> <p>16 value. And if that were the case, the thing that</p> <p>17 really comes out from that presentation is the lysing</p> <p>18 of biofilms, which is a real issue.</p> <p>19       So in the realm of endocarditis, for short-</p> <p>20 term use, you know, you're going to have to use your</p> <p>21 antibiotics for six weeks. But for short-term use, the</p> <p>22 question I have is, could this be of value in lysing</p>	<p style="text-align: right;">Page 21</p> <p>1 study that emboli phenomenon in, you know, we didn't</p> <p>2 see anything in the animals. We're obviously</p> <p>3 interested in that in Phase 2. We have enrolled</p> <p>4 patients with endocarditis left and right sided</p> <p>5 endocarditis. So far we haven't have had any serious</p> <p>6 adverse events that are considered to be related either</p> <p>7 by us or by investigators to study drugs. So that's</p> <p>8 all I can tell you. I'm blinded right now.</p> <p>9       Regarding the neutralizing, non-neutralizing</p> <p>10 in the clinic, of course the ADA's emerged in Phase 1</p> <p>11 at 14 to 28 days. Our single dose is a single dose.</p> <p>12 So we don't expect treatment emerging ADA's to be an</p> <p>13 issue. That being said, there are some people in</p> <p>14 nature who have cross-reactive antibodies to 301 as you</p> <p>15 would expect. It's a naturally occurring substance.</p> <p>16 So we are planning to look at that as some of our</p> <p>17 exploratory endpoints in the current ongoing study.</p> <p>18       MR. HOPE: So can you speak to the point of</p> <p>19 unmet medical need for staphylococcal infections?</p> <p>20 That's the first question. The second is as the case</p> <p>21 was presented and according to, you know, the regs</p> <p>22 classification of traditional versus non -- this seems</p>

<p style="text-align: right;">Page 22</p> <p>1 pretty traditional to me. You can measure it, you can  2 -- you have experimental models, you have PK, you can  3 construct exposure response relationships and you're  4 sort of the clinical pathway, it just looks like the  5 ARREST trial except you're replacing Rifampicin or  6 Rifampin with your compound. So could you just maybe -  7 - could you just speak to those points?  8 MS. BOUCHER: Me? You want me to take that?  9 Okay. I'll take that one. Okay. So unmet medical  10 need, I think we thought about that, where would be a  11 place where there's a need. There have been a number  12 of recent drugs approved for staph. There's a pretty  13 good staph aureus armamentarium. All of those agents  14 with the exception of Dapto have indications for skin  15 and soft tissue infections and that was their  16 development pathway.  17 The shelf is a little more spare in terms of  18 agents for treating staph aureus endocarditis  19 bacteremia. And we're -- when I say bacteremia, we're  20 focused on complicated bacteremia. Those bacteremias  21 that are more likely to be biofilm associated and I  22 take your point, that's one of our thoughts too, that</p>	<p style="text-align: right;">Page 24</p> <p>1 correct. We have some non-traditional things that we  2 know, that we're learning about 301 regarding the  3 synergy with conventional antibiotics. We'll see how  4 that plays out in clinic where we feel fortunate that  5 we're able to use traditional approaches, antimicrobial  6 susceptibility testing, PK/PD. But we know from the in  7 vitro work that there are some very interesting non-  8 traditional activities like, when used in combination  9 in the lab, suppressing the emergence of resistance in  10 studies designed and that do avidly show the emergence  11 of resistance for Dapto for oxacillin for Vanco. So  12 this is a traditional approach, but this compound has  13 some traditional and some non-traditional features.  14 MR. BLACK: I just had a clarifying, can you  15 tell us the tested cure criteria? Was that imaging the  16 vegetations or bacteremia, I wasn't quite clear what  17 the endpoint was?  18 MS. CASSINO: It's actually, we are looking at  19 both of those as separate and we have secondary  20 endpoints of microbiologic response at the same time  21 points as we're looking at clinical response. So  22 actually it's a clinical response. And that was the</p>
<p style="text-align: right;">Page 23</p> <p>1 the biofilm activity here is very, very interesting,  2 and may be one of the ways that 301 together with the  3 conventional antibiotics actually form a good couple.  4 If you look at the Daptomycin published  5 results from the Phase 3 non-inferiority trial, which  6 compared Dapto to standard of care, which was basically  7 everything else available, not semi-synthetic  8 penicillins, first generation cephalosporins and  9 vancomycin. The test of cure, the clinical outcomes at  10 test of cure which is the registration endpoint for  11 that trial were less than 50% response rate.  12 Granted that was partially dependent on the  13 structure and the analyses and there are a lot of  14 factors in there, but we felt that that gives us an  15 opportunity to improve and so a place where a treatment  16 in addition to that with a similar study design and  17 similar definitions would allow us to potentially be  18 able to show above and beyond efficacy with 301 in  19 addition. So that was the unmet need.  20 What, I'm sorry, you had another point that  21 you raised? I lost it. Traditional, yeah. Well,  22 we're following a very traditional pathway, that's</p>	<p style="text-align: right;">Page 25</p> <p>1 registration endpoint as close as we could get this to  2 be to the Dapto study. So it's based on the patient  3 still being alive, the patient's signs and symptoms  4 having resolved, the absence of further spread or  5 metastatic foci of infection and these are the salient  6 features and the absence of the need to use additional  7 step-up in care. In other words, throwing additional  8 antibiotics on or changing antibiotics.  9 There are a few other criteria, less than 12,  10 so if you need more than 12 weeks of antibiotics, that  11 would constitute a non-response, but those are the  12 salient features. It's really based on clinical  13 aspects and we do have an independent clinical  14 adjudication committee. So the PI's at the site  15 determine their view of the clinical outcome. And then  16 we have both diagnosis, complicated and uncomplicated  17 bacteremia endocarditis being adjudicated as well as  18 the outcomes at 7 days, 14 days, which is our primary  19 efficacy objective here, end of treatment and test of  20 cure.  21 MR. HOPE: Well, maybe so -- well, I'll keep  22 going. So given the hypothetical, I thought when that</p>

<p style="text-align: right;">Page 26</p> <p>1 -- the case was presented by the FDA about the  2 advantages potentially or just picking up from the  3 discussions from yesterday about the potential for  4 decolonization and a medicine to -- for prophylaxis  5 and, you know, decreasing surgical site infections as  6 one possible new avenue and then the point that you  7 just made, the other societal benefit or even patient  8 benefit is that you could get away from glycopeptides  9 if you can restore susceptibility to MRSA.</p> <p>10 So that, just listening again, well, I mean,  11 I'd be interested to hear what others in the room say,  12 but you generally don't get into a lot of trouble with  13 gram-positive infections with the drugs that are  14 available and the combinations that are available and  15 surgery, so those sort of other potential. So Helen is  16 going to say something, I can see. But the other --  17 but the more novel potentially advantages of decreasing  18 glycopeptide usage would be incredibly advantageous  19 given that, you know, these compounds are nephrotoxic.</p> <p>20 MR. DUBOVSKY: May be the other thing which  21 kind of cropped up in my brain was thinking about  22 prosthesis, joints that goes sour. And if you truly</p>	<p style="text-align: right;">Page 28</p> <p>1 patients, especially the group you mentioned, I think  2 the patients treated with glycopeptides do worse than  3 those treated with beta-lactams, right? People with  4 MSSA do better, it's a superior therapy. So that  5 avenue I think is really potentially exciting.</p> <p>6 I'm a little concerned about the complexities  7 of the clinical trials in bloodstream infection. You  8 know, these endpoints are very complicated. We're  9 measuring a lot of things and the predominant reason  10 for that, less than 50% success rate in the daptomycin  11 trial was the use of potentially effective non-study  12 antibiotics. It wasn't staph aureus and metastatic  13 foci and such.</p> <p>14 And these are complicated issues that we still  15 struggle with and it's part of the reason nobody else  16 has done a trial in over 10 years, as limited as that  17 trial was on many levels. So I think it's really  18 admirable that you're doing the trial, but I share some  19 of the caution, I guess, about the expectations.</p> <p>20 I think the idea of capitalizing on the  21 biofilm, no one has mentioned catheters but, you know,  22 catheters, even peripheral IVs still are associated</p>
<p style="text-align: right;">Page 27</p> <p>1 have a biofilm lytic mechanism of action, then there  2 may be some benefit there.</p> <p>3 MS. CASSINO: Yeah. We're definitely  4 interested in that. We had to start somewhere, right?  5 We had to start somewhere that had some sort of a  6 measurable and some kind of a pathway where we could  7 start. So between the animal data driving us to the  8 endocarditis and our clinical advisory board, this  9 seems like a reasonable starting point, but we are  10 interested and thinking about ways to look at  11 prosthetic joint infections, and quite frankly the  12 case, Helen, that you've presented yesterday comes to  13 mind of a person or a case or a situation with  14 complexities.</p> <p>15 MS. BOUCHER: So thanks. I mean, I agree,  16 William, with your comments, but I would offer that  17 staph aureus still has predictable morbidity and  18 mortality that's significant, right? So study after  19 study, even with all the limitations of the studies we  20 have, all comers with staph aureus in the blood,  21 mortality 15% to 25%, so we could do better. And I  22 think that's the medical need. And clearly we have</p>	<p style="text-align: right;">Page 29</p> <p>1 with staph aureus bloodstream infection in the best  2 hospitals in 2018. So anything that could, you know,  3 could this affect a biofilm on catheters as well as  4 prosthetic joints? I think those would be things that  5 would be really potentially interesting to explore.</p> <p>6 MR. KALEKO: Can this penetrate a staph  7 abscess? I mean, once you have multiple abscesses all  8 around your body, you're in a lot of trouble. Is there  9 any way to -- can this get into them?</p> <p>10 MS. CASSINO: We'll probably learn a lot from  11 the Phase 2 study. We've had a few cases of that. We  12 haven't looked at abscess penetration per se. We have  13 pretty good bio-distribution from the animal studies  14 for what that's worth.</p> <p>15 With regard to the catheters, we're interested  16 in that also. We recently did a pilot with Jamie Dwyer  17 at Vanderbilt, a nephrologist. It was actually his  18 idea which was to look at hemodialysis catheters  19 removed from patients as part of clinical care, who  20 have staph aureus, hemodialysis patients with staph  21 aureus bloodstream infection. So our lab analyzed a  22 catheter containing staph biofilm on the interior and</p>



<p style="text-align: right;">Page 30</p> <p>1 301 worked, you know, ex vivo of course very well. And  2 so we're thinking about -- we have a plan to follow  3 that up with a more robust study and think about where  4 we can go with that. Thanks. Thanks for the comment  5 on that.</p> <p>6 MR. HOPE: Can I ask you then about the  7 strategy of -- so you have -- you present these data  8 about our traditional approach, so you can show  9 logarithmic killing in laboratory animals. So let me  10 be heretical and ask you why you just wouldn't use this  11 as standalone therapy, and why it has to be additional  12 and you take the risk? Notwithstanding what Helen said  13 about suboptimal outcomes with staphylococcal  14 infections arrest shows the potential of an adjunct is  15 maybe difficult to demonstrate, and that the risk of  16 not being able to show superiority and where that would  17 leave you?</p> <p>18 MS. CASSINO: Yeah. Yeah. So we wouldn't  19 rule that out. This is a starting point, you know.  20 This was a starting point that we thought would give  21 the best opportunity to study and improve on clinical  22 outcomes as opposed to doing a non-inferiority</p>	<p style="text-align: right;">Page 32</p> <p>1 of concept studies because a lot of these alternatives  2 are going into these either direct organ, topical,  3 intranasal types of approaches to try to validate.  4 Is there -- do you see any value in that given  5 that the clinical outcomes there are kind of  6 questionable about what it tells you in terms of  7 potential for systemic therapies?</p> <p>8 MS. CASSINO: Yes. So that's a great, great  9 point. One of the things we're interested in is the  10 bone and joint, prosthetic joint scenario. We know  11 from the animal models, the animal data, we have that  12 the penetration is lower, not surprising, in bone. And  13 so we're thinking about and we have actually gotten  14 some suggestions from ways of looking at topical  15 administration. We're thinking about it. It's  16 definitely something we're interested in the setting  17 of, for example, a prosthetic joint.</p> <p>18 So that's something we're thinking about for  19 the future. And non-traditional ways of administering  20 the drug might be a way to think about it. But again  21 that's we're looking forward to our top line results  22 from this study. But that's definitely a direction.</p>
<p style="text-align: right;">Page 31</p> <p>1 approach, which is what we would be doing. And it is  2 sort of a big step to take a non-traditional compound  3 with some of these issues into a non-inferiority trial  4 with a standard traditional antibiotic without some  5 additional data.</p> <p>6 So we wouldn't rule that out. We would have  7 to do some additional work. Small company, additional  8 tox work. We'll see, we're looking forward to top line  9 results at the end of the year and that will probably  10 inform us of where we're going next.</p> <p>11 MR. RUBIN: Todd?</p> <p>12 MR. BLACK: So I still think one of the  13 challenges and unknowns on these large protein or large  14 kind of molecule therapeutics is the bio distribution  15 and the potential for the infection types. And so  16 there seems to be this emphasis on bacteremia or places  17 where you do think you're going to have exposure.</p> <p>18 So, I guess, one, do you have any data really  19 on the bio distribution of the lysin relative to other  20 large proteins and I think this also goes to  21 monoclonals. And just a question to Dr. Weinstein's  22 comments on the value of these topical types of proof</p>	<p style="text-align: right;">Page 33</p> <p>1 So we haven't focused. I will be -- I will  2 say, we haven't focused on the preventative  3 decolonization as in the case. That hasn't been a  4 focus of our company. We've been more focused on  5 treating something as opposed to preventing, that could  6 be a second step. We'll learn a lot from the  7 randomized controlled trial.</p> <p>8 MR. WEINSTEIN: So thank you for the question  9 in terms of the topical, potential of the topical use  10 of the drug such as the hypothetical lysin. I think  11 one of the problems is that when you're starting an  12 initial therapy, you're uncertain what the causative  13 pathogen might be for skin and soft tissue infections.  14 Classically it's staph and strep. So you need to cover  15 the strep at the start.</p> <p>16 A place where it might be, just thinking out  17 loud, interesting would be if you are talking about  18 secondary prevention, if you have like from the days in  19 the clinic, there are patients who would come with  20 recurrent staph aureus skin infections. And oftentimes  21 they go through different kinds of topical rituals to  22 try and prevent re-infection. And in the worst case</p>

