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IMMUNOMODULATOR/ENHANCERS PRODUCT DEVELOPMENT

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PROCEEDINGS

MR. RUBIN: (In progress) the nontraditional therapies workshop. We'd like to get started, if you could please take your seats. Today I don't think we're going to be going around the table and doing the introductions again. We'd like to move into the last case study of the workshop which is on lysin product development. And for this I'd like to turn it over to my colleague, Dr. Ed Weinstein.

MR. WEINSTEIN: Hi. Good morning. Ed Weinstein. I'm a clinical reviewer in the division of anti-infective products, CDER, FDA. And I'm pleased to present the last case study which is a hypothetical case of a chimeric bacteriophage endolysin called drug Z-4.

So this drug is a recombinant chimeric protein of 30 kD in size that's composed of an ectolysin domain from a bacteriophage enzyme fused to a staphylococcus binding domain of bacterial origin. The development program is intended to treat staphylococcus aureus skin infections via topical administration and endocarditis via intravenous infusion. There's no activity against

gram-positive or gram-negative bacterial species.

The nonclinical safety data profile includes rats and mini-pigs. Intravenous administration was tolerated at doses up to five times the proposed human equivalent when administered daily for 2 consecutive weeks. There was no dose limiting toxicity. Transient fevers of less than 24 hours duration were noted in some animals. This was suspected to be due to endotoxin, the drug substances produced by batch fermentation of E coli cultures.

Anti-drug antibodies were identified in rats at day 28. Perivascular neutrophilic infiltrates were noted at the injection site. Significant toxicity in related ectolysins include severe, irreversible vasculitis due to off-target activity. In mice and rabbits, the topical solution at the proposed clinical dose was applied to abraded skin daily for 14 days without significant toxicity.

The nonclinical microbiology program revealed that drug Z-4 is only active versus staphylococcal species and this includes staph aureus and coagulase-negative species. The MICs follow the normal

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distribution for staph aureus with an MIC range from 0.03 to 16 mg/L; MIC 90 8 mg/L. There was no overdose resistance noted in the screening panel. Time-kill study revealed a 4-log reduction in MRSA USA300 counts following 15 minutes exposure at four times the MIC concentration in vitro. There were insufficient data to establish a pharmacodynamic model.

The nonclinical microbiology and PK/PD program revealed that the predicted PK/PD properties associated with bacterial killing revealed a linear relationship between killing and drug concentration, with the mode of action characterized by irreversible binding to the target consistent with protein-protein interaction.

In animal infection models, drug Z-4 was effective in treating staphylococcus aureus infections in two different animal models. This was judged by a reduction in CFU/g and thigh infection in peritonitis models. There was a survival benefit that was seen in the peritonitis model.

There are two clinical studies that were completed. There was a Phase 1A, 24 healthy volunteers, single and multiple dose nasal ointment at

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the proposed dose of 1% by weight. In general, drug Z-4 was well tolerated, there were no discontinuations or serious adverse events reported. One subject with transient fevers 4 hours after administration was noted.

There was a Phase 1B proof of concept study that was involved in nasal decolonization. This open label study conducted in 20 healthy patients with MRSA nasal colonization, the drug Z-4 ointment was given topically three times daily at several doses for five days. The study endpoint was daily quantitation of MRSA by lavage from the nares 3 minutes before administration, 30 minutes after drug administration and 4 hours following the evening application.

The only efficacy analysis that displayed a significant difference between drug and placebo in staph aureus clearance was the highest dose group, 30 minutes after drug administration, but the difference appeared at the 4-hour time point. This was only seen on the first day.

One adverse event, a fever and leukocytosis, 4 hours post administration was noted on day 5 in one

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subject. No other areas of AEs of concern were observed. The drug was not detected systemically, but one subject was positive for anti Z-4 antibodies at day 20.

This raises a bunch of interesting questions for the panel to consider. The first is the clinical trial design, which indications in patient populations should be recommended for a clinical trial involving a single-course, single-genus therapy, where a trial be feasible if enrollment is limited to the pathogens of interest and outcomes are confounded by the administration and effective empiric therapy?

And secondly, considerations of safety. Given the potential immunogenicity of a drug derived from foreign proteins, how would you ensure that a patient would receive a limited exposure when you screen for the presence of anti-drug antibodies? Thanks.

MR. RUBIN: Thank You, Ed. We'll now have an industry perspective from Dr. Cassino from ContraFect.

MS. CASSINO: Good morning. And thank you for including us. Thanks for the opportunity to speak with you about our experience with our lead lysin candidate

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CF-301. I'm Cara Casino. I'm the chief medical officer and the head of R&D at ContraFect. So just a word on lysin technology just so in case everybody is -- everybody's familiar. Lysins are bacteriophage-derived cell wall hydrolase enzymes. In nature phage secrete the lysin in order to release progeny phage. The cell wall hydrolase breaks through this peptidoglycan cell wall from the inside out, releases the progeny phage. And what we're looking at doing then is to harness that ability to break through the peptidoglycan cell wall associated with rapid bacteriolysis and turn that into a medicine, medicinalize it so to speak.

And so our approach has been to follow the science to where we are now. Currently CF-301, which is an anti-staphylococcal lysin, is in Phase 2 clinical study which is evaluating a single dose of CF-301 administered intravenously for the treatment of known or suspected staph aureus bacteremia and/or endocarditis.

So a few things that led us to this Phase 2 study. First of all I would comment, the company did a

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lot of upfront work and took a while taking a brand new concept, taking the concept of harnessing one of the killing elements from the phage and turning it into a recombinantly administered medicine free of phage remnants. It took the company a while to get through the upfront processes, be able to file the IND and move on into clinic, but through that process learned a lot.

CF-301 has some hallmark features. Rapid potent targeted bacteriolysis, active against all staphylococcal specie and a few strep, not surprising actually given the specificity of phage. Strikingly rapid biofilm eradication both in vivo, in vitro and more recently in biofilms formed in the setting of human infection, synergy with conventional antibiotics in vivo and in vitro. And in vivo again and again replicatively shown in the rabbit infective endocarditis model and the rat infective endocarditis model, thanks to Arnie Bayer at UCLA who performed those models for us.

And to give you an idea of what that looked like, that was a single dose of 301 administered in addition to human therapeutic equivalent doses of

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daptomycin in rats and subsequently in rabbits, with induced infective endocarditis, wherein 4 days of daptomycin resulted in a three log drop in CFU's and the addition of 301 resulted in an additional three log drop in CFU's.

Those features we believe may be the core of this new class of lysins because we're observing very similar collection of features in our antipseudomonal lysin discovery program which, thanks to CARB-X, we are working on. Thank you very much. And we have now got 15 leads that we're going to be bringing into in vivo studies.

A couple of other things about 301. One of the things we're fortunate with is because of that potent killing, we're also able to actually leverage traditional antimicrobial susceptibility testing. We've been able to develop an MIC methodology for use in clinic that has been validated, CLSI approved. And we've also been able to develop a PK assay and therefore leverage relatively standard PK/PD approach to determining dose, to determining PK driver of efficacy, and to determine the dose to take through in

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Phase 2.

Animal studies did show the potential for anti-drug antibody development, that's not surprising. And in the animals, those ADA's were non-neutralizing. I'll tell you what happened in Phase 1. We conducted a Phase 1 trial of 20 patients. Four doses of 301 and placebo taken in, in a single escalating dose Phase 1 study. And in that study, it was a very quiet Phase 1 study. No serious adverse events. This was healthy volunteer study. No adverse events of hypersensitivity reported and overall generally well tolerated. PK profile linear and we're grateful for that because that allowed us to use popPK from Phase 1 and our animal PK to estimate our dose for Phase 2.

And in the arena of antidrug antibodies and immunogenicity, ADA's were present and emerged 14 to 28 days post dose in healthy volunteers. The ADA's waned or were completely gone by 180 days. And the interesting thing we noted was that ADA's were not associated with IgE or basophil activation, so not associated with typical markers of allergic type 1 hypersensitivity.

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So we moved on, and so currently we're conducting a randomized double-blind placebo-controlled study in, as I said, bacteremia endocarditis. We went in this direction. There are a couple of directions we could have gone in. I think there was an extensive discussion yesterday about the directions you can take, a non-traditional therapy.

We had a number of options at our disposal. We thought the high unmet medical need for new treatments to address biofilm associated staph infections and the fact that our animal data repetitively showed us from the infective endocarditis models, the potential for efficacy in this clinical setting and the fact that the last drug approved, the last small molecule, the last approved drug for endocarditis bacteremia due to staph was Dapto back in, I'd say, over a decade ago. We leveraged the Dapto Phase 3 study.

We worked with folks like Helen who was on our first clinical advisory board. We worked really closely with Vance Fowler, he still is working with us in the -- as our lead PI. And so we've been able to --

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we opened the study last year, enrolled our first patient in May. We are now beyond or thereabouts around 75% enrolled. Our target enrollment is 115 patients randomized 3 to 2.

This is a single dose of 301 administered in addition to conventional standard of care antibiotics, IV administration. And our primary endpoint is clinical response at day 14. We're also looking at response at end of treatment and test of cure, the traditional endpoints. Again leveraged a lot from Dapto study, definitions, endpoints, some features of the study design. We have a data safety monitoring board in place. They met last week. They told us to continue the study as planned.

We are of course still blinded as the sponsor. But as I stand here today, we've had no SUSAR's, no adverse events of hypersensitivity considered related to study drug. And we are quite encouraged by our progress to date. We're tracking towards a goal of having data by the end of this year, top line results.

And, you know, all I can say is we're pleased by our progress. We continue to learn from 301 and we

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continue to learn from what we're doing. Recent observations, some things we're going to be presenting. We have a upcoming presentation in Lisbon. As we've observed that in vitro 301 appears to have the ability to re-sensitize MRSA to penicillin derivatives in vitro and in vivo from the infective endocarditis study. We're planning to follow that up, but we're starting to talk about that.

We've also observed low propensity for resistance with 301 in vitro, and we've also observed this very interesting thing that if you administer 301 together with conventional antibiotic in 26 days serial passage studies, not only does 301 not manifest resistance to itself, it suppresses the emergence of resistance to the conventional antibiotics.

So we think there's more to learn about the potential use of lysins, but as I said, we're encouraged by our progress and we're happy to be here to share this story. And I guess to discuss, we look forward to the discussion around the future, where we go from here and perhaps how we think about augmentation because of course based on the trial

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design, we're doing a superiority comparison of 301 in addition to standard of care, compared to standard of care alone.

So the question is what percentage of clinical betterness, clinical response will constitute what's considered a substantial evidence of efficacy. And I'm looking forward to hearing what the panel thinks. So thank you.

MR. RUBIN: Thank you. We'll now have additional FDA comments from Dr. Weinstein.

MR. WEINSTEIN: Thank you. Thank you, Dr. Cassino, for your comments. I just have some brief points I'd like to add. The first is that the case I presented was a hypothetical case. It's not an actual product. You know, lysins in general, they're familiar in the sense that they have a direct killing mechanism. But they have two areas of development challenge that make them non-traditional.

You know, the first is that these are narrow spectrum agents. In this case, it targets a single genus and that creates difficulties with clinical trial design that John Rex had described on day one.

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Second, they are foreign proteins and they may induce host-immune responses. This was less of a concern yesterday when we were talking about humanized monoclonals, but lysins are fully foreign proteins. So the range of host-immune responses may not only include IgE mediated hypersensitivity reactions, but also more subtle complications.

So there's the potential for host mediated resistance to therapy in the form of anti-drug antibodies. We don't often think about host resistance, but in other areas where host resistance has occurred such as rheumatology, it's in the context of a chronic non-life threatening disease. So this creates challenges for appropriate dosing and therapeutic monitoring.

