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FOOD AND DRUG ADMINISTRATION

VIRTUAL PUBLIC WORKSHOP OF THE DRUG DEVELOPMENT  
CONSIDERATIONS FOR EMPIRIC ANTIBACTERIAL THERAPY IN  
FEBRILE NEUTROPENIC PATIENTS

First Session Moderated by Dr. Robert Pease and  
Dr. Andrea Zimmer

Second Session Moderated by Dr. Radu Botgros and  
Dr. Daniel Rubin

Panel Discussion Moderated by Dr. Randy Taplitz and  
Dr. Dmitri Iarikov

Tuesday, April 23, 2024

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Remote Proceeding

Washington, D.C. 20005

Reported by: Chanyri Figueroa Monsanto

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<p>1 APPEARANCES</p> <p>2 List of Attendees:</p> <p>3 Dr. Peter Kim, FDA</p> <p>4 Dr. Randy Taplitz, City of Hope National Medical</p> <p>5 Center</p> <p>6 Dr. Andrea Zimmer, University of Nebraska Medical</p> <p>7 College</p> <p>8 Dr. Kimberly Hanson, University of Utah</p> <p>9 Dr. Anita Sheoran, BARDA</p> <p>10 Dr. Douglas Girgenti, Melinta Therapeutics</p> <p>11 Dr. Robert Pease, FDA</p> <p>12 Dr. Rama Kapoor, FDA</p> <p>13 Dr. Daniel Rubin, FDA</p> <p>14 Dr. Radu Botgros, European Medicines Agency (EMA)</p> <p>15 Dr. Katsuhiko Ichimaru, Pharmaceuticals and Medical</p> <p>16 Devices Agency (PMDA)</p> <p>17 Dr. Dmitri Iarikov, Panel Moderator</p> <p>18 Kimberly Browne, Captioner</p> <p>19 Dr. Catherine Liu</p> <p>20 Dr. John Farley, FDA</p> <p>21 Dr. Gary Lyman, Fred Hutchinson</p> <p>22 Dr. Kieren Marr, Elion Therapeutics</p>	<p>1 CONTENTS</p> <p>2 PAGE</p> <p>3 Dr. Peter Kim 6, 175</p> <p>4 Dr. Robert Pease 11, 50, 57, 75</p> <p>5 Dr. Andrea Zimmer 12, 27, 121, 132, 146</p> <p>6 Dr. Randy Taplitz 13, 120, 130, 132, 137, 141, 145</p> <p>7 149, 177, 186, 187</p> <p>8 Dr. Kimberly Hanson 37, 134, 137, 146, 150</p> <p>9 Dr. Anita Sheoran 50</p> <p>10 Dr. Douglas Girgenti 57, 152, 159, 181, 183</p> <p>11 Dr. Radu Botgros 73, 84, 110, 130, 163</p> <p>12 Dr. Daniel Rubin 74, 98</p> <p>13 Dr. Rama Kapoor 85</p> <p>14 Dr. Katsuhiko Ichimaru 116</p> <p>15 Dr. Juan Gea-Banacloche 123, 144, 166</p> <p>16 Dr. Catherine Liu 126, 148</p> <p>17 Dr. Kieren Marr 127, 141, 147, 161, 168, 172, 176</p> <p>18 185, 189</p> <p>19 Dr. Gary Lyman 139, 186</p> <p>20 Dr. Dmitri Iarikov 151, 158, 170, 173, 183, 189</p> <p>21 Dr. John Farley 168, 171</p> <p>22 Dr. Alison Freifeld 178</p>
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<p style="text-align: right;">Page 6</p> <p>1 PROCEEDINGS</p> <p>2 DR. KIM: Good morning, everyone.</p> <p>3 THE REPORTER: Who's speaking?</p> <p>4 DR. KIM: Next slide.</p> <p>5 THE REPORTER: One second.</p> <p>6 DR. KIM: This is Peter Kim.</p> <p>7 Next slide.</p> <p>8 THE REPORTER: One instruction for</p> <p>9 everyone before you speak. Just identify yourself for</p> <p>10 the record, so I know who's speaking.</p> <p>11 DR. KIM: Absolutely.</p> <p>12 Next slide, please. Next slide.</p> <p>13 Good morning. My name is Peter Kim.</p> <p>14 I'm the Director of the Division of Anti-Infectives in</p> <p>15 the Office of Infectious Diseases, OND, CDER, FDA.</p> <p>16 And I'd like to welcome you to our virtual public</p> <p>17 workshop on drug development considerations for</p> <p>18 empiric antibacterial therapy in febrile neutropenic</p> <p>19 patients.</p> <p>20 Next slide, please.</p> <p>21 Our workshop objectives. During</p> <p>22 today's workshop, we will bring together key</p>	<p style="text-align: right;">Page 8</p> <p>1 Of note, the patients in these</p> <p>2 literature accounts were leukemia and cancer patients</p> <p>3 with Pseudomonas aeruginosa bacteremia.