<p style="text-align: right;">Page 34</p> <p>1 scenario they would end up on systemic antibacterials  2 in that particular patient population which are pretty  3 easy to find. There might be a benefit for a product  4 such as this.</p> <p>5 MR. KALEKO: This might reach into your  6 pipeline a bit, but can you tell me, is the lytic part  7 of this, the lytic component of the lysin, is that  8 enzymatic? Does a single hit kill the bacterium?</p> <p>9 MS. CASSINO: Yes, yes, it's enzymatic. So  10 it's a 26 -- 301 is 26 kDa native lysin, it's not  11 engineered or chimeric as in the example. It has a  12 binding domain and a catalytic domain and --</p> <p>13 MR. KALEKO: But a single hit is lytic?</p> <p>14 MS. CASSINO: That's what we think, yeah.</p> <p>15 MR. KALENO: Okay. Are there some for gram  16 negatives?</p> <p>17 MS. CASSINO: Yes, we're working on that.</p> <p>18 MR. KALENO: Okay.</p> <p>19 MS. CASSINO: We have an active discovery  20 program in our lab in Yonkers, New York. And we were  21 pleased that we received support from CARB-X to run  22 our gram negative -- start our gram negative lysin</p>	<p style="text-align: right;">Page 36</p> <p>1 antibodies and that in some of the animals, some of the  2 rodent species, if you re-administered the drug after a  3 hiatus, you could dose out for 6 or 7 days, something  4 like that or if you sensitize the animal and re-dosed  5 let's say a month later, there was a hypersensitivity  6 oid, not confirmed, clinical reaction.</p> <p>7 So going into Phase 1, this was a very  8 carefully orchestrated Phase 1 study. We had a DSMB in  9 place that reviewed each dosing and dose escalation  10 point. Thankfully there was nothing to be seen, there  11 wasn't much clinical, we did see ADAs. So 9 of the 13  12 subjects dosed with 301 developed ADAs, there was one  13 transient IgE above the cut point, there were no  14 basophil activation test positive post dose. None of  15 those subjects in Phase 1 had preexisting ADAs, they  16 were screened out. That was the decision the company  17 made, it was actually made before my time. So that was  18 just the decision for how the trial was going to be run  19 and then I think an abundance of caution and a healthy  20 volunteer trial.</p> <p>21 Phase 2, we realized and we met with the  22 agency and we talked about it, we looked at all the</p>
<p style="text-align: right;">Page 35</p> <p>1 discovery program. So right now we're focused on  2 antipseudomonal lysins.</p> <p>3 And so we have 15 identified in vitro out of a  4 field of about 500 that we were able to clone and/or  5 engineer. So we're going to be bringing them next step  6 into animals, and we look forward to moving them  7 forward.</p> <p>8 MR. KALENO: Okay. Last question then. Do  9 they work as antibody drug conjugates?</p> <p>10 MS. CASSINO: We haven't, I don't have any  11 data on that. We haven't looked at that yet.</p> <p>12 MR. HOPE: So since the question has been hung  13 out there by the FDA, just tell us about the propensity  14 for antibody generation, the safety of re-administering  15 the compound both in terms of decreased or absent  16 efficacy, but perhaps more importantly hypersensitivity  17 and anaphylaxis for re-administration and the steps  18 that were required or that you undertook to diminish  19 that possibility.</p> <p>20 MS. CASSINO: Sure, so, where do I start with  21 that. Okay. So what we know from the animals, when we  22 filed the IND, we knew animals made anti-drug</p>	<p style="text-align: right;">Page 37</p> <p>1 totality of the immunogenicity data that we had. We  2 know that some patients, some individuals do have  3 preexisting ADAs or antibodies that cross-react with  4 301, but we didn't screen them out in Phase 2. It  5 wouldn't really have been feasible and it would really  6 probably not be feasible to use the drug medicinally in  7 this way if you had to do a complicated ADA screen  8 while your patient has an acute infection.</p> <p>9 So we have gone forward with that and as I  10 said, clinically we've seen no evidence of  11 hypersensitivity during the conduct of the study. And  12 we are blinded and our DSMB has raised no cause for  13 concern. Now this study is an in hospital study and it  14 is a single dose. So when we put the protocol  15 together, we put in the requirements for observation of  16 the patient during dosing and we educated the PIs on  17 anaphylaxis should that occur and what to look out for  18 and we provided all the information. Fortunately knock  19 on linoleum or whatever that is, we haven't -- we're  20 pretty far through. I mean we dosed beyond 75% of our  21 115 or around 75%. So we haven't seen that. Now  22 that's a single dose, I can't comment on re-dosing per</p>

<p style="text-align: right;">Page 38</p> <p>1 se. What I can comment on is that when we looked at  2 all of our ADA data that we had, we were encouraged by  3 the fact that we didn't see IgE, we didn't see basophil  4 activation, we haven't seen that and we haven't  5 analyzed the Phase 2 data, but we haven't seen that  6 post single doze.</p> <p>7 So the single dose at the dose that we are  8 administering now may not be re-sensitizing the patient  9 for a type 1 hypersensitivity, we don't know, but  10 that's something that we are thinking about. So for  11 this indication, were this trial to have positive  12 results, single dose upfront, the things that we are  13 thinking about understanding better would be the  14 potential for re-dosing down the line, what would be  15 the time frame for that, how could we look at that,  16 that would be stuff that if we are successful, we would  17 be -- if this works out, we will be talking to the  18 agency about different ways we might be able to sort  19 that out.</p> <p>20 There are a couple of paradigms out there as  21 to how this was handled for other foreign proteins. So  22 there is the Xiaflex clostridium collagenase used for</p>	<p style="text-align: right;">Page 40</p> <p>1 considered and/or sort of monitored for other periods  2 of time or any other lessons to be learned from  3 immunologic products or the immune system is such a  4 broad thing and obviously the hypersensitivity would be  5 the most urgent issue, but are there things like, I  6 don't know cancer risk or other immune related things  7 to consider?</p> <p>8 MS. CASSINO: So for a single dose of a  9 product with a 6 hour half-life and the fact that we  10 haven't seen anything considered to be related and our  11 DSMB hasn't advised us of any needs to change what we  12 are doing right now. We're blinded. We haven't seen  13 any signals. The only other thing we did a little  14 thinking about was a serum sickness kind of phenomenon.  15 Blinded, we haven't seen anything that looks or smells  16 like that in the timeframe that one would expect it to  17 happen, again blinded post-study dose drug  18 administration. So, but we'll know more when we have  19 all the data.</p> <p>20 I think it changes if we think about it as a  21 multi-dose product. So that would be something else,  22 again not off the table. It certainly would, but it</p>
<p style="text-align: right;">Page 39</p> <p>1 Dupuytren's contracture et cetera was a subject of an  2 FDA advisory committee some time in recent years.  3 Because even though that's a locally administered drug,  4 patients do develop ADAs. It turns out that drug has  5 been able to be administered in repeat dosing fashion  6 on a regular basis. So that's one analogue to look at.  7 Going back in history, streptokinase is another one  8 that comes to mind back in the (inaudible) old care  9 when I was treating patients before there were other  10 options.</p> <p>11 So that sort of had a precautionary statement  12 of not to re-dose, although we are looking at labels  13 elsewhere because I don't think it is available in U.S.  14 anymore, those labels have also softened in terms of  15 the duration of time you could re-dose between, before  16 7 days or -- and after X amount, 6 months or whatever  17 for patient use. So those are kinds of things we are  18 thinking about depending on how that trial comes out.</p> <p>19 MS. BOUCHER: So I just had a little question  20 along those lines. So sort of appreciate the IgE path  21 and your comments about the ADAs weaning by 180 days,  22 but are there other immune responses that need to be</p>	<p style="text-align: right;">Page 41</p> <p>1 would require an investment into sorting through  2 whether there are any other risks, but we know from the  3 animals, we can dose. I think the acute allergic  4 hypersensitivity was the first worry and we know we can  5 -- we are expecting we could dose out to about 7 days,  6 if we wanted to do that from that. And of course if we  7 look at our pantheon of antibiotics of current and  8 previous, there are some common antibiotics out there  9 that have anaphylaxis and the warning and precaution  10 statement right up front, so we all know what they are.</p> <p>11 So I think for in hospital dosing, it would be  12 one thing, benefit risk, if this really improves the  13 outcomes, it would be one thing and then we would have  14 to think about where we would go from here. But this  15 is a good question where we have -- we are thinking  16 about it. Thank you.</p> <p>17 MR. KALEKO: To follow up on that question, it  18 was kind of a red flag in the presentation, may be you  19 could comment on it, related, license, cause and  20 irreversible vasculitis. Is that understood or is your  21 mechanism sufficiently different that you are not  22 worried about that? Did I read that correctly on the</p>