In terms of this case, it's not uncommon to have a dataset such as this in the early phases of clinical development. Consider this an advertisement for early engagement with the agency. You know, we're open to pre-IND discussions regarding development plans. Proof of concept study linked to changes in CFU. In this case it's interesting, but it's not

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valuable without a link to a clinical outcome.
So, for example, if the outcome or a reduction in surgical site infections, then that's a tangible benefit to the patients, that could be readily understood. So the study reflects some of the conundrums that we wrestled with on day one.
In this case, as a summary, the study was highly feasible. It's estimated that 20% to 30% of people have staph aureus in their nose. But the endpoint was without clinical meaning. The results could not be interpreted. The treatment effect was only one point in time and appeared to be transient. A durable treatment effect is important.
The generalizability was unclear. It's unknown which patient population would benefit. Defining a patient population likely to benefit from a treatment has been a recurring theme in this workshop. So I'll stop there with those comments and turn it back to the panel.
MR. RUBIN: Thank you, Ed. We'll now move to the moderated discussion starting with the panel and then allowing questions from the audience or from WebEx

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if you could just get my attention by turning your nametag up or otherwise getting my attention or that of Dr. Hope, and I'll start right there.
MR. KALEKO: I'm not sure if I should comment on the hypothetical or the real at this point. But when I look at immunogenicity, yes, it's a safety issue and I agree with you. It's probably more an -- as much an efficacy issue as a safety issue. I heard that the antibodies in the animals were not neutralizing, that's a little surprising to me. I come from gene therapy and vectors get wiped out by antibodies.
I didn't hear whether or not they were neutralizing in the humans. But in either case, it would suggest to me that if this is going to be used systemically, it would have a short timeframe for its value. And if that were the case, the thing that really comes out from that presentation is the lysing of biofilms, which is a real issue.
So in the realm of endocarditis, for short-term use, you know, you're going to have to use your antibiotics for six weeks. But for short-term use, the question I have is, could this be of value in lysing

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vegetations in the heart and potentially saving heart valves?
On the other hand, could this be a problem in lysing vegetations in the heart and potentially releasing emboli? So I was -- well, that seems to me to be a great indication though, it was getting rid of the biofilm short term so that you can then blast away with your antibiotics. I'm sorry for that longwinded statement.
MR. WEINSTEIN: So thank you for the question, and it seemed that there were a few components to it. The first part was the potential role of neutralizing antibodies and the spirit of the hypothetical case was to address that. Saying that if there are drug neutralizing antibodies, is this a consideration and what would be the appropriate steps to address it.
In terms of your very insightful second question, in terms of the effect upon biofilm and the potential for the release of vegetations as emboli, we don't know. We'll have to see what the data ends up showing us.
MS. CASSINO: Yeah. So we weren't able to

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study that emboli phenomenon in, you know, we didn't see anything in the animals. We're obviously interested in that in Phase 2. We have enrolled patients with endocarditis left and right sided endocarditis. So far we haven't have had any serious adverse events that are considered to be related either by us or by investigators to study drugs. So that's all I can tell you. I'm blinded right now.
Regarding the neutralizing, non-neutralizing in the clinic, of course the ADA's emerged in Phase 1 at 14 to 28 days. Our single dose is a single dose. So we don't expect treatment emerging ADA's to be an issue. That being said, there are some people in nature who have cross-reactive antibodies to 301 as you would expect. It's a naturally occurring substance. So we are planning to look at that as some of our exploratory endpoints in the current ongoing study.
MR. HOPE: So can you speak to the point of unmet medical need for staphylococcal infections? That's the first question. The second is as the case was presented and according to, you know, the regs classification of traditional versus non -- this seems

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pretty traditional to me. You can measure it, you can -- you have experimental models, you have PK, you can construct exposure response relationships and you're sort of the clinical pathway, it just looks like the ARREST trial except you're replacing Rifampicin or Rifampin with your compound. So could you just maybe -- could you just speak to those points?

MS. BOUCHER: Me? You want me to take that? Okay. I'll take that one. Okay. So unmet medical need, I think we thought about that, where would be a place where there's a need. There have been a number of recent drugs approved for staph. There's a pretty good staph aureus armamentarium. All of those agents with the exception of Dapto have indications for skin and soft tissue infections and that was their development pathway.

The shelf is a little more spare in terms of agents for treating staph aureus endocarditis bacteremia. And we're -- when I say bacteremia, we're focused on complicated bacteremia. Those bacteremias that are more likely to be biofilm associated and I take your point, that's one of our thoughts too, that

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the biofilm activity here is very, very interesting, and may be one of the ways that 301 together with the conventional antibiotics actually form a good couple.

If you look at the Daptomycin published results from the Phase 3 non-inferiority trial, which compared Dapto to standard of care, which was basically everything else available, not semi-synthetic penicillins, first generation cephalosporins and vancomycin. The test of cure, the clinical outcomes at test of cure which is the registration endpoint for that trial were less than 50% response rate.

Granted that was partially dependent on the structure and the analyses and there are a lot of factors in there, but we felt that that gives us an opportunity to improve and so a place where a treatment in addition to that with a similar study design and similar definitions would allow us to potentially be able to show above and beyond efficacy with 301 in addition. So that was the unmet need.

What, I'm sorry, you had another point that you raised? I lost it. Traditional, yeah. Well, we're following a very traditional pathway, that's

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correct. We have some non-traditional things that we know, that we're learning about 301 regarding the synergy with conventional antibiotics. We'll see how that plays out in clinic where we feel fortunate that we're able to use traditional approaches, antimicrobial susceptibility testing, PK/PD. But we know from the in vitro work that there are some very interesting non-traditional activities like, when used in combination in the lab, suppressing the emergence of resistance in studies designed and that do avidly show the emergence of resistance for Dapto for oxacillin for Vanco. So this is a traditional approach, but this compound has some traditional and some non-traditional features.

MR. BLACK: I just had a clarifying, can you tell us the tested cure criteria? Was that imaging the vegetations or bacteremia, I wasn't quite clear what the endpoint was?

MS. CASSINO: It's actually, we are looking at both of those as separate and we have secondary endpoints of microbiologic response at the same time points as we're looking at clinical response. So actually it's a clinical response. And that was the

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registration endpoint as close as we could get this to be to the Dapto study. So it's based on the patient still being alive, the patient's signs and symptoms having resolved, the absence of further spread or metastatic foci of infection and these are the salient features and the absence of the need to use additional step-up in care. In other words, throwing additional antibiotics on or changing antibiotics.

There are a few other criteria, less than 12, so if you need more than 12 weeks of antibiotics, that would constitute a non-response, but those are the salient features. It's really based on clinical aspects and we do have an independent clinical adjudication committee. So the PI's at the site determine their view of the clinical outcome. And then we have both diagnosis, complicated and uncomplicated bacteremia endocarditis being adjudicated as well as the outcomes at 7 days, 14 days, which is our primary efficacy objective here, end of treatment and test of cure.

MR. HOPE: Well, maybe so -- well, I'll keep going. So given the hypothetical, I thought when that

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-- the case was presented by the FDA about the advantages potentially or just picking up from the discussions from yesterday about the potential for decolonization and a medicine to -- for prophylaxis and, you know, decreasing surgical site infections as one possible new avenue and then the point that you just made, the other societal benefit or even patient benefit is that you could get away from glycopeptides if you can restore susceptibility to MRSA.

So that, just listening again, well, I mean, I'd be interested to hear what others in the room say, but you generally don't get into a lot of trouble with gram-positive infections with the drugs that are available and the combinations that are available and surgery, so those sort of other potential. So Helen is going to say something, I can see. But the other -- but the more novel potentially advantages of decreasing glycopeptide usage would be incredibly advantageous given that, you know, these compounds are nephrotoxic.

MR. DUBOVSKY: May be the other thing which kind of cropped up in my brain was thinking about prosthesis, joints that goes sour. And if you truly

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have a biofilm lytic mechanism of action, then there may be some benefit there.

MS. CASSINO: Yeah. We're definitely interested in that. We had to start somewhere, right? We had to start somewhere that had some sort of a measurable and some kind of a pathway where we could start. So between the animal data driving us to the endocarditis and our clinical advisory board, this seems like a reasonable starting point, but we are interested and thinking about ways to look at prosthetic joint infections, and quite frankly the case, Helen, that you've presented yesterday comes to mind of a person or a case or a situation with complexities.

MS. BOUCHER: So thanks. I mean, I agree, William, with your comments, but I would offer that staph aureus still has predictable morbidity and mortality that's significant, right? So study after study, even with all the limitations of the studies we have, all comers with staph aureus in the blood, mortality 15% to 25%, so we could do better. And I think that's the medical need. And clearly we have

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patients, especially the group you mentioned, I think the patients treated with glycopeptides do worse than those treated with beta-lactams, right? People with MSSA do better, it's a superior therapy. So that avenue I think is really potentially exciting.

I'm a little concerned about the complexities of the clinical trials in bloodstream infection. You know, these endpoints are very complicated. We're measuring a lot of things and the predominant reason for that, less than 50% success rate in the daptomycin trial was the use of potentially effective non-study antibiotics. It wasn't staph aureus and metastatic foci and such.

And these are complicated issues that we still struggle with and it's part of the reason nobody else has done a trial in over 10 years, as limited as that trial was on many levels. So I think it's really admirable that you're doing the trial, but I share some of the caution, I guess, about the expectations.

I think the idea of capitalizing on the biofilm, no one has mentioned catheters but, you know, catheters, even peripheral IVs still are associated

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with staph aureus bloodstream infection in the best hospitals in 2018. So anything that could, you know, could this affect a biofilm on catheters as well as prosthetic joints? I think those would be things that would be really potentially interesting to explore.

MR. KALEKO: Can this penetrate a staph abscess? I mean, once you have multiple abscesses all around your body, you're in a lot of trouble. Is there any way to -- can this get into them?

MS. CASSINO: We'll probably learn a lot from the Phase 2 study. We've had a few cases of that. We haven't looked at abscess penetration per se. We have pretty good bio-distribution from the animal studies for what that's worth.

With regard to the catheters, we're interested in that also. We recently did a pilot with Jamie Dwyer at Vanderbilt, a nephrologist. It was actually his idea which was to look at hemodialysis catheters removed from patients as part of clinical care, who have staph aureus, hemodialysis patients with staph aureus bloodstream infection. So our lab analyzed a catheter containing staph biofilm on the interior and

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301 worked, you know, ex vivo of course very well. And so we're thinking about -- we have a plan to follow that up with a more robust study and think about where we can go with that. Thanks. Thanks for the comment on that.

MR. HOPE: Can I ask you then about the strategy of -- so you have -- you present these data about our traditional approach, so you can show logarithmic killing in laboratory animals. So let me be heretical and ask you why you just wouldn't use this as standalone therapy, and why it has to be additional and you take the risk? Notwithstanding what Helen said about suboptimal outcomes with staphylococcal infections arrest shows the potential of an adjunct is maybe difficult to demonstrate, and that the risk of not being able to show superiority and where that would leave you?

MS. CASSINO: Yeah. Yeah. So we wouldn't rule that out. This is a starting point, you know. This was a starting point that we thought would give the best opportunity to study and improve on clinical outcomes as opposed to doing a non-inferiority

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approach, which is what we would be doing. And it is sort of a big step to take a non-traditional compound with some of these issues into a non-inferiority trial with a standard traditional antibiotic without some additional data.