</p> <p>4 Next slide, please.</p> <p>5 Cefepime and IV Ciprofloxacin in</p> <p>6 combination with Piperacillin sodium are the only</p> <p>7 FDA-approved antibacterial drugs for empiric therapy</p> <p>8 for febrile neutropenic patients. No new</p> <p>9 antibacterials have been approved for this indication</p> <p>10 in over a quarter of a century.</p> <p>11 No oral antibacterial drugs have been</p> <p>12 approved for this indication. There are scientific</p> <p>13 and practical challenges that affect feasibility of</p> <p>14 clinical trials in febrile neutropenia.</p> <p>15 Next slide, please.</p> <p>16 Some of the challenges. We note that</p> <p>17 there is heterogeneity of the patient population, such</p> <p>18 as in the characterization of febrile neutropenia</p> <p>19 episodes which may be microbiologically documented,</p> <p>20 clinically documented, or due to an unexplained</p> <p>21 etiology.</p> <p>22 We also have questions such as how best</p>
<p style="text-align: right;">Page 7</p> <p>1 stakeholders from academia, industry, a federal</p> <p>2 partner, and international regulators to have an open</p> <p>3 scientific discussion regarding the current state of</p> <p>4 development and need for antibacterial drugs for</p> <p>5 empiric therapy in febrile neutropenic patients.</p> <p>6 We will also discuss design and</p> <p>7 operational challenges of clinical trials in febrile</p> <p>8 neutropenia. We note that workshops are an</p> <p>9 opportunity for stakeholders to come together to</p> <p>10 discuss ideas regarding a scientific challenge.</p> <p>11 Workshops are not advisory to the agency, and the</p> <p>12 agency will not be providing specific drug development</p> <p>13 advice.</p> <p>14 Next slide.</p> <p>15 Some background. Generally, febrile</p> <p>16 neutropenia is considered a medical emergency</p> <p>17 requiring early recognition and initiation of empiric</p> <p>18 systemic antibacterial therapy to avoid potential</p> <p>19 progression to sepsis or death. There are literature</p> <p>20 accounts of high mortality among febrile neutropenia</p> <p>21 patients prior to the use of empiric</p> <p>22 Carbenicillin-based treatment.</p>	<p style="text-align: right;">Page 9</p> <p>1 to define the primary analysis population. Are there</p> <p>2 ways to enrich for patients most likely to have</p> <p>3 bacterial infections?</p> <p>4 There are also trial design</p> <p>5 considerations. Should the trials be designed to</p> <p>6 assess for superiority of one drug versus -- care or</p> <p>7 non-inferiority? If non-inferiority, there would be a</p> <p>8 need for adequate justification of a NI margin.</p> <p>9 Next slide, please.</p> <p>10 There are also considerations related</p> <p>11 to the primary endpoint in these trials. Should the</p> <p>12 endpoint be mortality or a composite of clinically</p> <p>13 meaningful assessments? And there are also</p> <p>14 feasibility considerations related to sample size.</p> <p>15 Next slide.</p> <p>16 Now for the program overview. During</p> <p>17 session one, we will begin with a historical</p> <p>18 perspective on empiric therapy for febrile</p> <p>19 neutropenia. And that presentation will be followed</p> <p>20 by discussions related to current treatment options,</p> <p>21 diagnostic testing, antibacterial management for</p> <p>22 febrile neutropenic patients following a nuclear</p>