<p style="text-align: right;">Page 42</p> <p>1 screen, I thought that's what it said?</p> <p>2 MR. WEINSTEIN: Yeah, that's correct. Thank</p> <p>3 you for the question. So in some related products and</p> <p>4 animal models, there has been off target binding and</p> <p>5 enzymatic activity against great vessels.</p> <p>6 MS. CASSINO: So, where do I start with that.</p> <p>7 Okay. We haven't observed enzymatic activity per se.</p> <p>8 We have observed some perivascular and I want to say</p> <p>9 infiltration at doses well above where we are dosing.</p> <p>10 But those are doses well above where we are dosing. So</p> <p>11 we are dosing below, we are first, so it is hard to</p> <p>12 know where you belong and the potency of this is such</p> <p>13 that we learned from our PK/PD that low doses are</p> <p>14 pretty potent. So far we are well below that</p> <p>15 threshold.</p> <p>16 MS. NAMBIAR: Dan, can I ask a question? So</p> <p>17 Cara, a more general question moving away from the</p> <p>18 issue of hypersensitivity, I mean, this is a difficult</p> <p>19 indication to study. So I was wondering if you would</p> <p>20 be willing to share with the group strategies that you</p> <p>21 might have used because that sounds like you are able</p> <p>22 to enroll fair number of patients in a fairly short</p>	<p style="text-align: right;">Page 44</p> <p>1 enrollment. So we opened in May of last year in the</p> <p>2 U.S. and we have had really good enrollment in our U.S.</p> <p>3 sites, which is really nice. We work really closely</p> <p>4 with our investigators and I have to thank Elena,</p> <p>5 wherever she is, Elena, who is our lead medical monitor</p> <p>6 who answers every time her cell phone rings, every</p> <p>7 question that comes from everyone, which I think made a</p> <p>8 huge difference, I really do, because it is complicated</p> <p>9 to know whether the patient even fits in the study and</p> <p>10 then there is always a twist. So it takes a village to</p> <p>11 enroll these patients. So having someone on the other</p> <p>12 end of the phone makes a big difference. So those are</p> <p>13 the -- otherwise I don't know that there is any magic,</p> <p>14 oh, except to say our investigators were uniformly very</p> <p>15 enthusiastic. So they really were happy to be in this</p> <p>16 study and very enthusiastic to see a non-traditional</p> <p>17 being applied in a semi-traditional manner. So that's</p> <p>18 probably what helped.</p> <p>19 MR. DUBOVSKY: Did you try to control the</p> <p>20 standard of care or did you allow them to do whatever</p> <p>21 they wanted?</p> <p>22 MS. CASSINO: We tried to put some guidelines</p>
<p style="text-align: right;">Page 43</p> <p>1 time frame. So the geographic distribution of where</p> <p>2 you have been able to enroll and if you did use some</p> <p>3 particular strategies to help enroll because I think a</p> <p>4 lot of the indications that we are discussing are going</p> <p>5 to be the difficult to study indications. There might</p> <p>6 be some lessons learned that you could share with the</p> <p>7 group?</p> <p>8 MS. CASSINO: Yeah, sure. Thank you for the</p> <p>9 question. We are pleased by our enrollment. We were</p> <p>10 worried from recent history that it could take a</p> <p>11 glacial pace. One of the things that probably helped,</p> <p>12 "there are a couple of things that probably helped".</p> <p>13 First of all, all patients enrolled in the study are</p> <p>14 getting what would be standard of care prescribed by</p> <p>15 their physicians. So that's one thing that I think was</p> <p>16 probably helpful for recruiting. So our investigators</p> <p>17 were able to say, well, we can give you this in</p> <p>18 addition, it is in clinical trial, it may help you. So</p> <p>19 that was one thing.</p> <p>20 I'm also really pleased to say and I don't</p> <p>21 know if this is true for other trials, but our U.S.</p> <p>22 sites have led the way on this trial in terms of</p>	<p style="text-align: right;">Page 45</p> <p>1 in to give -- but leave sufficient flexibility for</p> <p>2 prescribers because we are open now in 14 countries.</p> <p>3 So we had to leave flexibility. So basically standard</p> <p>4 of care defined by conventional guidelines, basically</p> <p>5 Dapto or Vanco for MRSA semi-synthetic penicillin or</p> <p>6 your choice, whatever it might be in your region or</p> <p>7 first generation cephalosporins or what we ask people</p> <p>8 to, if somebody was on something else like Teicoplanin</p> <p>9 or whatever. We ask them to, if they were thinking of</p> <p>10 enrolling the patient, to move them over to one of</p> <p>11 these standard agents unless there was a reason not to</p> <p>12 and we excluded a couple of -- we excluded the long</p> <p>13 acting, Oritavancin and Dalba.</p> <p>14 MR. RUBIN: To follow up on that, were there</p> <p>15 any restrictions on prior therapy?</p> <p>16 MS. CASSINO: So we tried to enroll patients</p> <p>17 that had -- we wanted to enroll patients that had no</p> <p>18 more than 48 hours of effective anti-staphylococcal</p> <p>19 therapy for the current infection, but we wound up</p> <p>20 saying they could enroll with up to 72 hours with a</p> <p>21 conversation with Elena and if Elena thought that the</p> <p>22 patient was. We are looking to enroll complicated</p>

<p style="text-align: right;">Page 46</p> <p>1 bacteremia. So we were trying to get away from the 2 simple bacteremias that would clear their infection by 3 the time we are dosing. So, but 72 hours was the 4 limit.</p> <p>5 MR. RUBIN: Right. So I know we had some 6 discussion earlier about non-inferiority and I guess 7 maybe one advantage of these add-on superiority trials 8 is that there could be less restrictions in terms of 9 those enrollment criteria. Of course the downside is 10 that could diminish the ability to show a treatment 11 effect.</p> <p>12 And related to that I would say that in add-on 13 superiority trial, there could be some more flexibility 14 in terms of what endpoints could be used because there 15 wouldn't necessarily have to be a justification of the 16 margin for the active comparator. So the daptomycin 17 trial endpoint wouldn't necessarily have to be used as 18 a template for these types of studies.</p> <p>19 And just to go back to the door comments, 20 we're talking about yesterday, if it's very difficult 21 to define each of these subjects with staph aureus 22 bacteremia as a success or failure, it may be possible</p>	<p style="text-align: right;">Page 48</p> <p>1 seemed like it might be a thing in and of itself. And 2 I'm just curious as to whether you have any insights 3 about that and did you have -- you were going to say 4 something or did you -- so the question is that, have 5 you -- do you have any insights even now from your 6 trial? You may have some more after you've un-blinded 7 your data, but the bacteremia as a disease?</p> <p>8 MS. CASSINO: And thank you. That's a great 9 question. Particularly since there may be different 10 kinds of bacteremia and for the -- given the biofilm 11 activity and some of the other comments, we wanted to 12 focus on biofilm associated bacteremia. And the 13 challenge, so called complicated bacteremia, and I 14 think the challenge there is that there are -- is some 15 literature on this, there are some punitive definitions 16 out there.</p> <p>17 We started off with a really narrow definition 18 and our -- first adjudication committee meeting or 19 adjudicators said, "okay, this is really too narrow 20 because this guy is clearly complicated and he doesn't 21 fit in this definition". So we worked really hard with 22 them and with Vance to define a construct for</p>
<p style="text-align: right;">Page 47</p> <p>1 to have a more granular endpoint in these types of 2 studies.</p> <p>3 MR. REX: So a comment and then a question. 4 My comment is that we're all cheering for you. I think 5 everybody has wished for a long time for the lysins or 6 the phages as their superset to finally show us a way 7 to be useful. And I realized there are a lot of -- you 8 know, you can always take things like this apart and 9 come up with other ideas, but I hope everybody in the 10 room appreciates how much effort goes in to raising the 11 money that makes it possible to do a trial like this. 12 It is a herculean endeavor and I want, you know, it 13 really is and so very helpful for your data.</p> <p>14 Have you learned anything about definitions of 15 bacteremia as a disease entity even at this point that 16 are worth sharing? That's one that comes up a lot. 17 How can I study bacteremia and we had a long series of 18 -- some years ago, there were several workshops at the 19 EMA (ph). I don't remember one specifically here, but 20 maybe there was, I mean, it all kind of runs together 21 in my head. But this notion of bacteremia as a disease 22 and staph aureus was the one setting where that almost</p>	<p style="text-align: right;">Page 49</p> <p>1 complicated bacteremia. So we're going to learn a lot 2 about that and how that works at the end of the day 3 from the study.</p> <p>4 It is -- the other thing I think I appreciate 5 is that it's going to -- it's hard for the treating 6 physician when the patient hits the door to no 7 necessarily, whether it's going to be complicated or 8 not because you got to treat them upfront. You're not 9 going to withhold therapy and see if they blossom. So 10 you're treating them upfront and you're saying, "well 11 is the renal failure patient a diabetic, they have this 12 and that". Occasionally they may already have a 13 metastatic focus, so that's clear, but there's a big 14 gray area. And so thinking about indications, we were 15 thinking along the lines of bacteremia not otherwise 16 specified and endocarditis because it would be hard to 17 limit it.</p> <p>18 There's no clear litmus test of what is 19 complicated and what isn't, but that's just our 20 preliminary thinking. I think once we're able to 21 dissect this patient population, after we're unblinded, 22 it'll tell us a lot.</p>

<p style="text-align: right;">Page 50</p> <p>1 MR. REX: In my experience as an ID doc, staph  2 aureus in the blood is one of those terrifying moments  3 and I watched a young IV drug abuser, she almost  4 dissolved before my eyes due to staph aureus. And what  5 she came in with was staph aureus bacteremia, but then  6 all of a sudden it was in this organ and in that organ  7 and a week later it was everywhere and then 10 days  8 later she was gone.  9 And that was despite what at the time was the  10 best available therapy. So staph is that one or it's  11 what I remember from the, particularly the EMA  12 workshop. Staph aureus is that one organism that has  13 the ability to sort of eat through everything. And,  14 yeah, it may have started over in this corner, but get  15 it in the blood and, man oh man, is that a dangerous  16 situation. So I think the idea of a drug for staph  17 aureus bacteremia, this does always seem to me to be  18 the one corner where you can do that.  19 MR. BLACK: I guess along that because of the  20 challenge in that development program with these kind  21 of limited bio-distribution types of compounds, are  22 there other options and so certainly in immuno-oncology</p>	<p style="text-align: right;">Page 52</p> <p>1 aminoglycoside X.  2 So joint replacement surgery is the most  3 common surgery in the United States today and very,  4 very few, thankfully, patients get infected, but when  5 they do it's a huge disaster of epic proportions. So  6 our surgery colleagues, they're desperate. How to do  7 that in as controlled setting with a compound that  8 isn't approved for systemic use, that's where I have  9 trouble starting to put my head around it.  10 It's a need for sure, but it's almost like you  11 need a bioengineer and a drug -- you sort of need  12 multiple things going on at once to understand sort of  13 the technological aspects of the delivery of these  14 compounds.  15 MR. DUBOVSKY: So one thing that what you said  16 just sparked in my mind is instead of going after  17 specific indication, whether it be VAP, skin or  18 whatever, to do some kind of composite indication of  19 serious staph disease. And I'd be curious from a  20 regulatory perspective if that's something that is  21 palatable. Realizing that you wouldn't be able to  22 demonstrate specific disease, specific endpoints just</p>
<p style="text-align: right;">Page 51</p> <p>1 there has been a big shift in the view on intratumoral  2 types of applications because that really does seem to  3 limit toxicity and have high efficacy.  4 Is there any opportunity in things like  5 osteomyelitis? So you talked about the sternum case  6 yesterday. Helen or other kind of source specific  7 indications where some of these types of alternative  8 therapies could be developed and really addressing an  9 unmet need?  10 MS. BOUCHER: Our orthopedic surgery  11 colleagues work really hard in this area and they do a  12 lot of things that are interesting, right? So they  13 make beads and they put different drugs in the beads  14 and so our guys are about to start a trial of one of  15 the long acting agents in these beads.  16 Well, what's the dose? How do you do it?  17 Does surgeon A do it the same as surgeon B? We've  18 reported cases from our institution of nephrotoxicity  19 due to aminoglycoside that was put in a joint. And the  20 only way we found it is because we got consulted to  21 treat the infection, but realized that he had renal  22 failure from no other cause and ordered a level of</p>	<p style="text-align: right;">Page 53</p> <p>1 because of the power and the size issues, but perhaps  2 if we think back to our vaccine side, like pneumococcal  3 vaccine which is licensed for invasive disease or I  4 think some antifungals may be licensed for invasive  5 disease, if that's an approach that could be useful.  6 MS. NAMBIAR: So this is a discussion we've  7 been having for the last several years. Is treating  8 the bug enough or does the body site of infection  9 matter. And I think we've seen in many development  10 programs where products work in a body site or maybe  11 more than one body site, but then there is a clear  12 deficit when it gets to another body site.  13 So I think it's hard to ignore the site of  14 infection. Treating the bug is only one part of it.  15 It also depends on where the organism resides. Having  16 said that, I think there are instances where we are  17 willing to look at a product where the study population  18 could be a mixture of infections. It's very important  19 that we have discussions around the study design and  20 the endpoint if such an approach is taken.  21 So now our unmet need guidance, we do say if  22 you're contemplating a superiority trial design, there</p>