So we wouldn't rule that out. We would have to do some additional work. Small company, additional tox work. We'll see, we're looking forward to top line results at the end of the year and that will probably inform us of where we're going next.

MR. RUBIN: Todd?

MR. BLACK: So I still think one of the challenges and unknowns on these large protein or large kind of molecule therapeutics is the bio distribution and the potential for the infection types. And so there seems to be this emphasis on bacteremia or places where you do think you're going to have exposure.

So, I guess, one, do you have any data really on the bio distribution of the lysin relative to other large proteins and I think this also goes to monoclonals. And just a question to Dr. Weinstein's comments on the value of these topical types of proof

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of concept studies because a lot of these alternatives are going into these either direct organ, topical, intranasal types of approaches to try to validate.

Is there -- do you see any value in that given that the clinical outcomes there are kind of questionable about what it tells you in terms of potential for systemic therapies?

MS. CASSINO: Yes. So that's a great, great point. One of the things we're interested in is the bone and joint, prosthetic joint scenario. We know from the animal models, the animal data, we have that the penetration is lower, not surprising, in bone. And so we're thinking about and we have actually gotten some suggestions from ways of looking at topical administration. We're thinking about it. It's definitely something we're interested in the setting of, for example, a prosthetic joint.

So that's something we're thinking about for the future. And non-traditional ways of administering the drug might be a way to think about it. But again that's we're looking forward to our top line results from this study. But that's definitely a direction.

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So we haven't focused. I will be -- I will say, we haven't focused on the preventative decolonization as in the case. That hasn't been a focus of our company. We've been more focused on treating something as opposed to preventing, that could be a second step. We'll learn a lot from the randomized controlled trial.

MR. WEINSTEIN: So thank you for the question in terms of the topical, potential of the topical use of the drug such as the hypothetical lysin. I think one of the problems is that when you're starting an initial therapy, you're uncertain what the causative pathogen might be for skin and soft tissue infections. Classically it's staph and strep. So you need to cover the strep at the start.

A place where it might be, just thinking out loud, interesting would be if you are talking about secondary prevention, if you have like from the days in the clinic, there are patients who would come with recurrent staph aureus skin infections. And oftentimes they go through different kinds of topical rituals to try and prevent re-infection. And in the worst case

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scenario they would end up on systemic antibacterials in that particular patient population which are pretty easy to find. There might be a benefit for a product such as this.

MR. KALEKO: This might reach into your pipeline a bit, but can you tell me, is the lytic part of this, the lytic component of the lysin, is that enzymatic? Does a single hit kill the bacterium?

MS. CASSINO: Yes, yes, it's enzymatic. So it's a 26 -- 301 is 26 kDa native lysin, it's not engineered or chimeric as in the example. It has a binding domain and a catalytic domain and --

MR. KALEKO: But a single hit is lytic?

MS. CASSINO: That's what we think, yeah.

MR. KALENO: Okay. Are there some for gram negatives?

MS. CASSINO: Yes, we're working on that.

MR. KALENO: Okay.

MS. CASSINO: We have an active discovery program in our lab in Yonkers, New York. And we were pleased that we received support from CARB-X to run our gram negative -- start our gram negative lysin

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discovery program. So right now we're focused on antipseudomonal lysins.

And so we have 15 identified in vitro out of a field of about 500 that we were able to clone and/or engineer. So we're going to be bringing them next step into animals, and we look forward to moving them forward.

MR. KALENO: Okay. Last question then. Do they work as antibody drug conjugates?

MS. CASSINO: We haven't, I don't have any data on that. We haven't looked at that yet.

MR. HOPE: So since the question has been hung out there by the FDA, just tell us about the propensity for antibody generation, the safety of re-administering the compound both in terms of decreased or absent efficacy, but perhaps more importantly hypersensitivity and anaphylaxis for re-administration and the steps that were required or that you undertook to diminish that possibility.

MS. CASSINO: Sure, so, where do I start with that. Okay. So what we know from the animals, when we filed the IND, we knew animals made anti-drug

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antibodies and that in some of the animals, some of the rodent species, if you re-administered the drug after a hiatus, you could dose out for 6 or 7 days, something like that or if you sensitize the animal and re-dosed let's say a month later, there was a hypersensitivity oid, not confirmed, clinical reaction.

So going into Phase 1, this was a very carefully orchestrated Phase 1 study. We had a DSMB in place that reviewed each dosing and dose escalation point. Thankfully there was nothing to be seen, there wasn't much clinical, we did see ADAs. So 9 of the 13 subjects dosed with 301 developed ADAs, there was one transient IgE above the cut point, there were no basophil activation test positive post dose. None of those subjects in Phase 1 had preexisting ADAs, they were screened out. That was the decision the company made, it was actually made before my time. So that was just the decision for how the trial was going to be run and then I think an abundance of caution and a healthy volunteer trial.

Phase 2, we realized and we met with the agency and we talked about it, we looked at all the

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totality of the immunogenicity data that we had. We know that some patients, some individuals do have preexisting ADAs or antibodies that cross-react with 301, but we didn't screen them out in Phase 2. It wouldn't really have been feasible and it would really probably not be feasible to use the drug medicinally in this way if you had to do a complicated ADA screen while your patient has an acute infection.

So we have gone forward with that and as I said, clinically we've seen no evidence of hypersensitivity during the conduct of the study. And we are blinded and our DSMB has raised no cause for concern. Now this study is an in hospital study and it is a single dose. So when we put the protocol together, we put in the requirements for observation of the patient during dosing and we educated the PIs on anaphylaxis should that occur and what to look out for and we provided all the information. Fortunately knock on linoleum or whatever that is, we haven't -- we're pretty far through. I mean we dosed beyond 75% of our 115 or around 75%. So we haven't seen that. Now that's a single dose, I can't comment on re-dosing per

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se. What I can comment on is that when we looked at all of our ADA data that we had, we were encouraged by the fact that we didn't see IgE, we didn't see basophil activation, we haven't seen that and we haven't analyzed the Phase 2 data, but we haven't seen that post single doze.

So the single dose at the dose that we are administering now may not be re-sensitizing the patient for a type 1 hypersensitivity, we don't know, but that's something that we are thinking about. So for this indication, were this trial to have positive results, single dose upfront, the things that we are thinking about understanding better would be the potential for re-dosing down the line, what would be the time frame for that, how could we look at that, that would be stuff that if we are successful, we would be -- if this works out, we will be talking to the agency about different ways we might be able to sort that out.

There are a couple of paradigms out there as to how this was handled for other foreign proteins. So there is the Xiaflex clostridium collagenase used for

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Dupuytren's contracture et cetera was a subject of an FDA advisory committee some time in recent years. Because even though that's a locally administered drug, patients do develop ADAs. It turns out that drug has been able to be administered in repeat dosing fashion on a regular basis. So that's one analogue to look at. Going back in history, streptokinase is another one that comes to mind back in the (inaudible) old care when I was treating patients before there were other options.

So that sort of had a precautionary statement of not to re-dose, although we are looking at labels elsewhere because I don't think it is available in U.S. anymore, those labels have also softened in terms of the duration of time you could re-dose between, before 7 days or -- and after X amount, 6 months or whatever for patient use. So those are kinds of things we are thinking about depending on how that trial comes out.

MS. BOUCHER: So I just had a little question along those lines. So sort of appreciate the IgE path and your comments about the ADAs weaning by 180 days, but are there other immune responses that need to be

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considered and/or sort of monitored for other periods of time or any other lessons to be learned from immunologic products or the immune system is such a broad thing and obviously the hypersensitivity would be the most urgent issue, but are there things like, I don't know cancer risk or other immune related things to consider?

MS. CASSINO: So for a single dose of a product with a 6 hour half-life and the fact that we haven't seen anything considered to be related and our DSMB hasn't advised us of any needs to change what we are doing right now. We're blinded. We haven't seen any signals. The only other thing we did a little thinking about was a serum sickness kind of phenomenon. Blinded, we haven't seen anything that looks or smells like that in the timeframe that one would expect it to happen, again blinded post-study dose drug administration. So, but we'll know more when we have all the data.

I think it changes if we think about it as a multi-dose product. So that would be something else, again not off the table. It certainly would, but it

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would require an investment into sorting through whether there are any other risks, but we know from the animals, we can dose. I think the acute allergic hypersensitivity was the first worry and we know we can -- we are expecting we could dose out to about 7 days, if we wanted to do that from that. And of course if we look at our pantheon of antibiotics of current and previous, there are some common antibiotics out there that have anaphylaxis and the warning and precaution statement right up front, so we all know what they are.

So I think for in hospital dosing, it would be one thing, benefit risk, if this really improves the outcomes, it would be one thing and then we would have to think about where we would go from here. But this is a good question where we have -- we are thinking about it. Thank you.

MR. KALEKO: To follow up on that question, it was kind of a red flag in the presentation, may be you could comment on it, related, license, cause and irreversible vasculitis. Is that understood or is your mechanism sufficiently different that you are not worried about that? Did I read that correctly on the

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screen, I thought that's what it said?
MR. WEINSTEIN: Yeah, that's correct. Thank you for the question. So in some related products and animal models, there has been off target binding and enzymatic activity against great vessels.
MS. CASSINO: So, where do I start with that. Okay. We haven't observed enzymatic activity per se. We have observed some perivascular and I want to say infiltration at doses well above where we are dosing. But those are doses well above where we are dosing. So we are dosing below, we are first, so it is hard to know where you belong and the potency of this is such that we learned from our PK/PD that low doses are pretty potent. So far we are well below that threshold.
MS. NAMBIAR: Dan, can I ask a question? So Cara, a more general question moving away from the issue of hypersensitivity, I mean, this is a difficult indication to study. So I was wondering if you would be willing to share with the group strategies that you might have used because that sounds like you are able to enroll fair number of patients in a fairly short

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time frame. So the geographic distribution of where you have been able to enroll and if you did use some particular strategies to help enroll because I think a lot of the indications that we are discussing are going to be the difficult to study indications. There might be some lessons learned that you could share with the group?
MS. CASSINO: Yeah, sure. Thank you for the question. We are pleased by our enrollment. We were worried from recent history that it could take a glacial pace. One of the things that probably helped, "there are a couple of things that probably helped". First of all, all patients enrolled in the study are getting what would be standard of care prescribed by their physicians. So that's one thing that I think was probably helpful for recruiting. So our investigators were able to say, well, we can give you this in addition, it is in clinical trial, it may help you. So that was one thing.
I'm also really pleased to say and I don't know if this is true for other trials, but our U.S. sites have led the way on this trial in terms of

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enrollment. So we opened in May of last year in the U.S. and we have had really good enrollment in our U.S. sites, which is really nice. We work really closely with our investigators and I have to thank Elena, wherever she is, Elena, who is our lead medical monitor who answers every time her cell phone rings, every question that comes from everyone, which I think made a huge difference, I really do, because it is complicated to know whether the patient even fits in the study and then there is always a twist. So it takes a village to enroll these patients. So having someone on the other end of the phone makes a big difference. So those are the -- otherwise I don't know that there is any magic, oh, except to say our investigators were uniformly very enthusiastic. So they really were happy to be in this study and very enthusiastic to see a non-traditional being applied in a semi-traditional manner. So that's probably what helped.
MR. DUBOVSKY: Did you try to control the standard of care or did you allow them to do whatever they wanted?
MS. CASSINO: We tried to put some guidelines

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in to give -- but leave sufficient flexibility for prescribers because we are open now in 14 countries. So we had to leave flexibility. So basically standard of care defined by conventional guidelines, basically Dapto or Vanco for MRSA semi-synthetic penicillin of your choice, whatever it might be in your region or first generation cephalosporins or what we ask people to, if somebody was on something else like Teicoplanin or whatever. We ask them to, if they were thinking of enrolling the patient, to move them over to one of these standard agents unless there was a reason not to and we excluded a couple of -- we excluded the long acting, Oritavancin and Dalba.
MR. RUBIN: To follow up on that, were there any restrictions on prior therapy?
MS. CASSINO: So we tried to enroll patients that had -- we wanted to enroll patients that had no more than 48 hours of effective anti-staphylococcal therapy for the current infection, but we wound up saying they could enroll with up to 72 hours with a conversation with Elena and if Elena thought that the patient was. We are looking to enroll complicated

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bacteremia. So we were trying to get away from the simple bacteremias that would clear their infection by the time we are dosing. So, but 72 hours was the limit.