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<p>1 detonation incident, and an industry perspective.</p> <p>2 Next slide.</p> <p>3 During session two, we will hear</p> <p>4 presentations on pathways and programs to expedite</p> <p>5 drug development, regulatory considerations on</p> <p>6 clinical trial design, statistical considerations.</p> <p>7 And we will also hear from our colleagues at the</p> <p>8 European Medicines Agency and Japan's Pharmaceutical</p> <p>9 and Medical Devices Agency regarding their</p> <p>10 perspectives.</p> <p>11 Session two will be followed by a</p> <p>12 moderated panel discussion.</p> <p>13 Next slide, please.</p> <p>14 During the panel session, we would like</p> <p>15 to discuss the greatest unmet needs for empiric</p> <p>16 treatment of febrile neutropenia, including comment on</p> <p>17 an ideal drug profile, strategies for enrichment of</p> <p>18 the study population, trial design consideration.</p> <p>19 And if there's time, we'd like to</p> <p>20 discuss the potential need, utility, and feasibility</p> <p>21 of obtaining efficacy and safety data for new drugs in</p> <p>22 the treatment of neutropenic patients with defined</p>	<p>1 but we'll have a discussion session with our panel</p> <p>2 this afternoon. Please feel free to type your</p> <p>3 questions into the Q&amp;A box in Zoom. We'll try to</p> <p>4 address these in the Q&amp;A box or during a related panel</p> <p>5 question discussion as time permits.</p> <p>6 I'll turn it over to Dr. Zimmer, who</p> <p>7 will introduce herself and our first speaker.</p> <p>8 DR. ZIMMER: Again, I'm Dr. Andrea</p> <p>9 Zimmer from the University of Nebraska Medical Center.</p> <p>10 I'm an associate professor and an infectious diseases</p> <p>11 physician, and I direct the oncology infectious</p> <p>12 diseases service line at the Fred and Pamela Buffett</p> <p>13 Cancer Center.</p> <p>14 It's my pleasure to introduce our first</p> <p>15 speaker today, Dr. Randy Taplitz, who will be</p> <p>16 discussing historical perspectives on prophylaxis and</p> <p>17 empiric therapy of febrile neutropenia. Dr. Taplitz</p> <p>18 is an infectious diseases physician and chairperson of</p> <p>19 the Department of Medicine at City of Hope National</p> <p>20 Medical Center.</p> <p>21 Her areas of interest and expertise are</p> <p>22 in the prevention, diagnosis, and treatment of</p>
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<p>1 systemic bacterial infections.</p> <p>2 Next slide.</p> <p>3 We look forward to a robust discussion.</p> <p>4 Thank you. We'll now begin with session one.</p> <p>5 I'd like to ask Dr. Zimmer and</p> <p>6 Dr. Pease to take it away.</p> <p>7 DR. PEASE: Great. Well, thank you,</p> <p>8 Dr. Kim.</p> <p>9 And good morning, everyone. My name is</p> <p>10 Robert Pease, and I'm a medical officer in the</p> <p>11 Division of Anti-Infectives at the FDA, and I have the</p> <p>12 pleasure of co-moderating our first session with</p> <p>13 Dr. Andrea Zimmer from the University of Nebraska.</p> <p>14 Our first session is on the background</p> <p>15 of clinical considerations, diagnostic testing, and</p> <p>16 challenges in the development of drugs for the</p> <p>17 treatment of febrile neutropenia. This slide depicts</p> <p>18 our session one speakers of today's workshop that will</p> <p>19 help set the stage for panel discussions at the end of</p> <p>20 today as well as our future considerations.</p> <p>21 Some housekeeping, we are not going to</p> <p>22 be able to address questions after each presentation,</p>	<p>1 infections in immunocompromised cancer patients.</p> <p>2 Thank you, Dr. Taplitz.</p> <p>3 Next slide, please.</p> <p>4 DR. TAPLITZ: Great. Thank you.</p> <p>5 And good morning, everyone. Thank you</p> <p>6 for joining us today.</p> <p>7 So next slide, please.</p> <p>8 In the next ten minutes, I'm going to</p> <p>9 really describe a historical framework of the</p> <p>10 relationship of leukemia with febrile neutropenia and</p> <p>11 infection. Here's a timeline. And basically,</p> <p>12 infection was recognized as a complication of leukemia</p> <p>13 in case reports in really the, you know, kind of</p> <p>14 mid-1800s.</p> <p>15 But really the age of discovery really</p> <p>16 starts in the kind of the early mid-1940s to 1971 when</p> <p>17 a more clear relationship between lower white count</p> <p>18 and increased infection in the setting of leukemia was</p> <p>19 understood.</p> <p>20 And in the '60s and '70s, there were</p> <p>21 more sort of discrete descriptions of relationships</p> <p>22 between leukopenia in the setting of cytotoxic</p>