<p style="text-align: right;">Page 54</p> <p>1 might be an option to pool across body sites. However,  2 you have to make sure that you have adequate  3 representation of patients who have the most severe of  4 infections because that's the area that you're seeing  5 the deficit.  6 So there is a risk in that approach because if  7 there is a deficit with the product in a body site, so  8 you might not be able to understand that or that might  9 not be revealed in the study as it would have been had  10 you done an independent study of that body site. So I  11 think there are scientific concerns with just going  12 after an indication, which is to treat an organism  13 because the site of the infection is just as important  14 as the organism.  15 MR. DUBOVSKY: So presumably you'd want to see  16 at least a trend in each of the disease entities, yeah?  17 Or would that be adequate?  18 MS. NAMBIAR: Yeah. I think first and  19 foremost is you have to have a clear rationale for which  20 indications you're lumping in this multi-body site  21 study. And then you have to make sure you have an  22 adequate representation. Yes, you would like a trend,</p>	<p style="text-align: right;">Page 56</p> <p>1 it's such a burden on an efficacy study. I wonder if  2 our challenge is to try and get better understanding  3 penetration.  4 MS. NAMBIAR: I mean I think it's, given that  5 those pieces of information will be available before  6 you decide to go ahead with such a study. I think some  7 evidence that the drug reaches where it's supposed to  8 reach and treat the infection that you're trying to  9 target. I think the absence of all of that I think is  10 extremely risky to even try to do such a study. Yeah.  11 MR. BEVILACQUA: If you could just maybe  12 comment further, one of the places where multiple body  13 sites are brought together somewhat by an event or  14 surgical procedures. You just talked about the  15 orthopedic surgery were very large problem and I agree.  16 But also there are surgeries all over the body and  17 there's a wound, right? So while the sites of the body  18 are indeed different, there is a path of physiology of  19 the wound also. And certainly staph aureus is a player  20 in almost -- in many of those sites. So I wonder if  21 you'd comment about another path of physiological event  22 that occurs over multiple body sites. Does it</p>
<p style="text-align: right;">Page 55</p> <p>1 but again when it's a very small sample size, your  2 trend may or may not be a true finding, even a trend in  3 the wrong direction, that may not be a true finding.  4 So I think there are a lot of shortcomings  5 with that approach. So ideally I think studying it in  6 a body site or body sites is probably the best thing to  7 do, but if there is really a product that can address  8 an unmet need, we're willing to take the uncertainties  9 around the demonstration of the benefit with the  10 product. With some caveats, we might be willing to  11 consider a multi-body site study, but there are a lot  12 of details that need to be worked out and lot of other  13 information that would be needed that you're  14 comfortable going into those body sites as well.  15 MS. BOUCHER: Just because I was going to talk  16 back to this point. I wonder if there's other things  17 that we could do to understand that issue of body site  18 rather than doing that in an efficacy clinical trial  19 such as understanding the clinical pharmacology  20 exposure at the body site and use that to support.  21 Especially when we're talking about looking at these  22 pathogens and really needing to follow the pathogens,</p>	<p style="text-align: right;">Page 57</p> <p>1 influence your reason or your thought process?  2 MS. NAMBIAR: I want to make sure I  3 understand your question. So is the question,  4 potentially an indication such as surgical site  5 infection, but the site of the surgery could be maybe  6 the abdomen, it could be another?  7 MR. BEVILACQUA: Exactly. The  8 pathophysiological event is the wound, but again it is  9 influenced by body site.  10 MS. NAMBIAR: Right.  11 MR. BEVILACQUA: But not entirely.  12 MS. NAMBIAR: Right. I mean, I don't think  13 that -- I mean, that doesn't pose the same kind of  14 challenges as we're talking about multi-body site. I  15 think what might be different there is the  16 heterogeneity in the patient population, patient has an  17 abdominal surgery versus some other kind of surgery.  18 But if really you're targeting gram positive  19 pathogens, which are typical causes of surgical site  20 infections and then you have a mixture of patients with  21 different kinds of surgical procedures, I think that is  22 a lot easier to justify than when you're lumping, say,</p>

<p style="text-align: right;">Page 58</p> <p>1 a pneumonia and a urinary tract infection in one step.</p> <p>2 MR. RUBIN: So we have about 10 more minutes</p> <p>3 before the break and at this point, I'd like to ask if</p> <p>4 anyone from the audience has a question or comment.</p> <p>5 MS. LIU: I guess I have a question. My name</p> <p>6 is Mei Liu. I am from Center for Phage Technology and</p> <p>7 -- you hear me better? Okay. My name is Mei Liu. I'm</p> <p>8 from Center for Phage Technology from Texas A&amp;M</p> <p>9 University. This is my first time to attend this kind</p> <p>10 of regulation meeting and I really learned a lot.</p> <p>11 So just a little bit background. Our center</p> <p>12 is led by Dr. Ry Young and we were involved in the well</p> <p>13 reported Tom Patterson Phage Therapy case as well. So</p> <p>14 after that case, we are looking -- right now we're</p> <p>15 looking for partnerships with clinician networks and</p> <p>16 we, based on our existing phage libraries, we are</p> <p>17 trying to build several well characterized phage banks</p> <p>18 for selected groups of multi-drug resistant bacteria.</p> <p>19 So I guess I just have a general question on</p> <p>20 the patient enrolment criteria for lysin product.</p> <p>21 Because just like phage, lysins can be very narrow host</p> <p>22 range and I think in this case, hypothetical case Z-4</p>	<p style="text-align: right;">Page 60</p> <p>1 receiving it, there is that possibility that they may</p> <p>2 have some preexisting response that has become</p> <p>3 anamnestic. So I would answer that at baseline you</p> <p>4 would be concerned about the presence of anti-drug</p> <p>5 antibodies. And this was part of the screening that</p> <p>6 was described for the ContraFect trial.</p> <p>7 The second question, it's a little bit of more</p> <p>8 in terms of the trial size. It really -- the size of</p> <p>9 the trial will be determined by the treatment effect</p> <p>10 that you anticipate. I don't think anyone goes into a</p> <p>11 clinical trial expecting or hoping for a small</p> <p>12 treatment effect. But based upon the earlier</p> <p>13 experiences from, say, animal models or a smaller</p> <p>14 clinical trial, so you may have an idea from Phase 2</p> <p>15 what kind of treatment effect that they can expect.</p> <p>16 And then they will power the trial to statistically</p> <p>17 confirm that there is a treatment effect.</p> <p>18 So I think in general, the idea is to have a</p> <p>19 trial that is efficient. So not any larger than you</p> <p>20 need it to be.</p> <p>21 MR. RUBIN: All right. So we'll go to --</p> <p>22 MR. WEINSTEIN: I think that answers some, but</p>
<p style="text-align: right;">Page 59</p> <p>1 product has okay host range and the effect was</p> <p>2 transient, but the host range seems to be okay.</p> <p>3 So for, I guess, my question is very general.</p> <p>4 So is prescreening, for Dr. Cassino as well, so is</p> <p>5 prescreening the patient for sensitivity for the</p> <p>6 product, is that a good criteria? Is that a good</p> <p>7 practice to conduct a clinical trial? Because we know</p> <p>8 that maybe not for staph aureus, for other bacteria,</p> <p>9 for certain bacteria only personalized approach is the</p> <p>10 only way, only effective way to go.</p> <p>11 So I guess for the panel, I'd like to know</p> <p>12 that, would you rather see a very small sample size</p> <p>13 clinical trial with very good curing rate or would you</p> <p>14 rather see a large sample sized clinical trial with not</p> <p>15 so good effect from the product?</p> <p>16 MR. WEINSTEIN: So there is a lot to unpackage</p> <p>17 there, so thank you for the questions. I'll see if</p> <p>18 I've got this right. The first question involves</p> <p>19 concern about sensitization to such a drug product from</p> <p>20 the environment. And, yes, if you have a protein that</p> <p>21 there's a possibility that someone would come in</p> <p>22 contact during the course of their life before</p>	<p style="text-align: right;">Page 61</p> <p>1 probably not all of your questions.</p> <p>2 MR. RUBIN: Dr. Cassino, to follow up on that</p> <p>3 and then to Dr. (inaudible).</p> <p>4 MS. CASSINO: Okay. Thank you. So first on</p> <p>5 the prescreening for sensitization. Just to clarify,</p> <p>6 that was done for the Phase 1 study in healthy</p> <p>7 volunteers. The first human ever administration of</p> <p>8 this drug to a healthy human and the company opted to</p> <p>9 screen out anyone with a positive preexisting ADA,</p> <p>10 reactive basophil test or which were low in number for</p> <p>11 whatever reason in IgE above the cut point against our</p> <p>12 antibody testing assays.</p> <p>13 In Phase 2, we are not doing that. We are not</p> <p>14 prescreening anyone out. We are taking patients in.</p> <p>15 We think that's an important experience for us to</p> <p>16 gather. We put all the bells and whistles and</p> <p>17 precautions in place in our protocol in the event that</p> <p>18 we expect some people and we know some people in the</p> <p>19 study have preexisting antibodies of some sort, but</p> <p>20 we've seen no issues. We've had no hypersensitivity</p> <p>21 reported. We had no hypersensitivity reported as far</p> <p>22 as I remember and certainly none related to study drug.</p>



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<p>1 So that's where we are. And we are collecting  2 information and we're going to learn a lot from this  3 because we'll do analysis on whether or not the low in  4 number, but people who may have some cross-reactive ADA  5 baseline, what does that actually mean in terms of  6 their response, their PK, et cetera, et cetera. So  7 we're going to learn that. We factored that into the  8 trial from the get go in our sizing and our design.  9 And then just on the diagnosis. So we're  10 requiring patients to have known or suspected staph  11 aureus. So that's known either by traditional blood  12 culture, by staph aureus bacteremia. So either by  13 traditional blood culture, by rapid diagnostic or by a  14 KOH positive test with a positive gram stain of a blood  15 culture. So that's the baseline. So they have to have  16 the infection under study.  17 And then in terms of susceptibility to 301,  18 we've been doing surveillance studies. So far we  19 haven't -- we've seen MICs below the level that, from  20 what we can tell, we would expect to be susceptible in  21 all of our general population surveillance study. So  22 we haven't screened anybody pre. We'll be looking at</p>	<p>1 one decide on what is the additional benefit one is  2 looking for? What's the basis for coming to that  3 decision? But more important to follow up on what Dan  4 Rubin was saying is, this to me is an opportunity to  5 think about nontraditional endpoints because is it the  6 idea that you have to beat the base therapy on the  7 endpoint for which it was approved. So does it have to  8 be the test of cure, mortality? And that to me seems  9 like that's not necessarily what you're aiming for  10 here. You're aiming for some benefit and maybe the  11 benefit can be a different kind of endpoint such as  12 time to analysis. Maybe you don't beat it on the test  13 of cure or mortality, but the time to event, you know,  14 quicker cures or some other endpoint or some composite  15 endpoint and I'd be interested in having the panel  16 discuss that this kind of paradigm where you're adding  17 adjunctive therapy to theoretically effective  18 treatment, what kind of endpoints is one looking for  19 and this is an opportunity where we need to look for  20 nontraditional endpoints and things are a little bit  21 lesser than clinical cure, death, et cetera.  22 MR. RUBIN: Thank you. So we have one</p>
<p>1 the isolates throughout the trial, for their  2 susceptibility patterns to antibiotics and to 301. And  3 of course the patients are expected to be on adequate  4 antibiotic therapy to drugs, antibiotics to which their  5 drug is sensitive. And our adjudication committee is  6 looking at that in terms of evaluating endpoints, et  7 cetera.  8 UNIDENTIFIED SPEAKER: Yes, I would -- so this  9 is a very interesting paradigm that we're discussing  10 here, which is adding a new therapy to what's  11 theoretically effective treatment. And that's a  12 paradigm that is definitely non-traditional as we  13 haven't done very often. We've added -- we've used  14 combination therapies like (inaudible), but the theory  15 there is that you're adding something to address  16 resistance to the base therapy, but I don't believe  17 that this paradigm is specifically trying to address  18 resistance to the base therapy. It's trying to improve  19 on the base therapy. So this is failure of the base  20 therapy and related to resistance.  21 So that to me is a very interesting paradigm  22 and it raises two challenges to me. One is, how does</p>	<p>1 question from WebEx before we summarize and have a  2 break and this question is, for mixture infections that  3 often occur in clinic, we need a therapy against the  4 indicator, but not one pathogen. What will happen if  5 we just kill staph aureus from multiple infections?  6 Will this help other microbes grow better or not? Any  7 comments from the panel?  8 MR. DUBOVSKY: All of these pathogen specific  9 approaches, many we've talked about over the last 2  10 days have to deal with that issue, right? So and I  11 think it's part of the reason why there are concerns  12 about either replacement or outgrowth and that has a  13 lot to do with how you define your endpoint. Yeah.  14 UNIDENTIFIED SPEAKER: Dan if you can respond  15 to Ian's comment.  16 MS. NAMBIAR: I think there was a question  17 from Ian for the panel about whether we are willing to  18 consider other endpoints, he called them nontraditional  19 endpoints, I guess, different from what we've typically  20 done with antibacterial drugs for these kinds of  21 products. And I think the answer is, if there are  22 other endpoints which are clinically meaningful, I</p>