MR. RUBIN: Right. So I know we had some discussion earlier about non-inferiority and I guess maybe one advantage of these add-on superiority trials is that there could be less restrictions in terms of those enrollment criteria. Of course the downside is that could diminish the ability to show a treatment effect.

And related to that I would say that in add-on superiority trial, there could be some more flexibility in terms of what endpoints could be used because there wouldn't necessarily have to be a justification of the margin for the active comparator. So the daptomycin trial endpoint wouldn't necessarily have to be used as a template for these types of studies.

And just to go back to the door comments, we're talking about yesterday, if it's very difficult to define each of these subjects with staph aureus bacteremia as a success or failure, it may be possible

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to have a more granular endpoint in these types of studies.

MR. REX: So a comment and then a question. My comment is that we're all cheering for you. I think everybody has wished for a long time for the lysins or the phages as their superset to finally show us a way to be useful. And I realized there are a lot of -- you know, you can always take things like this apart and come up with other ideas, but I hope everybody in the room appreciates how much effort goes in to raising the money that makes it possible to do a trial like this. It is a herculean endeavor and I want, you know, it really is and so very helpful for your data.

Have you learned anything about definitions of bacteremia as a disease entity even at this point that are worth sharing? That's one that comes up a lot. How can I study bacteremia and we had a long series of -- some years ago, there were several workshops at the EMA (ph). I don't remember one specifically here, but maybe there was, I mean, it all kind of runs together in my head. But this notion of bacteremia as a disease and staph aureus was the one setting where that almost

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seemed like it might be a thing in and of itself. And I'm just curious as to whether you have any insights about that and did you have -- you were going to say something or did you -- so the question is that, have you -- do you have any insights even now from your trial? You may have some more after you've un-blinded your data, but the bacteremia as a disease?

MS. CASSINO: And thank you. That's a great question. Particularly since there may be different kinds of bacteremia and for the -- given the biofilm activity and some of the other comments, we wanted to focus on biofilm associated bacteremia. And the challenge, so called complicated bacteremia, and I think the challenge there is that there are -- is some literature on this, there are some punitive definitions out there.

We started off with a really narrow definition and our -- first adjudication committee meeting or adjudicators said, "okay, this is really too narrow because this guy is clearly complicated and he doesn't fit in this definition". So we worked really hard with them and with Vance to define a construct for

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complicated bacteremia. So we're going to learn a lot about that and how that works at the end of the day from the study.

It is -- the other thing I think I appreciate is that it's going to -- it's hard for the treating physician when the patient hits the door to no necessarily, whether it's going to be complicated or not because you got to treat them upfront. You're not going to withhold therapy and see if they blossom. So you're treating them upfront and you're saying, "well is the renal failure patient a diabetic, they have this and that". Occasionally they may already have a metastatic focus, so that's clear, but there's a big gray area. And so thinking about indications, we were thinking along the lines of bacteremia not otherwise specified and endocarditis because it would be hard to limit it.

There's no clear litmus test of what is complicated and what isn't, but that's just our preliminary thinking. I think once we're able to dissect this patient population, after we're unblinded, it'll tell us a lot.

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MR. REX: In my experience as an ID doc, staph aureus in the blood is one of those terrifying moments and I watched a young IV drug abuser, she almost dissolved before my eyes due to staph aureus. And what she came in with was staph aureus bacteremia, but then all of a sudden it was in this organ and in that organ and a week later it was everywhere and then 10 days later she was gone.

And that was despite what at the time was the best available therapy. So staph is that one or it's what I remember from the, particularly the EMA workshop. Staph aureus is that one organism that has the ability to sort of eat through everything. And, yeah, it may have started over in this corner, but get it in the blood and, man oh man, is that a dangerous situation. So I think the idea of a drug for staph aureus bacteremia, this does always seem to me to be the one corner where you can do that.

MR. BLACK: I guess along that because of the challenge in that development program with these kind of limited bio-distribution types of compounds, are there other options and so certainly in immuno-oncology

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there has been a big shift in the view on intratumoral types of applications because that really does seem to limit toxicity and have high efficacy.

Is there any opportunity in things like osteomyelitis? So you talked about the sternum case yesterday. Helen or other kind of source specific indications where some of these types of alternative therapies could be developed and really addressing an unmet need?

MS. BOUCHER: Our orthopedic surgery colleagues work really hard in this area and they do a lot of things that are interesting, right? So they make beads and they put different drugs in the beads and so our guys are about to start a trial of one of the long acting agents in these beads.

Well, what's the dose? How do you do it? Does surgeon A do it the same as surgeon B? We've reported cases from our institution of nephrotoxicity due to aminoglycoside that was put in a joint. And the only way we found it is because we got consulted to treat the infection, but realized that he had renal failure from no other cause and ordered a level of

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aminoglycoside X.

So joint replacement surgery is the most common surgery in the United States today and very, very few, thankfully, patients get infected, but when they do it's a huge disaster of epic proportions. So our surgery colleagues, they're desperate. How to do that in as controlled setting with a compound that isn't approved for systemic use, that's where I have trouble starting to put my head around it.

It's a need for sure, but it's almost like you need a bioengineer and a drug -- you sort of need multiple things going on at once to understand sort of the technological aspects of the delivery of these compounds.

MR. DUBOVSKY: So one thing that what you said just sparked in my mind is instead of going after specific indication, whether it be VAP, skin or whatever, to do some kind of composite indication of serious staph disease. And I'd be curious from a regulatory perspective if that's something that is palatable. Realizing that you wouldn't be able to demonstrate specific disease, specific endpoints just

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because of the power and the size issues, but perhaps if we think back to our vaccine side, like pneumococcal vaccine which is licensed for invasive disease or I think some antifungals may be licensed for invasive disease, if that's an approach that could be useful.

MS. NAMBIAR: So this is a discussion we've been having for the last several years. Is treating the bug enough or does the body site of infection matter. And I think we've seen in many development programs where products work in a body site or maybe more than one body site, but then there is a clear deficit when it gets to another body site.

So I think it's hard to ignore the site of infection. Treating the bug is only one part of it. It also depends on where the organism resides. Having said that, I think there are instances where we are willing to look at a product where the study population could be a mixture of infections. It's very important that we have discussions around the study design and the endpoint if such an approach is taken.

So now our unmet need guidance, we do say if you're contemplating a superiority trial design, there

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might be an option to pool across body sites. However, you have to make sure that you have adequate representation of patients who have the most severe of infections because that's the area that you're seeing the deficit.

So there is a risk in that approach because if there is a deficit with the product in a body site, so you might not be able to understand that or that might not be revealed in the study as it would have been had you done an independent study of that body site. So I think there are scientific concerns with just going after an indication, which is to treat an organism because the site of the infection is just as important as the organism.

MR. DUBOVSKY: So presumably you'd want to see at least a trend in each of the disease entities, yeah? Or would that be adequate?

MS. NAMBIAR: Yeah. I think first and foremost is you have to have a clear rational for which indications you're lumping in this multi-body site study. And then you have to make sure you have an adequate representation. Yes, you would like a trend,

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but again when it's a very small sample size, your trend may or may not be a true finding, even a trend in the wrong direction, that may not be a true finding.

So I think there are a lot of shortcomings with that approach. So ideally I think studying it in a body site or body sites is probably the best thing to do, but if there is really a product that can address an unmet need, we're willing to take the uncertainties around the demonstration of the benefit with the product. With some caveats, we might be willing to consider a multi-body site study, but there are a lot of details that need to be worked out and lot of other information that would be needed that you're comfortable going into those body sites as well.

MS. BOUCHER: Just because I was going to talk back to this point. I wonder if there's other things that we could do to understand that issue of body site rather than doing that in an efficacy clinical trial such as understanding the clinical pharmacology exposure at the body site and use that to support. Especially when we're talking about looking at these pathogens and really needing to follow the pathogens,

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it's such a burden on an efficacy study. I wonder if our challenge is to try and get better understanding penetration.

MS. NAMBIAR: I mean I think it's, given that those pieces of information will be available before you decide to go ahead with such a study. I think some evidence that the drug reaches where it's supposed to reach and treat the infection that you're trying to target. I think the absence of all of that I think is extremely risky to even try to do such a study. Yeah.

MR. BEVILACQUA: If you could just maybe comment further, one of the places where multiple body sites are brought together somewhat by an event or surgical procedures. You just talked about the orthopedic surgery were very large problem and I agree. But also there are surgeries all over the body and there's a wound, right? So while the sites of the body are indeed different, there is a path of physiology of the wound also. And certainly staph aureus is a player in almost -- in many of those sites. So I wonder if you'd comment about another path of physiological event that occurs over multiple body sites. Does it

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influence your reason or your thought process?

MS. NAMBIAR: I want to make sure I understand your question. So is the question, potentially an indication such as surgical site infection, but the site of the surgery could be maybe the abdomen, it could be another?

MR. BEVILACQUA: Exactly. The pathophysiological event is the wound, but again it is influenced by body site.

MS. NAMBIAR: Right.

MR. BEVILACQUA: But not entirely.

MS. NAMBIAR: Right. I mean, I don't think that -- I mean, that doesn't pose the same kind of challenges as we're talking about multi-body site. I think what might be different there is the heterogeneity in the patient population, patient has an abdominal surgery versus some other kind of surgery.