<p style="text-align: right;">Page 14</p> <p>1 chemotherapy and their infection risks. And it was  2 really the beginning of the description of studies  3 showing empiric antibiotics in febrile neutropenia  4 actually reduced mortality.</p> <p>5 In the 1980s, that period of time was  6 characterized by a panoply of studies with the use of  7 antibiotics in febrile neutropenia, and I will talk  8 about that in some detail.</p> <p>9 In the age of antibiotic glory, we had  10 a number of different antibiotics approved, not  11 necessarily for febrile neutropenia, but just approved  12 for use, as well as G-CSF, granulocyte colony  13 stimulating factor in 1991.</p> <p>14 And really that was a period of time  15 where there was a refinement of the understanding of  16 risk factors that led to the development of febrile  17 neutropenia.</p> <p>18 Moving on into the era of the 2000s,  19 it's really been characterized by the rise of  20 resistant bacteria in febrile neutropenia patients.  21 And then the development of new antibiotics for  22 resistant gram-negative rods, not, again, for febrile</p>	<p style="text-align: right;">Page 16</p> <p>1 between the number of circulating leukocytes and  2 infection in patients with acute leukemia. And you  3 can look at the graph and see that infection is the  4 major cause of death in the setting of acute leukemia.</p> <p>5 The second slide which I like because I  6 could never get a clear picture of it, but describes  7 the, you know, this as a very clear quantitative  8 relationship where when you get to a leukocyte count  9 of less than a thousand, you increase your risk of  10 infection.</p> <p>11 And then the final was a seminal paper  12 that was mentioned in the first slide set that was a  13 study of Carbenicillin plus Gentamicin by Schimpiff  14 et al., and then a series of other studies that were  15 somewhat similar that shows that in the setting of  16 febrile neutropenia, there are response rates in the  17 60 to 67 percent range and improved outcome in  18 patients with febrile neutropenia.</p> <p>19 And really, following these kinds of  20 studies in the early 70s, empiric antibiotics in the  21 setting of febrile neutropenic became really a  22 generally accepted practice.</p>
<p style="text-align: right;">Page 15</p> <p>1 neutropenia necessarily but just in general.</p> <p>2 So next slide.</p> <p>3 I'm a clinician at heart, and so I like  4 to start with a case that's illustrative. This is a  5 56-year-old man who presented with progressive  6 fatigue. He was found to have a high white count with  7 a lot of blasts, and bone marrow biopsy showed AML.</p> <p>8 He was started on pretty standard  9 seven plus three induction with Cytarabine and  10 Daunorubicin and given fairly standard prophylaxis,  11 Levofloxacin, Posaconazole, and Acyclovir. He  12 developed febrile neutropenia and was treated with  13 empiric Cefepime.</p> <p>14 So next slide.</p> <p>15 So here what we have is some slides  16 that sort of depict the timeline of the association of  17 leukopenia with febrile neutropenia and really how to  18 treat. And this was based on a lot of studies done in  19 the 60s and 70s, but a couple of really seminal  20 studies.</p> <p>21 On the left you can see 1966 was really  22 the first description of a quantitative relationship</p>	<p style="text-align: right;">Page 17</p> <p>1 Now, one thing to remember is that  2 during that period of time, empirical antibiotic  3 treatment could really not be with a single drug  4 because there wasn't a single drug that could provide  5 the coverage that was needed for gram-positives and  6 gram-negatives. So combination therapy was  7 general --</p> <p>8 Next slide.</p> <p>9 So in the 1980s, there was really kind  10 of a refinement of the use of antibiotics for febrile  11 neutropenia, and there were a lot of studies that  12 looked at in-vitro synergy, serum bactericidal  13 activity, concentration of antibiotics, kind of which  14 antibiotics to use, how to use them. And a number of  15 these studies were published in the 1980s.</p> <p>16 But what happened in the mid-1980s was  17 another seminal paper that showed that a single  18 antibiotic, Ceftazidime alone versus combination  19 therapy in cancer patients with febrile neutropenia,  20 was equally safe and effective with failure rates that  21 were quite low in the 5 percent and 4 percent range,  22 respectively.</p>