<p style="text-align: right;">Page 66</p> <p>1 think we're certainly willing to consider them and if I 2 understood Cara correctly, they are evaluating a series 3 of secondary endpoints. And I think eventually they 4 will pick, hopefully pick an appropriate endpoint for 5 the Phase 3 trial. So that's, I think that highlights 6 the importance of doing these kinds of Phase 2 studies 7 and learning and hopefully identifying other potential 8 endpoints that might be more relevant to products such 9 as these. I don't know Cara if you want to add to 10 that.</p> <p>11 MS. CASSINO: Yeah. Thank you. Thank you, 12 Dr. Nambiar. That's correct. We picked actually the 13 14 day efficacy endpoint which is already not what has 14 been the standard approval endpoint for this indication 15 at least because we thought it might be more reflective 16 and give us an earlier signal of efficacy because of 17 the way the drug works and then we're collecting quite 18 a few secondary endpoints, which will help us look at 19 things that have been raised today. We're looking at 20 the echos for the endocarditis patients. We'll be able 21 to evaluate time to certain endpoints. We're also 22 collecting health resource utilization endpoints, et</p>	<p style="text-align: right;">Page 68</p> <p>1 appears uncertain. There was quite a lot of discussion 2 about adjunctive learning that can occur about disease 3 processes and pathogenesis given the new molecules that 4 are being generated here including study endpoints, 5 infection of bodily sites, response to infections and 6 whether they can be used and harnessed to guide the 7 development of future medicines. And I think something 8 that was also discussed is that nontraditional 9 molecules or molecules out of the, well, that are not 10 small, are likely to bring idiosyncrasies in CMC and 11 immunopharmacology that need to be expected and 12 investigated. Dan.</p> <p>13 MR. RUBIN: Thank you. That covered it from 14 my perspective as well. So we'll now take a break 15 until 10:40 and then reconvene. Thank you.</p> <p>16 (Recess)</p> <p>17 MR. REX: Okay. So we're all going to sit 18 down now I think and get started. We're all going to 19 sit down now and get started. Okay. We're almost 20 there. So with any luck, I guess, my slides are still 21 up. So we have about an hour on the schedule and what 22 Ed and I have agreed to do is, I've got a few slides to</p>
<p style="text-align: right;">Page 67</p> <p>1 cetera.</p> <p>2 So we're hoping to get like a 360 view and 3 hopefully that will help us plan better for Phase 3, 4 but Ian, thanks for the comment because we're hoping to 5 learn from this. I know where you are.</p> <p>6 MR. HOPE: All right. So I think we've come 7 to end and just a brief summary from both of us then. 8 So I think that we debated at the very beginning about 9 whether this was a traditional or nontraditional 10 program and pathway and we're going to talk about that 11 after the break. I think that there was a sense that 12 even though if you label a compound as nontraditional, 13 still there are traditional pathways that need to be 14 followed and that we still have to address medically 15 issues and needs that are real and that are valuable to 16 the patient and the society.</p> <p>17 The use of pathways that are outside that 18 paradigm such as decolonization and reduced spread seem 19 to be difficult at the moment, but nevertheless 20 potentially important. The use and relevance of 21 adjunctive data such as clearance of organism at non- 22 sterile sites to de-risk programs was discussed and</p>	<p style="text-align: right;">Page 69</p> <p>1 show you that summarize some of the things that I think 2 that I heard, Ed's going to riff off that and then very 3 interested in comments or things that didn't get 4 brought up, that wasn't the right space for previously 5 and so forth. And we're realizing that those -- it's 6 not projecting on the little things on the inside I 7 don't know how to fix that, sorry. Sorry about that. 8 You may have to turn around and look at the slides, to 9 the left or overhead. We're delighted we've gotten 10 this much to present.</p> <p>11 So here are the five things that I think that 12 I heard. The first one is that the label 13 nontraditional is very broad and requires 14 qualification, structure versus goal may help a bit, 15 and I'm going to go into each one of these in a little 16 bit more detail in subsequent slide.</p> <p>17 Second is that current development tools are 18 often suitable. There may be some gaps and I've 19 identified a couple of the gaps here on this slide, and 20 again, we'll drill into that. The lack of a tool or a 21 path can be managed. It's really we should view it as 22 an opportunity to come forward with a really concrete</p>

<p style="text-align: right;">Page 70</p> <p>1 idea as a sponsor. And new approaches have been and 2 will hopefully continue to be developed.</p> <p>3 The product's whole effect must be considered, 4 don't be seduced by a pretty mechanism is going to be 5 the subtext there. And a high level guidance document, 6 a high level guidance document might be useful, but 7 we're not ready to commit, I don't think, to very many 8 details.</p> <p>9 So now digging a little deeper. The phrase 10 nontraditional is broad and language matters and I just 11 stumbled into one of this quote. When I use the word 12 Humpty Dumpty said in a rather scornful tone, it means 13 just what I choose it to mean, neither more nor less. 14 The question is (inaudible) whether you can make words 15 mean so many different things.</p> <p>16 Nontraditional is too broad and needs a lot of 17 qualification. Alternatives to antibiotics is no 18 better as a label. I didn't hear any other really 19 strong ideas come forward. I think we're going to end 20 up with the phrase nontraditional. The closest I've 21 got is that structure versus goals seems to help a 22 little bit with categories, but the deeper question for</p>	<p style="text-align: right;">Page 72</p> <p>1 suitable. The challenges that came up were more often 2 than not, not unique to nontraditionals. Small effects 3 are hard to measure and rare events or rare pathogens 4 require large trials. I mean, that's true in lots of 5 settings.</p> <p>6 But let me talk about three specific potential 7 gaps. Gap number one is the measure of indirect or 8 delayed benefit. And here it spins out of the question 9 of microbiome and colonization and the theme that I 10 like, I think it was Scott that picked up -- proposed 11 the word surrogate. It's -- the shape of your 12 microbiome or your colonization is a surrogate for 13 something that may happen down the road to you or to 14 somebody near you. And there are a few settings where 15 we do treat carriage of a specific pathogen as 16 tantamount to an active infection. Group A strep in a 17 surgeon, group B strep in the third trimester of 18 pregnancy, a serious (ph) meningitis in the nose in 19 anybody are things that we take as very serious events 20 and we respond to them.</p> <p>21 And I think the question that I heard being 22 discussed is, are there other such things? What would</p>
<p style="text-align: right;">Page 71</p> <p>1 me really is, within the space of this thing we call 2 nontraditional, what buckets of conversation would be 3 most productive? And are there ways to chop up the 4 space to drive a workshop that would help you create a 5 general answer that would be useful to more than one 6 developer? So some ideas for buckets that have come to 7 me, I mentioned these yesterday, host directed versus 8 pathogen directed, and it might be that we need a 9 workshop on host directed therapies. We understand 10 pathogen directed, but maybe host directed. Please go 11 into presentation mode it says, okay. Try that, does 12 that make a difference? I hope it's not worse. Okay. 13 Is that the same? All right. Makes it bigger though, 14 it's true. Thank you.</p> <p>15 The question of direct or immediate benefit 16 versus indirect or delayed benefits I think is a worthy 17 one. Maybe immunogenic versus non-immune response and 18 maybe explicit combinations versus single entity, so I 19 have some comments on some of these here in a minute.</p> <p>20 So theme number two, the current tools often 21 work. In listening to the cases we discussed, the 22 current program designs often seemed like they were</p>	<p style="text-align: right;">Page 73</p> <p>1 you measure? Do you want to look at infection 2 yourself? Do you want to look at transmission to 3 others? Do you want to look at infections in others? 4 What would you get at that would be compelling? And 5 that was we -- the conversation kind of ended there, 6 but that was the idea that sort of came to my mind.</p> <p>7 Gap number two, combinations. This is -- I 8 thought this was intriguing as well. How would you 9 evaluate a mixture of 5 to 10 antitoxin virulence 10 monoclonals? It might come up with something like 11 that which staph aureus makes a couple of dozen 12 virulence factors/toxins. And a factorial design is 13 not really possible. And so I'll ask the question, is 14 it okay to simply accept the sponsor's mix of 15 monoclonals? Treat it, call it -- treat it as a 16 polyclonal. The safety is on the mixture as is the 17 efficacy. The fact that dropping out one of the MABs 18 might reduce the cost of goods is kind of the sponsor's 19 problem and ditto for the dose of any one component 20 being wrong.</p> <p>21 And team Merck here can think about whether or 22 not, yes, they're pleased that they've got their cost</p>

<p style="text-align: right;">Page 74</p> <p>1 of goods down for their anti-C-diff monoclonal, but  2 what if you hadn't done that, yet it was out there  3 working, it's kind of interesting to muse on because  4 scientifically I'd wish to fully resolve all the  5 points, I understand what I'm saying is kind of  6 unscientific, it doesn't feel scientific. But if  7 there's an effect, there's an effect and it's kind of  8 an interesting thing to noodle on.  9 Right before the break, Ian Friedman stood up  10 and asked a question that I captured as this slide,  11 current tools and endpoints. Are there other endpoints  12 to consider? And Ian, if I've paraphrased your  13 question correctly, consider an add-on that doesn't  14 improve on the mortality effect of the base therapy.  15 So the base therapy versus the base therapy plus the  16 add-on, the mortality is 20%, equals 20% and its non-  17 inferior. But there's something else that you want to  18 show is better. And you could say that -- you could  19 generalize that, that's what we do for all  20 antimicrobials. I do -- I study my drug in complicated  21 UTI versus meropenem and I show that I'm not inferior  22 to meropenem, but the superiority is somewhere else and</p>	<p style="text-align: right;">Page 76</p> <p>1 concrete, be specific and think about the other  2 questions that's about value.  3 Don't be seduced by a pretty mechanism. The  4 mechanism is really important, consider the whole  5 effect. And Ed made us think yesterday about -- he  6 made up a case scenario that I've -- I think I've kind  7 of replicated here. For a hypothetical anti-staph  8 aureus toxin monoclonal, where you do a study and your  9 endpoint is nosocomial pneumonia, HAP/VAP and the staph  10 aureus nosocomial pneumonia rate goes down from 25% to  11 15%, that's nice, but the all cause mortality goes up  12 from 30% to 40%.  13 So the product did its bit, it absolutely  14 reduced staph aureus pneumonia, but did clearance of  15 staph aureus create other issues? Typo. So it's a  16 made up example, but you may want to think about what  17 that would mean. And I thought that the discussion of  18 intercurrent mortality around the C diff product was a  19 similar -- felt somewhat akin to that for me. And my  20 personal view is that the net effect in the enrolled  21 population which is hopefully the population going to  22 use it in the long run is what matters. And I'd argue</p>
<p style="text-align: right;">Page 75</p> <p>1 I want to show that somehow.  2 So I think the general question of what  3 measures are strong enough to be compelling is a good  4 one and I think that has been discussed probably in  5 other floor but perhaps we need to have a discussion,  6 perhaps, about this relative to anti-infective  7 products. I'm not sure whether that's the right thing  8 or not, but it's worth raising.  9 Number three, Owen McMaster's (ph) slide,  10 comments yesterday made me think about this, no path  11 yet, don't panic. Using existing tools is desirable  12 when possible. It's kind of like its less trouble, but  13 there won't always be a path yet. And this is an  14 opportunity for a sponsor to propose something new and  15 innovative. And I've heard repeatedly that the FDA, as  16 I know is the case with EMA as well, is very happy to  17 have discussions about how an innovative program might  18 progress. It's the sponsor's job though to drive this.  19 You've got to come up with something concrete and the  20 sponsor is the only person who really can do that or  21 the only group because you know more about your product  22 than anybody else in the universe. This is -- but be</p>	<p style="text-align: right;">Page 77</p> <p>1 that this is actually not a regulatory issue. If the  2 effect does not punch through real-life situations,  3 then the value proposition seems likely to me to be  4 weak.  5 It's intriguing to think about the door  6 approach, the hierarchical endpoints kind of approach  7 to showing some of this -- some value. And I think  8 that the previous slide where I pointed at the idea of,  9 are there other endpoints feeds into this? So  10 something to play with and maybe that's another kind of  11 workshop thing if we had a good question to focus on.  12 Anti-virulence and the whole effect, one more  13 slide. I just observed, and this came up a couple of  14 times, I talked about the pathogenesis and immune  15 response in animals. The animal models are incomplete,  16 imperfect. And I just pulled out two papers out of the  17 literature both of which conclude basically the same  18 thing. The animal models are a good hint, but they  19 don't always go to the same place as human beings. And  20 you may also find that there are limits on bio  21 distribution. There are things you can do in animals  22 that maybe you can't do as readily in humans in terms</p>