But if really you're targeting gram positive pathogens, which are typical causes of surgical site infections and then you have a mixture of patients with different kinds of surgical procedures, I think that is a lot easier to justify than when you're lumping, say,

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a pneumonia and a urinary tract infection in one step.
MR. RUBIN: So we have about 10 more minutes before the break and at this point, I'd like to ask if anyone from the audience has a question or comment.
MS. LIU: I guess I have a question. My name is Mei Liu. I am from Center for Phage Technology and -- you hear me better? Okay. My name is Mei Liu. I'm from Center for Phage Technology from Texas A&M University. This is my first time to attend this kind of regulation meeting and I really learned a lot.
So just a little bit background. Our center is led by Dr. Ry Young and we were involved in the well reported Tom Patterson Phage Therapy case as well. So after that case, we are looking -- right now we're looking for partnerships with clinician networks and we, based on our existing phage libraries, we are trying to build several well characterized phage banks for selected groups of multi-drug resistant bacteria.
So I guess I just have a general question on the patient enrolment criteria for lysin product. Because just like phage, lysins can be very narrow host range and I think in this case, hypothetical case Z-4

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product has okay host range and the effect was transient, but the host range seems to be okay.
So for, I guess, my question is very general. So is prescreening, for Dr. Cassino as well, so is prescreening the patient for sensitivity for the product, is that a good criteria? Is that a good practice to conduct a clinical trial? Because we know that maybe not for staph aureus, for other bacteria, for certain bacteria only personalized approach is the only way, only effective way to go.
So I guess for the panel, I'd like to know that, would you rather see a very small sample size clinical trial with very good curing rate or would you rather see a large sample sized clinical trial with not so good effect from the product?
MR. WEINSTEIN: So there is a lot to unpackage there, so thank you for the questions. I'll see if I've got this right. The first question involves concern about sensitization to such a drug product from the environment. And, yes, if you have a protein that there's a possibility that someone would come in contact during the course of their life before

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receiving it, there is that possibility that they may have some preexisting response that has become anamnestic. So I would answer that at baseline you would be concerned about the presence of anti-drug antibodies. And this was part of the screening that was described for the ContraFect trial.
The second question, it's a little bit of more in terms of the trial size. It really -- the size of the trial will be determined by the treatment effect that you anticipate. I don't think anyone goes into a clinical trial expecting or hoping for a small treatment effect. But based upon the earlier experiences from, say, animal models or a smaller clinical trial, so you may have an idea from Phase 2 what kind of treatment effect that they can expect. And then they will power the trial to statistically confirm that there is a treatment effect.
So I think in general, the idea is to have a trial that is efficient. So not any larger than you need it to be.
MR. RUBIN: All right. So we'll go to --
MR. WEINSTEIN: I think that answers some, but

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probably not all of your questions.
MR. RUBIN: Dr. Cassino, to follow up on that and then to Dr. (inaudible).
MS. CASSINO: Okay. Thank you. So first on the prescreening for sensitization. Just to clarify, that was done for the Phase 1 study in healthy volunteers. The first human ever administration of this drug to a healthy human and the company opted to screen out anyone with a positive preexisting ADA, reactive basophil test or which were low in number for whatever reason in IgE above the cut point against our antibody testing assays.
In Phase 2, we are not doing that. We are not prescreening anyone out. We are taking patients in. We think that's an important experience for us to gather. We put all the bells and whistles and precautions in place in our protocol in the event that we expect some people and we know some people in the study have preexisting antibodies of some sort, but we've seen no issues. We've had no hypersensitivity reported. We had no hypersensitivity reported as far as I remember and certainly none related to study drug.

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So that's where we are. And we are collecting information and we're going to learn a lot from this because we'll do analysis on whether or not the low in number, but people who may have some cross-reactive ADA baseline, what does that actually mean in terms of their response, their PK, et cetera, et cetera. So we're going to learn that. We factored that into the trial from the get go in our sizing and our design.

And then just on the diagnosis. So we're requiring patients to have known or suspected staph aureus. So that's known either by traditional blood culture, by staph aureus bacteremia. So either by traditional blood culture, by rapid diagnostic or by a KOH positive test with a positive gram stain of a blood culture. So that's the baseline. So they have to have the infection under study.

And then in terms of susceptibility to 301, we've been doing surveillance studies. So far we haven't -- we've seen MICs below the level that, from what we can tell, we would expect to be susceptible in all of our general population surveillance study. So we haven't screened anybody pre. We'll be looking at

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the isolates throughout the trial, for their susceptibility patterns to antibiotics and to 301. And of course the patients are expected to be on adequate antibiotic therapy to drugs, antibiotics to which their drug is sensitive. And our adjudication committee is looking at that in terms of evaluating endpoints, et cetera.

UNIDENTIFIED SPEAKER: Yes, I would -- so this is a very interesting paradigm that we're discussing here, which is adding a new therapy to what's theoretically effective treatment. And that's a paradigm that is definitely non-traditional as we haven't done very often. We've added -- we've used combination therapies like (inaudible), but the theory there is that you're adding something to address resistance to the base therapy, but I don't believe that this paradigm is specifically trying to address resistance to the base therapy. It's trying to improve on the base therapy. So this is failure of the base therapy and related to resistance.

So that to me is a very interesting paradigm and it raises two challenges to me. One is, how does

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one decide on what is the additional benefit one is looking for? What's the basis for coming to that decision? But more important to follow up on what Dan Rubin was saying is, this to me is an opportunity to think about nontraditional endpoints because is it the idea that you have to beat the base therapy on the endpoint for which it was approved. So does it have to be the test of cure, mortality? And that to me seems like that's not necessarily what you're aiming for here. You're aiming for some benefit and maybe the benefit can be a different kind of endpoint such as time to analysis. Maybe you don't beat it on the test of cure or mortality, but the time to event, you know, quicker cures or some other endpoint or some composite endpoint and I'd be interested in having the panel discuss that this kind of paradigm where you're adding adjunctive therapy to theoretically effective treatment, what kind of endpoints is one looking for and this is an opportunity where we need to look for nontraditional endpoints and things are a little bit lesser than clinical cure, death, et cetera.

MR. RUBIN: Thank you. So we have one

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question from WebEx before we summarize and have a break and this question is, for mixture infections that often occur in clinic, we need a therapy against the indicator, but not one pathogen. What will happen if we just kill staph aureus from multiple infections? Will this help other microbes grow better or not? Any comments from the panel?

MR. DUBOVSKY: All of these pathogen specific approaches, many we've talked about over the last 2 days have to deal with that issue, right? So and I think it's part of the reason why there are concerns about either replacement or outgrowth and that has a lot to do with how you define your endpoint. Yeah.

UNIDENTIFIED SPEAKER: Dan if you can respond to Ian's comment.

MS. NAMBIAR: I think there was a question from Ian for the panel about whether we are willing to consider other endpoints, he called them nontraditional endpoints, I guess, different from what we've typically done with antibacterial drugs for these kinds of products. And I think the answer is, if there are other endpoints which are clinically meaningful, I

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think we're certainly willing to consider them and if I understood Cara correctly, they are evaluating a series of secondary endpoints. And I think eventually they will pick, hopefully pick an appropriate endpoint for the Phase 3 trial. So that's, I think that highlights the importance of doing these kinds of Phase 2 studies and learning and hopefully identifying other potential endpoints that might be more relevant to products such as these. I don't know Cara if you want to add to that.

MS. CASSINO: Yeah. Thank you. Thank you, Dr. Nambiar. That's correct. We picked actually the 14 day efficacy endpoint which is already not what has been the standard approval endpoint for this indication at least because we thought it might be more reflective and give us an earlier signal of efficacy because of the way the drug works and then we're collecting quite a few secondary endpoints, which will help us look at things that have been raised today. We're looking at the echos for the endocarditis patients. We'll be able to evaluate time to certain endpoints. We're also collecting health resource utilization endpoints, et

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cetera.

So we're hoping to get like a 360 view and hopefully that will help us plan better for Phase 3, but Ian, thanks for the comment because we're hoping to learn from this. I know where you are.

MR. HOPE: All right. So I think we've come to end and just a brief summary from both of us then. So I think that we debated at the very beginning about whether this was a traditional or nontraditional program and pathway and we're going to talk about that after the break. I think that there was a sense that even though if you label a compound as nontraditional, still there are traditional pathways that need to be followed and that we still have to address medically issues and needs that are real and that are valuable to the patient and the society.

The use of pathways that are outside that paradigm such as decolonization and reduced spread seem to be difficult at the moment, but nevertheless potentially important. The use and relevance of adjunctive data such as clearance of organism at non-sterile sites to de-risk programs was discussed and

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appears uncertain. There was quite a lot of discussion about adjunctive learning that can occur about disease processes and pathogenesis given the new molecules that are being generated here including study endpoints, infection of bodily sites, response to infections and whether they can be used and harnessed to guide the development of future medicines. And I think something that was also discussed is that nontraditional molecules or molecules out of the, well, that are not small, are likely to bring idiosyncrasies in CMC and immunopharmacology that need to be expected and investigated. Dan.

MR. RUBIN: Thank you. That covered it from my perspective as well. So we'll now take a break until 10:40 and then reconvene. Thank you.

(Recess)

MR. REX: Okay. So we're all going to sit down now I think and get started. We're all going to sit down now and get started. Okay. We're almost there. So with any luck, I guess, my slides are still up. So we have about an hour on the schedule and what Ed and I have agreed to do is, I've got a few slides to

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show you that summarize some of the things that I think that I heard, Ed's going to riff off that and then very interested in comments or things that didn't get brought up, that wasn't the right space for previously and so forth. And we're realizing that those -- it's not projecting on the little things on the inside I don't know how to fix that, sorry. Sorry about that. You may have to turn around and look at the slides, to the left or overhead. We're delighted we've gotten this much to present.

So here are the five things that I think that I heard. The first one is that the label nontraditional is very broad and requires qualification, structure versus goal may help a bit, and I'm going to go into each one of these in a little bit more detail in subsequent slide.

Second is that current development tools are often suitable. There may be some gaps and I've identified a couple of the gaps here on this slide, and again, we'll drill into that. The lack of a tool or a path can be managed. It's really we should view it as an opportunity to come forward with a really concrete

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idea as a sponsor. And new approaches have been and will hopefully continue to be developed.

The product's whole effect must be considered, don't be seduced by a pretty mechanism is going to be the subtext there. And a high level guidance document, a high level guidance document might be useful, but we're not ready to commit, I don't think, to very many details.

So now digging a little deeper. The phrase nontraditional is broad and language matters and I just stumbled into one of this quote. When I use the word Humpty Dumpty said in a rather scornful tone, it means just what I choose it to mean, neither more nor less. The question is (inaudible) whether you can make words mean so many different things.

Nontraditional is too broad and needs a lot of qualification. Alternatives to antibiotics is no better as a label. I didn't hear any other really strong ideas come forward. I think we're going to end up with the phrase nontraditional. The closest I've got is that structure versus goals seems to help a little bit with categories, but the deeper question for

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me really is, within the space of this thing we call nontraditional, what buckets of conversation would be most productive? And are there ways to chop up the space to drive a workshop that would help you create a general answer that would be useful to more than one developer? So some ideas for buckets that have come to me, I mentioned these yesterday, host directed versus pathogen directed, and it might be that we need a workshop on host directed therapies. We understand pathogen directed, but maybe host directed. Please go into presentation mode it says, okay. Try that, does that make a difference? I hope it's not worse. Okay. Is that the same? All right. Makes it bigger though, it's true. Thank you.

The question of direct or immediate benefit versus indirect or delayed benefits I think is a worthy one. Maybe immunogenic versus non-immune response and maybe explicit combinations versus single entity, so I have some comments on some of these here in a minute.

So theme number two, the current tools often work. In listening to the cases we discussed, the current program designs often seemed like they were

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suitable. The challenges that came up were more often than not, not unique to nontraditionals. Small effects are hard to measure and rare events or rare pathogens require large trials. I mean, that's true in lots of settings.

But let me talk about three specific potential gaps. Gap number one is the measure of indirect or delayed benefit. And here it spins out of the question of microbiome and colonization and the theme that I like, I think it was Scott that picked up -- proposed the word surrogate. It's -- the shape of your microbiome or your colonization is a surrogate for something that may happen down the road to you or to somebody near you. And there are a few settings where we do treat carriage of a specific pathogen as tantamount to an active infection. Group A strep in a surgeon, group B strep in the third trimester of pregnancy, a serious (ph) meningitis in the nose in anybody are things that we take as very serious events and we respond to them.

And I think the question that I heard being discussed is, are there other such things? What would

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you measure? Do you want to look at infection yourself? Do you want to look at transmission to others? Do you want to look at infections in others? What would you get at that would be compelling? And that was we -- the conversation kind of ended there, but that was the idea that sort of came to my mind.

Gap number two, combinations. This is -- I thought this was intriguing as well. How would you evaluate a mixture of 5 to 10 antitoxin virulence monoclonals? It might comes up with something like that which staph aureus makes a couple of dozen virulence factors/toxins. And a factorial design is not really possible. And so I'll ask the question, is it okay to simply accept the sponsor's mix of monoclonals? Treat it, call it -- treat it as a polyclonal. The safety is on the mixture as is the efficacy. The fact that dropping out one of the MABs might reduce the cost of goods is kind of the sponsor's problem and ditto for the dose of any one component being wrong.