<p style="text-align: right;">Page 78</p> <p>1 of delivering product to a site. These are all the  2 reasons why you have to be careful about thinking about  3 the whole effect. And so again, personal view, my  4 sponsor needs to maintain a skeptical attitude. You're  5 going to have to start with the preclinical models and  6 maybe this is not one of those workshop spots.</p> <p>7 High level guidance document. My personal  8 view is, if we did one right now, it would need to be  9 very general. But actually I think it might be useful  10 because it is kind of the effect of encouraging work.  11 If there are sponsors trying to raise money and they  12 want to talk to the venture community about raising  13 money in an area. Having just a general sense of  14 direction from the agencies is a helpful thing in  15 making those presentations. That said, this -- the  16 conversation over the last 2 days has shown that there  17 are many details not yet ready to be nailed down. And  18 so here are a few of my thoughts for future workshops.  19 And I wouldn't -- if we did such things as a group, I  20 think you'd want to look for a reason to do that  21 workshop. So look through the CARB-X portfolio or  22 maybe things FDA is saying, is seeing and if there are</p>	<p style="text-align: right;">Page 80</p> <p>1 a couple of points just to sort of emphasize them. We  2 heard a lot of discussion about mechanism. And  3 mechanism is really exciting and mechanism is what gets  4 you to the new lead molecule that you want to develop,  5 and mechanism is -- tells you that you've got something  6 different that has got potential and its unique.</p> <p>7 But as you think about development, I want to  8 just encourage folks. As you move along in  9 development, use mechanism for everything that it's  10 worth. Help it inform your development program, help  11 it inform the indication that you're going to develop  12 the drug for. But as you're moving towards those later  13 stages, realize that then you're starting to look at  14 the patient. How is the patient doing? Is the patient  15 overall better off? So I just sort of put that in  16 there and I would say that really the ideal approach is  17 to use mechanism for all that its worth and it's very  18 important in the early stages, but also have in mind  19 the patient even at those early stages because I think  20 that's going to give you sort of the most complete view  21 of your development program. You'll start to  22 anticipate things that are going to become important to</p>
<p style="text-align: right;">Page 79</p> <p>1 a couple of them that have an interesting common core,  2 maybe that's a good reason to do a workshop on it.</p> <p>3 So the idea is that I thought of were host  4 directed, this question of indirect or delayed clinical  5 benefit. And the thing about animal models versus  6 human illness and I know that in each case there may  7 already be some data on this topic, but maybe we want  8 to have a conversation focused on the kinds of products  9 that we're interested in developing.</p> <p>10 And so my last slide is a reminder that  11 nontraditional just means we haven't done it yet and I  12 realize, I sometimes see that quote that all art was  13 once contemporary, the old art, that ancient art, well  14 it wasn't for the Romans, it was an ancient at all, it  15 was contemporary. And so I think for us what's  16 nontraditional today, it'd be interesting to see some  17 of these things become sort of routine practice in the  18 future. So with that, those are the thoughts that I  19 had. And then over to Dr. Cox.</p> <p>20 MR. COX: Yeah. Thanks John. Excellent  21 summary going through a whole range of things. And I  22 think what I'll do is really -- I just want to touch on</p>	<p style="text-align: right;">Page 81</p> <p>1 you later on.</p> <p>2 So I just want to throw that out there because  3 I know, we had a lot of discussion about this issue  4 over the course of the workshop. I think this is  5 really important as folks think about their development  6 programs and sort of how to look at their molecule, how  7 to think about the present, how to get as much out of  8 it as they can, but also to be thinking towards the  9 future. So there isn't something that you get to down  10 the road and say, oh I wish I had done whatever so.</p> <p>11 And then enrichment. So I thought the  12 conversation about enrichment was fascinating because  13 there were a couple of really important points that  14 came out in that. The initial discussion started  15 talking about, let's go to the patient population with  16 the highest event rate. It makes total sense as you  17 start to think about enrichment. But then something  18 else came up, which was, there's a lot of other events  19 that happen in that population. And if you're trying  20 to do a superiority trial and you have all these other  21 events, it can sort of cloud what it is that you're  22 trying to discern from the overall study.</p>

<p style="text-align: right;">Page 82</p> <p>1 So, and then there was the discussion of maybe  2 there's a U-shaped curve. There are patients who don't  3 have enough events, there's patients who have more  4 events and then there's patients that have disease that  5 is so severe that they couldn't respond anyway. So  6 this is sort of another piece of this sort of thinking  7 about enrichment. And then we also heard a comment of,  8 well, there are some patients and there's a patient  9 population in whom this disease is also important, but  10 their event rate is lower. But you might be able to  11 study this patient population because there are all  12 these other things going on that are going to confuse  13 your assessment trying to look for superiority.  14 So I think that discussion brought out a lot  15 of really important points to think about what really  16 is enrichment and how do you think about what patient  17 population to do your study in. And of course we would  18 like to see the drug studied in all the patient  19 populations that are relevant, but there are obviously  20 practical considerations as to what can be done first,  21 what is it -- in which area is a trial most likely to  22 be able to demonstrate the safety of a drug and the</p>	<p style="text-align: right;">Page 84</p> <p>1 of things in animal models of infection. And then the  2 other thing that came in, and I think this is an  3 important lesson and that is that the models can really  4 help to inform and to make rational decisions, but  5 they're not always right. There are going to be gaps  6 between what happens in the animals and what happens in  7 humans and we have seen that over and over again.  8 That's not to say don't do the animals. Of  9 course do the animals and of course try and learn as  10 much as you can. And as others have taught me too,  11 oftentimes what you're doing is, you're not just  12 looking at one animal model, but maybe you're looking  13 at a couple to try and see if they're sort of all  14 moving in the same direction to sort of help increase  15 the likelihood that what you've learned from the  16 animals has a greater chance of informing correctly  17 what it is that you expect to see in humans. So I  18 thought that was a really important point too.  19 And then we talked some about this issue about  20 which is again a lot of these things start to overlap,  21 the issue of replacement infections. If you impact on  22 one particular pathogen, is there something else in a</p>
<p style="text-align: right;">Page 83</p> <p>1 efficacy of a drug.  2 So just some things to think about, but I  3 thought that was really a good discussion. And then  4 there was also the -- part of this too is almost this  5 issue of competing risks if you will. It starts to  6 come in there because you've got the pure efficacy  7 assessment on the event that you're trying to  8 influence. But then you also have other events that  9 are going on at the same time too. So there's some  10 relationship I think with the competing risk issues  11 that also figures into this thinking and thinking about  12 how a clinical trial would be designed.  13 And then I think those are sort of the two  14 most important points that I just wanted to reiterate  15 that John made. There was the -- you heard the  16 discussion about pre-IND consultation. We welcome  17 folks coming in and talking about their toxicology  18 program, talking about their preclinical models.  19 That's obviously very important, something to be done  20 that can help to inform the development program. You  21 can start to look at not only toxicity issues, you can  22 also start to look at exposure response and those sorts</p>	<p style="text-align: right;">Page 85</p> <p>1 prevention study, is there something else that's going  2 to move in and take up the space for the pathogen that  3 you've knocked out and then what is the net overall, is  4 the patient better off.  5 So there's a lot of things and a lot of  6 similar themes that are coming up as we think about  7 these issues. And John, how do we want to do this? Do  8 people want to make any comments or ask any questions  9 at this point?  10 MR. REX: You can see doctor, I'm sort of  11 taking notes a little bit.  12 MR. COX: Okay.  13 MR. REX: I'm taking notes a little bit, so I  14 think this is the opportunity for everybody to align on  15 some of these ideas or suggest other workshops, propose  16 work for Ann Eakin to do, you know.  17 MR. COX: And I'm going to throw out -- I'll  18 throw out one more thing and then I'll pause. That'll  19 give folks a chance to think for a minute and see if  20 there's other points that they wanted to sort of  21 mention or bring up. But that is that, you can tell  22 from this workshop what we tried to do was come up with</p>

<p style="text-align: right;">Page 86</p> <p>1 examples that were as close to reality as we could.  2 And you see how imperfect. Despite coming up with  3 perfect hypothetical examples, if you will, I know a  4 tremendous amount of work going into these things.  5 Reality is always different. There's always something  6 that happens.  7 So and what I'm thinking about, John's talking  8 about future workshops, and I think if I reflect back,  9 we have been able to, at various points in times, and  10 I'm sort of just throwing this out there or something  11 to think about, obviously not something we're going to  12 do today because we're about to wrap up here. But as  13 we think about future workshops, one of the things that  14 can be very helpful is if companies are willing to  15 essentially come and talk about their development  16 programs. So we move from the hypothetical to actually  17 what's happening. And I realize that that's a very  18 delicate issue, that's why I'm mentioning it today  19 because we obviously won't do it today. But it's  20 something to think about because that can be very  21 instructive. Obviously a successful program is usually  22 much easier to talk about than one that hit bumps along</p>	<p style="text-align: right;">Page 88</p> <p>1 affairs, probably one of the few people here that do  2 that. You mentioned coming in early, prior, and I'm  3 looking at the scenario prior to your pre-IND meeting.  4 Could you speak just a little bit about the logistics  5 of how that would occur?  6 MR. COX: Yeah. So I mean we have under the  7 category of pre-IND meeting handled a range of  8 different topics if you will. And that is an  9 opportunity that we try and make available. It really  10 becomes an issue of just trying to manage all the  11 requests if you will. Sumati's division works very  12 hard, does great work and we're flattered by the level  13 of interest, if you will, that folks have and coming in  14 and talking with folks. But, yes, we can do that.  15 And like all meetings, the quality of the  16 meeting is dependent upon really the quality of the  17 materials and the submissions that come in. The  18 developer knows the developer's molecule very, very  19 well. They know where they're headed. So to the  20 extent that a lot of thought and preparation goes into  21 those meetings, that makes those meetings more valuable  22 for everybody. So that's just one more piece. So,</p>
<p style="text-align: right;">Page 87</p> <p>1 the road. But as I think about where we learn, we  2 learn oftentimes more from the programs that didn't  3 work out because there's something important there that  4 we didn't expect, we didn't anticipate and you learn, I  5 mean, it really is true. You think about it. People  6 say we learn more from our mistakes and I think that is  7 true. They're not mistakes. It's just the things that  8 we didn't understand that we now appreciate that can  9 inform development.  10 So I'll throw that out there as we're thinking  11 about future workshops. If people are mindful of that  12 because we do appreciate the presentations that were  13 made today and some folks did almost kind of start to  14 talk a little bit about their development program. So  15 maybe that next step would get us to a greater degree  16 of reality, which would help to move the discussions  17 along a little bit further at a future meeting.  18 So I'll stop there and let's open it up and  19 see if there are other comments or thoughts that people  20 have that they wanted to bring to the group here. So  21 please.  22 MR. BURD: You mentioned, I'm in regulatory</p>	<p style="text-align: right;">Page 89</p> <p>1 yes, we can do that and we do think that the quality of  2 that meeting is dependent upon the quality and the  3 thought that has gone into it and then it gives us more  4 to think about, it gives us more to dig into, to  5 provide advice on. So, yes, it is available. And when  6 you come in, put together a good package with good  7 questions and well thought out and that'll put  8 everybody in the best position to be able to move  9 things forward.  10 MR. BURD: Right. As a follow up, oftentimes  11 sponsors want to come in almost incrementally in their  12 early development because they have to make some very  13 big sort of long-term decisions at those very early  14 stages. And what that I think means in sponsor's  15 thinking is, can we have multiple interactions prior to  16 what they would consider a final pre-IND?  17 MS. NAMBIAR: All right. So I might be  18 getting into trouble here, less likely would Edward.  19 MR. COX: I felt guilty, I felt guilty telling  20 all the things that Sumati was going to do. I would  21 let her take the microphone and she can inject a dose  22 of reality into my discussion.</p>

<p style="text-align: right;">Page 90</p> <p>1 MS. NAMBIAR: Right, yes. Many of our team  2 members are here. So I think I'm going to get in  3 trouble with the larger team, less likely with Ed  4 because he doesn't have to deal with these meetings and  5 I have to. So, yes, I think there are so many  6 unanswered questions in this field and so many  7 uncertainties, and I think we're all learning in this  8 process together.</p> <p>9 So it really doesn't help the field or help us  10 as a community if we are very rigid and say, we've met  11 with you once, now we'll see you again in three years  12 as I don't think we're doing anybody a favor, not you,  13 not us and not the patient. So we try our best to  14 accommodate requests. There are some practical  15 limitations, our workload and number of people we have  16 working on it.</p> <p>17 But the truth is, we don't check off a box and  18 say we've met with you once, we've had pre-IND meeting,  19 now you're on your own. And then we also meet with  20 people at different stages in development. I think it  21 depends on the needs of the company. It depends on the  22 expertise they have. So sometimes we get programs</p>	<p style="text-align: right;">Page 92</p> <p>1 terms of timelines, I think helps. But I think the  2 division and the team and in particular people who work  3 in the division are really working extremely hard to  4 make this happen. So in that spirit, I think we're  5 more willing to work with you and have as many meetings  6 as needed.</p> <p>7 MR. COX: Other questions? Yes.</p> <p>8 MR. KALEKO: One of the issues that we  9 discussed yesterday, maybe I missed it, but I didn't  10 see it listed earlier was therapies that could help the  11 general population as much, perhaps even more than the  12 individual. Obviously those are limited by the fact  13 that you are relying on mechanism. It's -- they're  14 very hard to prove that you're helping the general  15 population. And the other limitation of course is  16 commercialization. Who's going to pay for something  17 that helps the population as opposed to the individual?  18 So in that regard it might not be the auspices of this  19 meeting, but is there some way to address whether or  20 not, for example, the government, which is responsible  21 for protecting the common good could help support  22 products that support the common good or is that</p>
<p style="text-align: right;">Page 91</p> <p>1 which are well thought out and you're sort of just  2 getting our okay. Some others, I think people who  3 might be relatively new in the field might want to ask  4 questions which are at a more basic level. So we try  5 our best, we try to accommodate all those requests.</p> <p>6 Sometimes if you're really early in development and you  7 just want to get our advice on, are you headed in the  8 right direction, we can do that where we can provide  9 responses in writing. It's still a pre-IND, but it's a  10 written response only meeting. That works very often  11 because you're just getting very clear-cut guidance  12 from us.</p> <p>13 Sometimes especially with these kinds of  14 products, there is a lot of value in having a  15 discussion because there's only so much you can  16 communicate in writing and those might -- when you are  17 at that point, I think it might be better to come in  18 and actually meet with us. So I think we try to adapt  19 based on the needs of the group that's requesting. But  20 I think folks just also have to be mindful, there's  21 only so many of us trying to answer questions to all of  22 you. So I think giving us a little bit of leeway in</p>	<p style="text-align: right;">Page 93</p> <p>1 outlandish?</p> <p>2 MR. COX: So that is way beyond the scope of  3 this meeting.</p> <p>4 MR. KALEKO: Apologies man. Sorry.</p> <p>5 MR. COX: But let's talk about it for a  6 minute. So the issue of can you show a benefit to a  7 population and you said you'd have to rely on  8 mechanism. And I think that the real question is, if  9 that benefit is actually happening frequently enough, I  10 mean, maybe you could actually show that clinical  11 benefit to folks. And if you can show that clinical  12 benefit, then you've got something and you can weigh  13 that benefit and try and figure out, does it, is it  14 something that's warranted based upon the risk because  15 in that sort of setting where it sounds like you're  16 going to be dosing or treating a lot of patients or  17 vaccinating a lot of patients or whatever the case may  18 be, then you have to sort of look at the risks  19 associated to that versus the benefits. So it becomes  20 a risk benefit analysis. With regards to who will pay  21 for this? Will somebody accept this in the  22 marketplace? Will it be successful from a commercial</p>



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<p>1 standpoint? We understand those are considerations  2 that somebody looking at such a development program  3 would need to think very carefully about. But that's  4 sort of beyond the scope of what I can answer.  5 MR. REX: Well, you might add that BARDA does  6 some of that for us right now. That's -- BARDA often  7 describes themselves as the U.S. government's  8 pharmaceutical company and they get busy developing  9 tools that they think that we might need in extreme  10 circumstances.  11 MR. COX: And I'll look to Ann, to Sammy (ph)  12 because I'm thinking BARDA, NIH and the granting  13 authority as such, anything else to add to that, Ann?  14 MS. EAKIN: Yeah. I mean, not really. I  15 think it is a pretty broad scope of how exactly that  16 would play out. I mean I definitely hear you and I do  17 see the sort of common good type needs and possibly  18 having government sponsorship of that work. But  19 without the specific example, I don't have much to add.  20 MR. TSE: Hi. There is a BARDA rep here.  21 I've been quiet for the majority of the meeting, so I  22 am happy to speak to this just in a general sense. I</p>	<p>1 another process on trying to improve the reimbursement  2 following on Commissioner Gottlieb's suggestions and  3 public comment about other models to support antibiotic  4 reimbursement at a more healthy level. If you want  5 access to that process, probably Greg Frank of Bio or  6 Amanda Jezek of IDSA would be good contact points for  7 any company person here. As well there're other  8 efforts, but I think those two will probably be good  9 people to connect to and can tell you. And Helen, do  10 you have anything else to say about that, you're IDSA  11 as well?  12 MS. BOUCHER: Yeah, no, I mean, I agree. I  13 guess, the other comment will be that this is some of  14 the agenda that PACCARB looks at in a kind of higher  15 level across the government way. And we're meeting  16 again in September, so there're other public meetings  17 where some of the stuff will be discussed. And that  18 allows some bridging with CMS, payers and others CDC  19 importantly who we haven't really mentioned, but in  20 terms of things like vaccine, certainly CDC is who  21 dictates who gets what vaccine for example.  22 So there are some other potential synergies</p>
<p>Page 95</p> <p>1 mean we always have to keep in mind, when we think of  2 ourselves as investors in the antibiotic field, our  3 mission space is squarely placed in the value of  4 biomedical security from the standpoint of, can we use  5 these streams to directly address biothreat agents?  6 And secondarily, can we offset the secondary and  7 opportunistic infections that would likely result as a  8 result of treating patients within the context of a  9 public health emergency?  10 So as long as we can frame things within that  11 context, we can make the argument that we can make  12 investments from a purchase standpoint of investing in  13 the R&amp;D component of that. Whether or not we can come  14 up with solutions related to poll incentives to solve  15 the marketplace issue, that is beyond the scope of what  16 I am able to speak to you today.  17 MR. OUTTERSON: Yeah. I will say something  18 briefly, madam, if I could add. So its way beyond the  19 scope of this meeting as Ed said, but there are other  20 meetings that if you're pining for additional meetings  21 in D.C. area. The Duke Margolis -- with the support of  22 the Wellcome Trust, Duke Margolis is kicking off yet</p>	<p>Page 97</p> <p>1 that could be addressed and I think the - I'm glad that  2 Kevin brought up the incentive piece because I think  3 really that's the biggest issue for all of these  4 medicines, whether they're regular drugs or  5 nontraditional therapies. So getting to the crux of  6 that is going to be really important.  7 MR. COX: And I'll throw out one other comment  8 that I'm just recollecting from a prior meeting. And  9 that is that if you think about the granting world,  10 it's a competitive world. There're a lot of folks out  11 there with ideas and so you -- to the extent that the  12 idea has scientific merit and that can be expressed,  13 that obviously puts you in the best position for  14 seeking the grant. So it is a competitive world for  15 granting and that's a good thing. I mean we want to  16 think about the proposals that are most likely to pan  17 out. So I just throw that out there as an additional  18 comment and I'm sure our colleague at NIH are working  19 very hard and likewise at BARDA as they're looking at  20 various different proposals and considering the merit  21 of those proposals as they try and decide where to use  22 their moneys. Are there questions, comments, Todd?</p>

<p style="text-align: right;">Page 98</p> <p>1 MR. BLACK: If I can, I think this is a bit of  2 follow-on on that because I think, you know, John says  3 net effect is really the critical parameter of the  4 clinical study, but we had a lot of conversation about  5 what is a significant net effect? What is the  6 significance of decolonization? If we use (inaudible)  7 example, so we went into this with real -- the  8 expectation that C diff recurrence is deadly diarrhea  9 and that there should be a mortality effect associated  10 with preventing recurrence. We had a significant  11 impact on recurrence, but actually in that study there  12 was not a mortality effect or been balancing that.  13 So if we hadn't had that assumption going in  14 that recurrence was the key endpoint in this case  15 because we're basing it on our medical assumptions of  16 the importance of that and mortality had been our  17 endpoint, then we would've never met superiority  18 endpoint. And so when I started looking at some of  19 these things that we're considering, do we really know  20 what the net clinical implication is and that maybe  21 where if there is some government or consortia approach  22 to really help us understand some of these net effects</p>	<p style="text-align: right;">Page 100</p> <p>1 work can be very important. And I think that at least  2 if you think about drug development, I think that is --  3 those public private partnerships have played an  4 important role. The folks at Citi have also been  5 working on trying to figure out ways to make HAP/VAP  6 trials more doable, by looking at some of these issues  7 of pre-consent.  8 That's the sort of work that no one individual  9 pharmaceutical company might find to be in their  10 interest to take on. But if -- its work that involves  11 folks from the government, folks from academia, folks  12 from the pharmaceutical industry, other interested  13 stakeholders, patient reps et cetera. Those groups may  14 be able to do the foundational work to try and  15 establish the pathways that will be relevant to each of  16 several different or to anyone who is interested in  17 developing a drug in a particular therapeutic area.  18 So we are trying to do some of that work.  19 Folks may recall the workshop that we had on drugs that  20 acts only against a single pathogen. And so from that  21 stemmed some grant proposals that we were able to fund  22 to try and work with both folks at NIH and at BARDA to</p>
<p style="text-align: right;">Page 99</p> <p>1 really are and like the transmission components  2 etcetera.  3 MR. COX: And you're reminding me, there has  4 been some work that has been done through the  5 foundations and National Institutes of Health to look  6 at various different endpoints. Skin infections,  7 community acquired pneumonia, hospital acquired  8 pneumonia and also some work on VAP too. So, and those  9 have been done through, I guess, what I would put in  10 the broader category, I might not have the definition  11 precisely correct of a public private partnership. And  12 part of that effort was fueled by the ability to use  13 previously conducted trials to understand both the  14 natural history of the disease and also the time to  15 response for various different endpoints.  16 And so that type of work, to understand the  17 natural history of disease, what changes over time and  18 I'm saying natural history, but there's natural history  19 from sort of the pre-antibiotic era and then there's  20 also what happens when somebody is getting treated,  21 what changes, when does it change, what's the clinical  22 significance of those changes. So, yeah, that type of</p>	<p style="text-align: right;">Page 101</p> <p>1 try and develop some animal models of infection to  2 further understand how these agents were performing in  3 serious infections caused by acinetobacter or caused by  4 pseudomonas aeruginosa, that work is ongoing. Yeah, so  5 that sort of work that's common to several development  6 programs are things that we're interested in and things  7 that we are trying to make progress on and working with  8 colleagues at NIH and BARDA. So it's a good point and  9 something we will continue to try and do. We recognize  10 that what we can do is limited, we can't do everything.  11 So we do try and hit the things that we think are most  12 important to the development community in general. And  13 that changes over time too. I'll stop there.  14 Are there questions thoughts? We'll do Filip  15 and then we'll go to Paul. And then I apologize, I  16 can't quite see your name tag, but then you're next,  17 okay, so. So Filip, please.  18 MR. DUBOVSKY: Yeah, Ed you just mentioned,  19 but it's also on my list. When I'm thinking about  20 buckets for John's things that -- the pathogen specific  21 bucket maybe one worth throwing on your list, maybe  22 it's redundant, but it may add something. And I came</p>

<p style="text-align: right;">Page 102</p> <p>1 into this workshop skeptical, but I thought the cases  2 were extremely valuable and without them it really  3 would've been a less useful meeting and I can say that  4 I'd be completely happy to talk about the real life  5 development of the products from a sponsor's  6 perspective. And I would've been happy to have done it  7 for first meeting as well. And, I guess, the last  8 thing is when we think --  9 MR. COX: Thank you for that.  10 MR. DUBOVSKY: When we think about these  11 alternate things, whether it be AMR or antibiotic  12 usage, I wouldn't anticipate they would be labeled  13 claims without a clinical benefit. But if your  14 medicine can demonstrate a clinical benefit in a  15 completely noble approach, if those could be stuck in  16 label because I do think they have true public health  17 value and value as infectious disease physician. If  18 those things could be made apparent in the label, maybe  19 that would start a new trend toward a sea change in the  20 how this is perceived both globally and in the  21 medicines environment. So, yes, I demonstrate clinical  22 evidence, but then again the tangled line says, does</p>	<p style="text-align: right;">Page 104</p> <p>1 pharmacometrics has been somebody getting hit by a bus  2 or a train or worse. And I think it's the -- it's  3 folks being willing to share not only their successes,  4 but their failures and what models they're using. They  5 think they failed because it was a model problem or  6 maybe drug just cleared like the wind in the patient  7 and that wasn't accounted for in those predictions.  8 So the successes and failures being talked in  9 an open way and also maybe what models were used to  10 make them feel so confident as to amount to Phase 2 or  11 Phase 3 trial.  12 MR. COX: In some ways it's too bad that we  13 call them failures because they are really not. They  14 are just an understanding of what actually happened.  15 And sometimes what actually happens is not the outcome  16 that you want, it's not a commercially viable  17 proposition at that point, but we learned and we  18 learned something that helped us to understand what the  19 molecule does. So it really is in some ways that it's  20 too bad that we call these things failures because it's  21 more just a learning that has helped to advance our  22 understanding of what's going on. But, yeah, no, and</p>
<p style="text-align: right;">Page 103</p> <p>1 not promote antimicrobial resistance. Useful.  2 MR. COX: All right. Thanks Filip. We  3 appreciate your comments and we'll look forward to the  4 next workshop. And is yours a follow up? No, okay,  5 okay. So then let's -- we'll just go to Paul.  6 MR. AMBROSE: Hi, we often hear people say in  7 our field that for small molecules or antibiotics that  8 the -- we're blessed because of these wonderful animal  9 models that are so predictive of what happens in  10 clinical trials. But I think it's useful to remember  11 how we got here, and we got here because Harry Eagle  12 started in the 1930s and '40s and then Bill Craig  13 picked it up and really perfected those models through  14 the '80s and '90s. And then along the way people began  15 looking at how well that they predict clinical trial  16 results based on clinical trials meeting their primary  17 endpoint. And so now we feel really confident. Now we  18 are talking about developing a whole new massive models  19 that we don't know if they work, they may work or some  20 very variant on them may forecast clinical efficacy.  21 So to build on what you said earlier, Dr. Cox,  22 everything I have really learned in my career in</p>	<p style="text-align: right;">Page 105</p> <p>1 it's not a criticism. I called them failures too, but  2 I shouldn't, I should find a better word for it. John  3 will help us with that.  4 MR. REX: Well, it's interesting to think  5 about that. There is a literature in other areas about  6 dealing with the problem, I'm going to use the word,  7 the language from infection or risk management, the  8 hospital of near misses. So in the hospital setting  9 the -- or if you are an airplane pilot, what do you do  10 when something almost went wrong and maybe you've made  11 a mistake and it almost went wrong, but you're glad you  12 got it. And so the kind of tools that people have come  13 up with about non-judgmental sharing of errors and  14 maybe there are some languages that we have as a  15 scientific community have failed to explore. It is  16 hard to do to get people to be comfortable with sharing  17 that sort of thing, but it has been done in other  18 fields.  19 MR. KIM: Just to continue the conversation on  20 follow-up workshops, throw out an idea. So at POE (ph)  21 we track these nontraditional candidates and if you  22 look at from a technology platform perspective, about</p>