And team Merck here can think about whether or not, yes, they're pleased that they've got their cost

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of goods down for their anti-C-diff monoclonal, but what if you hadn't done that, yet it was out there working, it's kind of interesting to muse on because scientifically I'd wish to fully resolve all the points, I understand what I'm saying is kind of unscientific, it doesn't feel scientific. But if there's an effect, there's an effect and it's kind of an interesting thing to noodle on.

Right before the break, Ian Friedman stood up and asked a question that I captured as this slide, current tools and endpoints. Are there other endpoints to consider? And Ian, if I've paraphrased your question correctly, consider an add-on that doesn't improve on the mortality effect of the base therapy. So the base therapy versus the base therapy plus the add-on, the mortality is 20%, equals 20% and its non-inferior. But there's something else that you want to show is better. And you could say that -- you could generalize that, that's what we do for all antimicrobials. I do -- I study my drug in complicated UTI versus meropenem and I show that I'm not inferior to meropenem, but the superiority is somewhere else and

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I want to show that somehow.

So I think the general question of what measures are strong enough to be compelling is a good one and I think that has been discussed probably in other floor but perhaps we need to have a discussion, perhaps, about this relative to anti-infective products. I'm not sure whether that's the right thing or not, but it's worth raising.

Number three, Owen McMaster's (ph) slide, comments yesterday made me think about this, no path yet, don't panic. Using existing tools is desirable when possible. It's kind of like its less trouble, but there won't always be a path yet. And this is an opportunity for a sponsor to propose something new and innovative. And I've heard repeatedly that the FDA, as I know is the case with EMA as well, is very happy to have discussions about how an innovative program might progress. It's the sponsor's job though to drive this. You've got to come up with something concrete and the sponsor is the only person who really can do that or the only group because you know more about your product than anybody else in the universe. This is -- but be

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concrete, be specific and think about the other questions that's about value.

Don't be seduced by a pretty mechanism. The mechanism is really important, consider the whole effect. And Ed made us think yesterday about -- he made up a case scenario that I've -- I think I've kind of replicated here. For a hypothetical anti-staph aureus toxin monoclonal, where you do a study and your endpoint is nosocomial pneumonia, HAP/VAP and the staph aureus nosocomial pneumonia rate goes down from 25% to 15%, that's nice, but the all cause mortality goes up from 30% to 40%.

So the product did its bit, it absolutely reduced staph aureus pneumonia, but did clearance of staph aureus create other issues? Typo. So it's a made up example, but you may want to think about what that would mean. And I thought that the discussion of intercurrent mortality around the C diff product was a similar -- felt somewhat akin to that for me. And my personal view is that the net effect in the enrolled population which is hopefully the population going to use it in the long run is what matters. And I'd argue

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that this is actually not a regulatory issue. If the effect does not punch through real-life situations, then the value proposition seems likely to me to be weak.

It's intriguing to think about the door approach, the hierarchical endpoints kind of approach to showing some of this -- some value. And I think that the previous slide where I pointed at the idea of, are there other endpoints feeds into this? So something to play with and maybe that's another kind of workshop thing if we had a good question to focus on.

Anti-virulence and the whole effect, one more slide. I just observed, and this came up a couple of times, I talked about the pathogenesis and immune response in animals. The animal models are incomplete, imperfect. And I just pulled out two papers out of the literature both of which conclude basically the same thing. The animal models are a good hint, but they don't always go to the same place as human beings. And you may also find that there are limits on bio distribution. There are things you can do in animals that maybe you can't do as readily in humans in terms

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of delivering product to a site. These are all the reasons why you have to be careful about thinking about the whole effect. And so again, personal view, my sponsor needs to maintain a skeptical attitude. You're going to have to start with the preclinical models and maybe this is not one of those workshop spots.

High level guidance document. My personal view is, if we did one right now, it would need to be very general. But actually I think it might be useful because it is kind of the effect of encouraging work. If there are sponsors trying to raise money and they want to talk to the venture community about raising money in an area. Having just a general sense of direction from the agencies is a helpful thing in making those presentations. That said, this -- the conversation over the last 2 days has shown that there are many details not yet ready to be nailed down. And so here are a few of my thoughts for future workshops. And I wouldn't -- if we did such things as a group, I think you'd want to look for a reason to do that workshop. So look through the CARB-X portfolio or maybe things FDA is saying, is seeing and if there are

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a couple of them that have an interesting common core, maybe that's a good reason to do a workshop on it.

So the idea is that I thought of were host directed, this question of indirect or delayed clinical benefit. And the thing about animal models versus human illness and I know that in each case there may already be some data on this topic, but maybe we want to have a conversation focused on the kinds of products that we're interested in developing.

And so my last slide is a reminder that nontraditional just means we haven't done it yet and I realize, I sometimes see that quote that all art was once contemporary, the old art, that ancient art, well it wasn't for the Romans, it was an ancient at all, it was contemporary. And so I think for us what's nontraditional today, it'd be interesting to see some of these things become sort of routine practice in the future. So with that, those are the thoughts that I had. And then over to Dr. Cox.

MR. COX: Yeah. Thanks John. Excellent summary going through a whole range of things. And I think what I'll do is really -- I just want to touch on

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a couple of points just to sort of emphasize them. We heard a lot of discussion about mechanism. And mechanism is really exciting and mechanism is what gets you to the new lead molecule that you want to develop, and mechanism is -- tells you that you've got something different that has got potential and its unique.

But as you think about development, I want to just encourage folks. As you move along in development, use mechanism for everything that it's worth. Help it inform your development program, help it inform the indication that you're going to develop the drug for. But as you're moving towards those later stages, realize that then you're starting to look at the patient. How is the patient doing? Is the patient overall better off? So I just sort of put that in there and I would say that really the ideal approach is to use mechanism for all that its worth and it's very important in the early stages, but also have in mind the patient even at those early stages because I think that's going to give you sort of the most complete view of your development program. You'll start to anticipate things that are going to become important to

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you later on.

So I just want to throw that out there because I know, we had a lot of discussion about this issue over the course of the workshop. I think this is really important as folks think about their development programs and sort of how to look at their molecule, how to think about the present, how to get as much out of it as they can, but also to be thinking towards the future. So there isn't something that you get to down the road and say, oh I wish I had done whatever so.

And then enrichment. So I thought the conversation about enrichment was fascinating because there were a couple of really important points that came out in that. The initial discussion started talking about, let's go to the patient population with the highest event rate. It makes total sense as you start to think about enrichment. But then something else came up, which was, there's a lot of other events that happen in that population. And if you're trying to do a superiority trial and you have all these other events, it can sort of cloud what it is that you're trying to discern from the overall study.

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So, and then there was the discussion of maybe there's a U-shaped curve. There are patients who don't have enough events, there's patients who have more events and then there's patients that have disease that is so severe that they couldn't respond anyway. So this is sort of another piece of this sort of thinking about enrichment. And then we also heard a comment of, well, there are some patients and there's a patient population in whom this disease is also important, but their event rate is lower. But you might be able to study this patient population because there are all these other things going on that are going to confuse your assessment trying to look for superiority.

So I think that discussion brought out a lot of really important points to think about what really is enrichment and how do you think about what patient population to do your study in. And of course we would like to see the drug studied in all the patient populations that are relevant, but there are obviously practical considerations as to what can be done first, what is it -- in which area is a trial most likely to be able to demonstrate the safety of a drug and the

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efficacy of a drug.

So just some things to think about, but I thought that was really a good discussion. And then there was also the -- part of this too is almost this issue of competing risks if you will. It starts to come in there because you've got the pure efficacy assessment on the event that you're trying to influence. But then you also have other events that are going on at the same time too. So there's some relationship I think with the competing risk issues that also figures into this thinking and thinking about how a clinical trial would be designed.

And then I think those are sort of the two most important points that I just wanted to reiterate that John made. There was the -- you heard the discussion about pre-IND consultation. We welcome folks coming in and talking about their toxicology program, talking about their preclinical models. That's obviously very important, something to be done that can help to inform the development program. You can start to look at not only toxicity issues, you can also start to look at exposure response and those sorts

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of things in animal models of infection. And then the other thing that came in, and I think this is an important lesson and that is that the models can really help to inform and to make rational decisions, but they're not always right. There are going to be gaps between what happens in the animals and what happens in humans and we have seen that over and over again.

That's not to say don't do the animals. Of course do the animals and of course try and learn as much as you can. And as others have taught me too, oftentimes what you're doing is, you're not just looking at one animal model, but maybe you're looking at a couple to try and see if they're sort of all moving in the same direction to sort of help increase the likelihood that what you've learned from the animals has a greater chance of informing correctly what it is that you expect to see in humans. So I thought that was a really important point too.

And then we talked some about this issue about which is again a lot of these things start to overlap, the issue of replacement infections. If you impact on one particular pathogen, is there something else in a

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prevention study, is there something else that's going to move in and take up the space for the pathogen that you've knocked out and then what is the net overall, is the patient better off.

So there's a lot of things and a lot of similar themes that are coming up as we think about these issues. And John, how do we want to do this? Do people want to make any comments or ask any questions at this point?

MR. REX: You can see doctor, I'm sort of taking notes a little bit.

MR. COX: Okay.

MR. REX: I'm taking notes a little bit, so I think this is the opportunity for everybody to align on some of these ideas or suggest other workshops, propose work for Ann Eakin to do, you know.

MR. COX: And I'm going to throw out -- I'll throw out one more thing and then I'll pause. That'll give folks a chance to think for a minute and see if there's other points that they wanted to sort of mention or bring up. But that is that, you can tell from this workshop what we tried to do was come up with

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examples that were as close to reality as we could. And you see how imperfect. Despite coming up with perfect hypothetical examples, if you will, I know a tremendous amount of work going into these things. Reality is always different. There's always something that happens.

So and what I'm thinking about, John's talking about future workshops, and I think if I reflect back, we have been able to, at various points in times, and I'm sort of just throwing this out there or something to think about, obviously not something we're going to do today because we're about to wrap up here. But as we think about future workshops, one of the things that can be very helpful is if companies are willing to essentially come and talk about their development programs. So we move from the hypothetical to actually what's happening. And I realize that that's a very delicate issue, that's why I'm mentioning it today because we obviously won't do it today. But it's something to think about because that can be very instructive. Obviously a successful program is usually much easier to talk about than one that hit bumps along

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the road. But as I think about where we learn, we learn oftentimes more from the programs that didn't work out because there's something important there that we didn't expect, we didn't anticipate and you learn, I mean, it really is true. You think about it. People say we learn more from our mistakes and I think that is true. They're not mistakes. It's just the things that we didn't understand that we now appreciate that can inform development.

So I'll throw that out there as we're thinking about future workshops. If people are mindful of that because we do appreciate the presentations that were made today and some folks did almost kind of start to talk a little bit about their development program. So maybe that next step would get us to a greater degree of reality, which would help to move the discussions along a little bit further at a future meeting.

So I'll stop there and let's open it up and see if there are other comments or thoughts that people have that they wanted to bring to the group here. So please.

MR. BURD: You mentioned, I'm in regulatory

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affairs, probably one of the few people here that do that. You mentioned coming in early, prior, and I'm looking at the scenario prior to your pre-IND meeting. Could you speak just a little bit about the logistics of how that would occur?