<p style="text-align: right;">Page 106</p> <p>1 two-thirds are composed of vaccines and monoclonal  2 antibodies and the other third are these clinical new  3 platform technology. So I am wondering if a workshop  4 that more focuses on these "more licensed or microbiome  5 related products" and expanded not beyond just  6 clinical, but I suspect there may be some questions  7 around CMC development and manufacturing as well.  8 Thank you.</p> <p>9 DR. COX: Thanks. Thanks for your comment.  10 We'll keep those ideas in mind. There is no question  11 we'll be having future workshops. We just haven't  12 settled on all the topics yet. We do try and be  13 mindful of what we see going on out there and where the  14 questions are coming up and which questions we are  15 receiving sort of that seem to be important to the  16 development community. So we appreciate your comments  17 and see you soon.</p> <p>18 MR.REX: And there's about to be a NIAID  19 microbiome workshop, right, and it's soon. Talk to  20 your microphone to tell them what the date is.</p> <p>21 MS. TRUONG: Yeah, hi, I just wanted to add a  22 little bit more to those pre-IND communications. One</p>	<p style="text-align: right;">Page 108</p> <p>1 endpoints that we can continue to explore in this  2 field.</p> <p>3 And finally I'd like to add that Aridis is  4 also willing to share our lessons learned in these  5 types of workshops. Thank you.</p> <p>6 MR. COX: Great. Thank you very much. Mary  7 Beth.</p> <p>8 MS. DORR: Thank you. So two things. These  9 guys over here just mentioned CMC, that's one of the  10 things that I keep coming back to when you talk about  11 multiple monoclonal antibodies. It's not  12 insignificant, the amount of CMC work that has to be  13 done for each individual monoclonal antibodies, it's  14 not just cost of goods and I know that at Merck, our  15 application would have been delayed if we had to file  16 both monoclonal antibodies. So I think small companies  17 that are just getting into this space may not realize  18 how complicated the CMC issues are for a biologic. So  19 you might want to find out about that early on in  20 development before you take them too much further. And  21 also I do think it's going to be an important aspect if  22 you do have a workshop specific to biologics to have</p>
<p style="text-align: right;">Page 107</p> <p>1 strategy we have taken is to divide those meetings from  2 clinical, non-clinical and the CMC and it gives  3 opportunity to continue those discussions as in drug  4 development. And I want to say, although I was a  5 little yesterday talking about the timelines in  6 responses. I do want to acknowledge that we have  7 received a lot of good responses, very collaborative  8 with the group, not only during the pre-IND stages, but  9 also during the IND and that continue communication  10 path. So we really appreciate and this division is  11 very responsive on the needs of our drug development  12 programs.</p> <p>13 I'd like to also echo the need for these  14 additional workshops and my need is really in those  15 clinical endpoint workshops to really look at endpoints  16 beyond all cause mortality for both superiority and  17 non-inferiority trials and really looking at the  18 benefit to the patients, quality of life et cetera. So  19 what other endpoints could we really consider? And I  20 know this is indication specific, but is I think just  21 having those key opinion leaders in a group like this  22 together to really explore what are those potential</p>	<p style="text-align: right;">Page 109</p> <p>1 both of those aspects cover to some extent.</p> <p>2 So the other thing, bringing up failures, Paul  3 brought up failures. I in particular am passionate  4 about C diff. And I think everyone who is familiar  5 with C diff knows that we've had quite a few failures  6 in this space and Merck in particular and other  7 pharmaceutical companies have a transparency policy.  8 And I think it would be in the best interest of all  9 those who are still working in this field for there to  10 be a workshop on why we've had failures with C diff so  11 that future studies we can design them better and  12 hopefully have better outcomes.</p> <p>13 MR. COX: Yeah, thank you, Mary Beth. And we  14 haven't really dealt with CMC issues, we haven't dealt  15 with manufacturing issues during this workshop. But  16 her advice is very good. We've seen applications that  17 have come along where essentially everything is in good  18 shape except for the manufacturing. And it can delay  19 the application getting to market by a year, two years,  20 sometimes even longer.</p> <p>21 So, and the other thing we're seeing now too  22 is that with some of the more streamlined development</p>

<p style="text-align: right;">Page 110</p> <p>1 programs, we hear that sometimes the folks involved  2 with the manufacturing didn't realize the timelines  3 were going to be quite so tight. And so the amount of  4 work that they need to do in this more compressed  5 timeframe is something that they didn't really have a  6 full understanding of and weren't quite able to plan  7 for.</p> <p>8 And again so the manufacturing can sometimes  9 bring up unanticipated surprises that can have a  10 profound impact on the application and it's obviously a  11 critically important part of an application to be able  12 to demonstrate that you can make the product and that  13 it's clean and that it's reproducible and those sorts  14 of things.</p> <p>15 The other thing and I'll make just one last  16 comment because this is another thing that we've seen  17 with manufacturing that comes up, they can be somewhat  18 frustrating to deal with and that is that we see a fair  19 bit of manufacturing that's done by contract. That's  20 perfectly fine; people can decide who they want to do  21 their manufacturing. But that may impact upon the  22 visibility of the firm that's actually has the</p>	<p style="text-align: right;">Page 112</p> <p>1 MR. COX: Do Wayne and, yeah, okay.</p> <p>2 MR. DANKER: So I think that's a good point  3 because we're in our development program and I keep  4 interacting with our CMC people because you have to  5 coordinate timelines, but I also think what people tend  6 to underestimate in the CMC is the cost. And if you  7 don't factor that into your development cost,  8 especially for a small company, you're going to get  9 caught with your pants down later on.</p> <p>10 MR. COX: Thanks and next.</p> <p>11 MR. BURD: Could you comment on whether you  12 could provide consultative services for a facility  13 development? Because many small companies, if they  14 contract out also have the option of developing the  15 real manufacturing facility. I know for my company,  16 we're doing a hybrid, one product we're making  17 exclusively in-house and then the other one we're going  18 to outsource. But we have to develop a GMP facility  19 from scratch and is there a consultative service  20 available? It could be through the field office or  21 some other way to provide guidance early in the  22 development of these GMP targeted facilities.</p>
<p style="text-align: right;">Page 111</p> <p>1 particular, I'll say, antibacterial product and what  2 maybe going on at the manufacturing facility where  3 they're contracting. So it's very important to be  4 mindful of keeping track of what's going on at that  5 facility if you've a contract manufacturer so that  6 again there aren't surprises at some point in time when  7 your application comes in that impacts upon your  8 application.</p> <p>9 And I mentioned that because we've seen it a  10 couple of times, it's not meant to be a comment on any  11 one particular sector, it's more just general  12 awareness. Obviously, you could have the same problem  13 within your own facility, with a facility that you  14 owned, but I just bring that up because sometimes if  15 it's not your own facility, there is a little bit  16 greater distance in time and space that it is worth  17 trying to minimize to the extent possible so that there  18 is an awareness of what's going on with your product  19 and what's going on with the manufacturing facility  20 that makes your product, even if it is not your own.  21 So I'll stop there. And I see --</p> <p>22 MR. DANKER: Two of us.</p>	<p style="text-align: right;">Page 113</p> <p>1 MR. COX: Okay. I'll start. I like to tell  2 stories. So our office of pharmaceutical quality and  3 compliance folks are available to evaluate facilities.  4 And so you might ask, I am not a CMC expert, but why do  5 I know anything about this and I don't claim to be  6 expert by any means. Well, if you think about it,  7 penicillins and beta-lactams and the allergenic  8 potential and manufacturing of those products is done  9 at a dedicated line and there are some issues about air  10 handling and all other sorts of things that need to be  11 thought about within the facility.</p> <p>12 And so, yes, from those experiences I do know  13 that that our pharmaceutical quality folks, our  14 compliant folks, can provide regulatory advice. We  15 tend to look at it as, our work as regulators, on  16 somebody's plans or proposal on their manufacturing  17 facility. So that is something that can be done. So  18 if there's blueprints in place for a future  19 manufacturing facility for a certain compound, that is  20 something that there is an opportunity from what I  21 understand to reach out to our folks and say, is our  22 air handling system going to do adhere correctly and</p>

<p style="text-align: right;">Page 114</p> <p>1 that sort of thing, to make sure that the facility  2 that's going to be built will be one that will sort of  3 meet the types of requirements that would be expected.  4 And so something to think about and certainly  5 just like we talked about with pre-IND consultation, to  6 the extent that you've engaged your experts and tried  7 to learn as much as you can about this and come in with  8 a good proposal, you will be in much better shape to  9 receive feedback from the folks here within FDA. Have  10 we -- other questions or we are good? I think we're  11 almost at time here too. So John, anything else or?  12 MR. REX: Thank you.  13 MR. COX: Okay. So let me extend thanks. And  14 Sumati and I will do this jointly, yeah?  15 MS. NAMBIAR: Good.  16 MR. COX: Okay. Well, I'm going to give you a  17 chance to say thanks. But we really do appreciate  18 everybody coming in and talking about, in this case  19 hypothetical programs and talking about their  20 experiences as they relate to the various different  21 examples that we put up. This takes a lot of your  22 time, it takes a lot of your dedication to; A, come to</p>	<p style="text-align: right;">Page 116</p> <p>1 sure if I have much more to add. I certainly want to  2 thank everybody, the presenters, participants, panel  3 members, members of the audience. Many months ago,  4 when we started planning this workshop, I think we were  5 all a little nervous. There was a lot of uncertainty  6 around what are we going to talk about, what does this  7 mean, what does nontraditional therapies mean. I'm not  8 sure if we have the answer to the question yet, but I  9 think there's a little more clarity now than we had  10 when we started a few months ago. So many thanks for  11 all of you for participating and helping us move the  12 feat forward. I think there are many more discussions  13 that need to be had. We've got some good thoughts on  14 what future workshops might look like and on a step  15 wise manner we hope we can address each of your areas  16 of interest.  17 I certainly want to thank Sunita sitting in  18 the back there, yeah, who has really taken the back  19 seat literally, but has been doing a lot of the work in  20 coordinating this workshop and our project managers who  21 help at the back. They're monitoring the web and  22 seeing other questions, so Jackie, Debra and Chris.</p>
<p style="text-align: right;">Page 115</p> <p>1 this workshop and even probably much more importantly  2 to work in this field. We greatly appreciate the  3 interest of folks who are continuing to work in the  4 area of bacterial diseases and trying to tackle the  5 problem of AMR. I learned a lot from the workshop, I  6 think that this will help us as we continue to think  7 forward. We do expect to have future workshops, topics  8 to be determined, but we are trying to be responsive to  9 the needs that we see out there and that we recognize  10 are going on in the field. And as many of you know  11 too, we're also engaged in meetings to try and provide  12 our regulatory advice on development programs through  13 the meeting that we do with companies.  14 So we look forward to future interactions and  15 the opportunity to continue to try and push the  16 envelope forward with regards to our knowledge in these  17 areas, in trial designs that will be informative to  18 help us understand how these products work. So greatly  19 appreciative and we look forward to a chance to meet  20 more in the future and then I want to pass it to Sumati  21 here.  22 MS. NAMBIAR: Thanks. Thanks Ed. I'm not</p>	<p style="text-align: right;">Page 117</p> <p>1 And then many thanks to Kevin and Dr. Rex for helping  2 us with the planning of this workshop. I know we've  3 had some very difficult discussions, particularly when  4 you came up with the last case that we discussed  5 yesterday.  6 So those meetings were meant to be half an  7 hour, then they extended to an hour, but then the day  8 came to an end and we said we had to quit. So I do  9 remember those discussions. So thank you all and we  10 look forward to more discussions. Safe travels and  11 thank you again.  12 MR. COX: Yeah, safe travels everybody. Take  13 care.  14  15  16  17  18  19  20  21  22</p>

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