MR. COX: Yeah. So I mean we have under the category of pre-IND meeting handled a range of different topics if you will. And that is an opportunity that we try and make available. It really becomes an issue of just trying to manage all the requests if you will. Sumati's division works very hard, does great work and we're flattered by the level of interest, if you will, that folks have and coming in and talking with folks. But, yes, we can do that.

And like all meetings, the quality of the meeting is dependent upon really the quality of the materials and the submissions that come in. The developer knows the developer's molecule very, very well. They know where they're headed. So to the extent that a lot of thought and preparation goes into those meetings, that makes those meetings more valuable for everybody. So that's just one more piece. So,

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yes, we can do that and we do think that the quality of that meeting is dependent upon the quality and the thought that has gone into it and then it gives us more to think about, it gives us more to dig into, to provide advice on. So, yes, it is available. And when you come in, put together a good package with good questions and well thought out and that'll put everybody in the best position to be able to move things forward.

MR. BURD: Right. As a follow up, oftentimes sponsors want to come in almost incrementally in their early development because they have to make some very big sort of long-term decisions at those very early stages. And what that I think means in sponsor's thinking is, can we have multiple interactions prior to what they would consider a final pre-IND?

MS. NAMBIAR: All right. So I might be getting into trouble here, less likely would Edward.

MR. COX: I felt guilty, I felt guilty telling all the things that Sumati was going to do. I would let her take the microphone and she can inject a dose of reality into my discussion.

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MS. NAMBIAR: Right, yes. Many of our team members are here. So I think I'm going to get in trouble with the larger team, less likely with Ed because he doesn't have to deal with these meetings and I have to. So, yes, I think there are so many unanswered questions in this field and so many uncertainties, and I think we're all learning in this process together.

So it really doesn't help the field or help us as a community if we are very rigid and say, we've met with you once, now we'll see you again in three years as I don't think we're doing anybody a favor, not you, not us and not the patient. So we try our best to accommodate requests. There are some practical limitations, our workload and number of people we have working on it.

But the truth is, we don't check off a box and say we've met with you once, we've had pre-IND meeting, now you're on your own. And then we also meet with people at different stages in development. I think it depends on the needs of the company. It depends on the expertise they have. So sometimes we get programs

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which are well thought out and you're sort of just getting our okay. Some others, I think people who might be relatively new in the field might want to ask questions which are at a more basic level. So we try our best, we try to accommodate all those requests. Sometimes if you're really early in development and you just want to get our advice on, are you headed in the right direction, we can do that where we can provide responses in writing. It's still a pre-IND, but it's a written response only meeting. That works very often because you're just getting very clear-cut guidance from us.

Sometimes especially with these kinds of products, there is a lot of value in having a discussion because there's only so much you can communicate in writing and those might -- when you are at that point, I think it might be better to come in and actually meet with us. So I think we try to adapt based on the needs of the group that's requesting. But I think folks just also have to be mindful, there's only so many of us trying to answer questions to all of you. So I think giving us a little bit of leeway in

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terms of timelines, I think helps. But I think the division and the team and in particular people who work in the division are really working extremely hard to make this happen. So in that spirit, I think we're more willing to work with you and have as many meetings as needed.

MR. COX: Other questions? Yes.

MR. KALEKO: One of the issues that we discussed yesterday, maybe I missed it, but I didn't see it listed earlier was therapies that could help the general population as much, perhaps even more than the individual. Obviously those are limited by the fact that you are relying on mechanism. It's -- they're very hard to prove that you're helping the general population. And the other limitation of course is commercialization. Who's going to pay for something that helps the population as opposed to the individual? So in that regard it might not be the auspices of this meeting, but is there some way to address whether or not, for example, the government, which is responsible for protecting the common good could help support products that support the common good or is that

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outlandish?

MR. COX: So that is way beyond the scope of this meeting.

MR. KALEKO: Apologies man. Sorry.

MR. COX: But let's talk about it for a minute. So the issue of can you show a benefit to a population and you said you'd have to rely on mechanism. And I think that the real question is, if that benefit is actually happening frequently enough, I mean, maybe you could actually show that clinical benefit to folks. And if you can show that clinical benefit, then you've got something and you can weigh that benefit and try and figure out, does it, is it something that's warranted based upon the risk because in that sort of setting where it sounds like you're going to be dosing or treating a lot of patients or vaccinating a lot of patients or whatever the case may be, then you have to sort of look at the risks associated to that versus the benefits. So it becomes a risk benefit analysis. With regards to who will pay for this? Will somebody accept this in the marketplace? Will it be successful from a commercial

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standpoint? We understand those are considerations that somebody looking at such a development program would need to think very carefully about. But that's sort of beyond the scope of what I can answer.

MR. REX: Well, you might add that BARDA does some of that for us right now. That's -- BARDA often describes themselves as the U.S. government's pharmaceutical company and they get busy developing tools that they think that we might need in extreme circumstances.

MR. COX: And I'll look to Ann, to Sammy (ph) because I'm thinking BARDA, NIH and the granting authority as such, anything else to add to that, Ann?

MS. EAKIN: Yeah. I mean, not really. I think it is a pretty broad scope of how exactly that would play out. I mean I definitely hear you and I do see the sort of common good type needs and possibly having government sponsorship of that work. But without the specific example, I don't have much to add.

MR. TSE: Hi. There is a BARDA rep here. I've been quiet for the majority of the meeting, so I am happy to speak to this just in a general sense. I

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mean we always have to keep in mind, when we think of ourselves as investors in the antibiotic field, our mission space is squarely placed in the value of biomedical security from the standpoint of, can we use these streams to directly address biothreat agents? And secondarily, can we offset the secondary and opportunistic infections that would likely result as a result of treating patients within the context of a public health emergency?

So as long as we can frame things within that context, we can make the argument that we can make investments from a purchase standpoint of investing in the R&D component of that. Whether or not we can come up with solutions related to poll incentives to solve the marketplace issue, that is beyond the scope of what I am able to speak to you today.

MR. OUTTERSON: Yeah. I will say something briefly, madam, if I could add. So its way beyond the scope of this meeting as Ed said, but there are other meetings that if you're pining for additional meetings in D.C. area. The Duke Margolis -- with the support of the Wellcome Trust, Duke Margolis is kicking off yet

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another process on trying to improve the reimbursement following on Commissioner Gottlieb's suggestions and public comment about other models to support antibiotic reimbursement at a more healthy level. If you want access to that process, probably Greg Frank of Bio or Amanda Jezek of IDSA would be good contact points for any company person here. As well there're other efforts, but I think those two will probably be good people to connect to and can tell you. And Helen, do you have anything else to say about that, you're IDSA as well?

MS. BOUCHER: Yeah, no, I mean, I agree. I guess, the other comment will be that this is some of the agenda that PACCARB looks at in a kind of higher level across the government way. And we're meeting again in September, so there're other public meetings where some of the stuff will be discussed. And that allows some bridging with CMS, payers and others CDC importantly who we haven't really mentioned, but in terms of things like vaccine, certainly CDC is who dictates who gets what vaccine for example.

So there are some other potential synergies

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that could be addressed and I think the - I'm glad that Kevin brought up the incentive piece because I think really that's the biggest issue for all of these medicines, whether they're regular drugs or nontraditional therapies. So getting to the crux of that is going to be really important.

MR. COX: And I'll throw out one other comment that I'm just recollecting from a prior meeting. And that is that if you think about the granting world, it's a competitive world. There're a lot of folks out there with ideas and so you -- to the extent that the idea has scientific merit and that can be expressed, that obviously puts you in the best position for seeking the grant. So it is a competitive world for granting and that's a good thing. I mean we want to think about the proposals that are most likely to pan out. So I just throw that out there as an additional comment and I'm sure our colleague at NIH are working very hard and likewise at BARDA as they're looking at various different proposals and considering the merit of those proposals as they try and decide where to use their moneys. Are there questions, comments, Todd?

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MR. BLACK: If I can, I think this is a bit of follow-on on that because I think, you know, John says net effect is really the critical parameter of the clinical study, but we had a lot of conversation about what is a significant net effect? What is the significance of decolonization? If we use (inaudible) example, so we went into this with real -- the expectation that C diff recurrence is deadly diarrhea and that there should be a mortality effect associated with preventing recurrence. We had a significant impact on recurrence, but actually in that study there was not a mortality effect or been balancing that.

So if we hadn't had that assumption going in that recurrence was the key endpoint in this case because we're basing it on our medical assumptions of the importance of that and mortality had been our endpoint, then we would've never met superiority endpoint. And so when I started looking at some of these things that we're considering, do we really know what the net clinical implication is and that maybe where if there is some government or consortia approach to really help us understand some of these net effects

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really are and like the transmission components etcetera.

MR. COX: And you're reminding me, there has been some work that has been done through the foundations and National Institutes of Health to look at various different endpoints. Skin infections, community acquired pneumonia, hospital acquired pneumonia and also some work on VAP too. So, and those have been done through, I guess, what I would put in the broader category, I might not have the definition precisely correct of a public private partnership. And part of that effort was fueled by the ability to use previously conducted trials to understand both the natural history of the disease and also the time to response for various different endpoints.

And so that type of work, to understand the natural history of disease, what changes over time and I'm saying natural history, but there's natural history from sort of the pre-antibiotic era and then there's also what happens when somebody is getting treated, what changes, when does it change, what's the clinical significance of those changes. So, yeah, that type of

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work can be very important. And I think that at least if you think about drug development, I think that is -- those public private partnerships have played an important role. The folks at Citi have also been working on trying to figure out ways to make HAP/VAP trials more doable, by looking at some of these issues of pre-consent.

That's the sort of work that no one individual pharmaceutical company might find to be in their interest to take on. But if -- its work that involves folks from the government, folks from academia, folks from the pharmaceutical industry, other interested stakeholders, patient reps et cetera. Those groups may be able to do the foundational work to try and establish the pathways that will be relevant to each of several different or to anyone who is interested in developing a drug in a particular therapeutic area.

So we are trying to do some of that work. Folks may recall the workshop that we had on drugs that acts only against a single pathogen. And so from that stemmed some grant proposals that we were able to fund to try and work with both folks at NIH and at BARDA to

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try and develop some animal models of infection to further understand how these agents were performing in serious infections caused by acinetobacter or caused by pseudomonas aeruginosa, that work is ongoing. Yeah, so that sort of work that's common to several development programs are things that we're interested in and things that we are trying to make progress on and working with colleagues at NIH and BARDA. So it's a good point and something we will continue to try and do. We recognize that what we can do is limited, we can't do everything. So we do try and hit the things that we think are most important to the development community in general. And that changes over time too. I'll stop there.

Are there questions thoughts? We'll do Filip and then we'll go to Paul. And then I apologize, I can't quite see your name tag, but then you're next, okay, so. So Filip, please.

MR. DUBOVSKY: Yeah, Ed you just mentioned, but it's also on my list. When I'm thinking about buckets for John's things that -- the pathogen specific bucket maybe one worth throwing on your list, maybe it's redundant, but it may add something. And I came

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into this workshop skeptical, but I thought the cases were extremely valuable and without them it really would've been a less useful meeting and I can say that I'd be completely happy to talk about the real life development of the products from a sponsor's perspective. And I would've been happy to have done it for first meeting as well. And, I guess, the last thing is when we think --

MR. COX: Thank you for that.

MR. DUBOVSKY: When we think about these alternate things, whether it be AMR or antibiotic usage, I wouldn't anticipate they would be labeled claims without a clinical benefit. But if your medicine can demonstrate a clinical benefit in a completely noble approach, if those could be stuck in label because I do think they have true public health value and value as infectious disease physician. If those things could be made apparent in the label, maybe that would start a new trend toward a sea change in the how this is perceived both globally and in the medicines environment. So, yes, I demonstrate clinical evidence, but then again the tangled line says, does

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not promote antimicrobial resistance. Useful.

MR. COX: All right. Thanks Filip. We appreciate your comments and we'll look forward to the next workshop. And is yours a follow up? No, okay, okay. So then let's -- we'll just go to Paul.

MR. AMBROSE: Hi, we often hear people say in our field that for small molecules or antibiotics that the -- we're blessed because of these wonderful animal models that are so predictive of what happens in clinical trials. But I think it's useful to remember how we got here, and we got here because Harry Eagle started in the 1930s and '40s and then Bill Craig picked it up and really perfected those models through the '80s and '90s. And then along the way people began looking at how well that they predict clinical trial results based on clinical trials meeting their primary endpoint. And so now we feel really confident. Now we are talking about developing a whole new massive models that we don't know if they work, they may work or some very variant on them may forecast clinical efficacy. So to build on what you said earlier, Dr. Cox, everything I have really learned in my career in

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pharmacometrics has been somebody getting hit by a bus or a train or worse. And I think it's the -- it's folks being willing to share not only their successes, but their failures and what models they're using. They think they failed because it was a model problem or maybe drug just cleared like the wind in the patient and that wasn't accounted for in those predictions.

So the successes and failures being talked in an open way and also maybe what models were used to make them feel so confident as to amount to Phase 2 or Phase 3 trial.

MR. COX: In some ways it's too bad that we call them failures because they are really not. They are just an understanding of what actually happened. And sometimes what actually happens is not the outcome that you want, it's not a commercially viable proposition at that point, but we learned and we learned something that helped us to understand what the molecule does. So it really is in some ways that it's too bad that we call these things failures because it's more just a learning that has helped to advance our understanding of what's going on. But, yeah, no, and

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it's not a criticism. I called them failures too, but I shouldn't, I should find a better word for it. John will help us with that.

MR. REX: Well, it's interesting to think about that. There is a literature in other areas about dealing with the problem, I'm going to use the word, the language from infection or risk management, the hospital of near misses. So in the hospital setting the -- or if you are an airplane pilot, what do you do when something almost went wrong and maybe you've made a mistake and it almost went wrong, but you're glad you got it. And so the kind of tools that people have come up with about non-judgmental sharing of errors and maybe there are some languages that we have as a scientific community have failed to explore. It is hard to do to get people to be comfortable with sharing that sort of thing, but it has been done in other fields.

MR. KIM: Just to continue the conversation on follow-up workshops, throw out an idea. So at POE (ph) we track these nontraditional candidates and if you look at from a technology platform perspective, about

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two-thirds are composed of vaccines and monoclonal antibodies and the other third are these clinical new platform technology. So I am wondering if a workshop that more focuses on these "more licensed or microbiome related products" and expanded not beyond just clinical, but I suspect there may be some questions around CMC development and manufacturing as well. Thank you.

DR. COX: Thanks. Thanks for your comment. We'll keep those ideas in mind. There is no question we'll be having future workshops. We just haven't settled on all the topics yet. We do try and be mindful of what we see going on out there and where the questions are coming up and which questions we are receiving sort of that seem to be important to the development community. So we appreciate your comments and see you soon.

MR.REX: And there's about to be a NIAID microbiome workshop, right, and it's soon. Talk to your microphone to tell them what the date is.

MS. TRUONG: Yeah, hi, I just wanted to add a little bit more to those pre-IND communications. One

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strategy we have taken is to divide those meetings from clinical, non-clinical and the CMC and it gives opportunity to continue those discussions as in drug development. And I want to say, although I was a little yesterday talking about the timelines in responses. I do want to acknowledge that we have received a lot of good responses, very collaborative with the group, not only during the pre-IND stages, but also during the IND and that continue communication path. So we really appreciate and this division is very responsive on the needs of our drug development programs.

I'd like to also echo the need for these additional workshops and my need is really in those clinical endpoint workshops to really look at endpoints beyond all cause mortality for both superiority and non-inferiority trials and really looking at the benefit to the patients, quality of life et cetera. So what other endpoints could we really consider? And I know this is indication specific, but is I think just having those key opinion leaders in a group like this together to really explore what are those potential

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endpoints that we can continue to explore in this field.

And finally I'd like to add that Aridis is also willing to share our lessons learned in these types of workshops. Thank you.

MR. COX: Great. Thank you very much. Mary Beth.

MS. DORR: Thank you. So two things. These guys over here just mentioned CMC, that's one of the things that I keep coming back to when you talk about multiple monoclonal antibodies. It's not insignificant, the amount of CMC work that has to be done for each individual monoclonal antibodies, it's not just cost of goods and I know that at Merck, our application would have been delayed if we had to file both monoclonal antibodies. So I think small companies that are just getting into this space may not realize how complicated the CMC issues are for a biologic. So you might want to find out about that early on in development before you take them too much further. And also I do think it's going to be an important aspect if you do have a workshop specific to biologics to have

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both of those aspects cover to some extent.

So the other thing, bringing up failures, Paul brought up failures. I in particular am passionate about C diff. And I think everyone who is familiar with C diff knows that we've had quite a few failures in this space and Merck in particular and other pharmaceutical companies have a transparency policy. And I think it would be in the best interest of all those who are still working in this field for there to be a workshop on why we've had failures with C diff so that future studies we can design them better and hopefully have better outcomes.

MR. COX: Yeah, thank you, Mary Beth. And we haven't really dealt with CMC issues, we haven't dealt with manufacturing issues during this workshop. But her advice is very good. We've seen applications that have come along where essentially everything is in good shape except for the manufacturing. And it can delay the application getting to market by a year, two years, sometimes even longer.

So, and the other thing we're seeing now too is that with some of the more streamlined development

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programs, we hear that sometimes the folks involved with the manufacturing didn't realize the timelines were going to be quite so tight. And so the amount of work that they need to do in this more compressed timeframe is something that they didn't really have a full understanding of and weren't quite able to plan for.

And again so the manufacturing can sometimes bring up unanticipated surprises that can have a profound impact on the application and it's obviously a critically important part of an application to be able to demonstrate that you can make the product and that it's clean and that it's reproducible and those sorts of things.

The other thing and I'll make just one last comment because this is another thing that we've seen with manufacturing that comes up, they can be somewhat frustrating to deal with and that is that we see a fair bit of manufacturing that's done by contract. That's perfectly fine; people can decide who they want to do their manufacturing. But that may impact upon the visibility of the firm that's actually has the

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particular, I'll say, antibacterial product and what maybe going on at the manufacturing facility where they're contracting. So it's very important to be mindful of keeping track of what's going on at that facility if you've a contract manufacturer so that again there aren't surprises at some point in time when your application comes in that impacts upon your application.

And I mentioned that because we've seen it a couple of times, it's not meant to be a comment on any one particular sector, it's more just general awareness. Obviously, you could have the same problem within your own facility, with a facility that you owned, but I just bring that up because sometimes if it's not your own facility, there is a little bit greater distance in time and space that it is worth trying to minimize to the extent possible so that there is an awareness of what's going on with your product and what's going on with the manufacturing facility that makes your product, even if it is not your own. So I'll stop there. And I see --

MR. DANKER: Two of us.

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MR. COX: Do Wayne and, yeah, okay.

MR. DANKER: So I think that's a good point because we're in our development program and I keep interacting with our CMC people because you have to coordinate timelines, but I also think what people tend to underestimate in the CMC is the cost. And if you don't factor that into your development cost, especially for a small company, you're going to get caught with your pants down later on.

MR. COX: Thanks and next.

MR. BURD: Could you comment on whether you could provide consultative services for a facility development? Because many small companies, if they contract out also have the option of developing the real manufacturing facility. I know for my company, we're doing a hybrid, one product we're making exclusively in-house and then the other one we're going to outsource. But we have to develop a GMP facility from scratch and is there a consultative service available? It could be through the field office or some other way to provide guidance early in the development of these GMP targeted facilities.

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MR. COX: Okay. I'll start. I like to tell stories. So our office of pharmaceutical quality and compliance folks are available to evaluate facilities. And so you might ask, I am not a CMC expert, but why do I know anything about this and I don't claim to be expert by any means. Well, if you think about it, penicillins and beta-lactams and the allergenic potential and manufacturing of those products is done at a dedicated line and there are some issues about air handling and all other sorts of things that need to be thought about within the facility.

And so, yes, from those experiences I do know that that our pharmaceutical quality folks, our compliant folks, can provide regulatory advice. We tend to look at it as, our work as regulators, on somebody's plans or proposal on their manufacturing facility. So that is something that can be done. So if there's blueprints in place for a future manufacturing facility for a certain compound, that is something that there is an opportunity from what I understand to reach out to our folks and say, is our air handling system going to do adhere correctly and

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that sort of thing, to make sure that the facility that's going to be built will be one that will sort of meet the types of requirements that would be expected.

And so something to think about and certainly just like we talked about with pre-IND consultation, to the extent that you've engaged your experts and tried to learn as much as you can about this and come in with a good proposal, you will be in much better shape to receive feedback from the folks here within FDA. Have we -- other questions or we are good? I think we're almost at time here too. So John, anything else or?

MR. REX: Thank you.

MR. COX: Okay. So let me extend thanks. And Sumati and I will do this jointly, yeah?

MS. NAMBIAR: Good.

MR. COX: Okay. Well, I'm going to give you a chance to say thanks. But we really do appreciate everybody coming in and talking about, in this case hypothetical programs and talking about their experiences as they relate to the various different examples that we put up. This takes a lot of your time, it takes a lot of your dedication to; A, come to

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this workshop and even probably much more importantly to work in this field. We greatly appreciate the interest of folks who are continuing to work in the area of bacterial diseases and trying to tackle the problem of AMR. I learned a lot from the workshop, I think that this will help us as we continue to think forward. We do expect to have future workshops, topics to be determined, but we are trying to be responsive to the needs that we see out there and that we recognize are going on in the field. And as many of you know too, we're also engaged in meetings to try and provide our regulatory advice on development programs through the meeting that we do with companies.

So we look forward to future interactions and the opportunity to continue to try and push the envelope forward with regards to our knowledge in these areas, in trial designs that will be informative to help us understand how these products work. So greatly appreciative and we look forward to a chance to meet more in the future and then I want to pass it to Sumati here.

MS. NAMBIAR: Thanks. Thanks Ed. I'm not

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sure if I have much more to add. I certainly want to thank everybody, the presenters, participants, panel members, members of the audience. Many months ago, when we started planning this workshop, I think we were all a little nervous. There was a lot of uncertainty around what are we going to talk about, what does this mean, what does nontraditional therapies mean. I'm not sure if we have the answer to the question yet, but I think there's a little more clarity now than we had when we started a few months ago. So many thanks for all of you for participating and helping us move the feat forward. I think there are many more discussions that need to be had. We've got some good thoughts on what future workshops might look like and on a step wise manner we hope we can address each of your areas of interest.

I certainly want to thank Sunita sitting in the back there, yeah, who has really taken the back seat literally, but has been doing a lot of the work in coordinating this workshop and our project managers who help at the back. They're monitoring the web and seeing other questions, so Jackie, Debra and Chris.

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And then many thanks to Kevin and Dr. Rex for helping us with the planning of this workshop. I know we've had some very difficult discussions, particularly when you came up with the last case that we discussed yesterday.

So those meetings were meant to be half an hour, then they extended to an hour, but then the day came to an end and we said we had to quit. So I do remember those discussions. So thank you all and we look forward to more discussions. Safe travels and thank you again.

MR. COX: Yeah, safe travels everybody. Take care.

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September 4, 2018
DATE JIMMY JACOB

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