<p style="text-align: right;">Page 18</p> <p>1 And following that, a number of studies  2 that affirmed that monotherapy in the setting of  3 febrile neutropenia could be safe and effective,  4 though, of course, patients with prolonged neutropenia  5 or those with documented infection were likely to need  6 an alteration of therapy.  7 Next slide.  8 I'm going to take just a minute to talk  9 about risk assessment because this will come up in  10 subsequent discussions.  11 But this was a period in the 1990s  12 where really researchers paid a lot of attention to  13 risk stratification. And Talcott just developed a  14 risk prediction model that identified patients who  15 were either at high risk or at low risk of acute  16 medical complications based on a series of factors.  17 And that basically folks with lower  18 risk potentially could be treated at home. And a  19 multi-center randomized trial confirmed that in this  20 particular setting, outpatient treatment could be  21 safe. Subsequently, you'll hear more about this  22 later. The MASCC and the CISNE scores were also</p>	<p style="text-align: right;">Page 20</p> <p>1 endogenous flora.  2 And so during this period of time,  3 there were a number of studies looking at  4 non-absorbable antibiotics and whether that could  5 decrease the incidence of febrile neutropenia and  6 adverse outcome. And really these showed diverse  7 outcomes, but the treatments themselves were not that  8 well-tolerated.  9 And in the '60s and '70s, the Bactrim  10 was used and studied in prophylaxis, and there were a  11 number of studies showing that bacteremia could be  12 prevented, and there could be reduced days of people  13 with the use of Bactrim prophylaxis.  14 And then as I mentioned earlier, when  15 Ciprofloxacin was approved, over 100 studies looking  16 at Fluoroquinolone prophylaxis. The issue is many  17 mixed populations, often studies are not randomized,  18 but definitely showed a reduction in bacteremia and  19 infection-related outcomes, but the data was not as  20 clear for mortality benefit.  21 And I'm just going to say that since  22 that time, there have been many studies. And since</p>
<p style="text-align: right;">Page 19</p> <p>1 developed and validated.  2 And really at this period of time, risk  3 assessments for modification of empiric antibiotics  4 based on specific features, do they have abdominal  5 pain, do they need anaerobic coverage, etcetera. So  6 there was really kind of a finetuning of this concept  7 of febrile neutropenia treatment.  8 During this period of time, also newer  9 antibiotics, as I mentioned, were developed and  10 approved. Ciprofloxacin was developed and approved in  11 1987, oral, well absorbed, good gram-negative  12 coverage, and was studied in both treatment and  13 prophylaxis.  14 And then as I mentioned, G-CSF  15 approved, and then Zosyn and Piperacillin-tazobactam  16 and Cefepime in 1993 and 1996, respectively.  17 Next slide.  18 I just want to spend a moment talking  19 about prophylaxis because you really can't talk about  20 treatment without talking about prophylaxis, I think.  21 It was recognized early on in the '60s and '70s that a  22 majority of the infections were associated with gut</p>	<p style="text-align: right;">Page 21</p> <p>1 2000, a number of studies, three, one randomized  2 controlled, one prospective observational, and an open  3 label randomized, as well as a number of new  4 meta-analysis of Fluoroquinolone prophylaxis, that  5 showed that although generally well tolerated and  6 there was a reduction in infection-related outcomes,  7 no clear mortality benefit.  8 Next slide.  9 So really, you know, at this point for  10 prophylaxis, there remains a variation in guidelines  11 recommendations because of this variation of data as  12 well as the concept of the risk of antibiotic  13 prophylaxis. And I think by here introducing  14 antibiotic prophylaxis -- risk of really alluding to  15 the risks of antibiotics at -- large.  16 So there are toxicities with  17 antibiotics. We know, for instance, that prophylaxis  18 in its -- prolongation for drug interactions, but,  19 very importantly, the consideration of antibiotic drug  20 resistance with the use of prophylaxis.  21 And one thing that's become very well  22 discussed in meetings and in the literature these</p>

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<p>1 days, is the perturbation of the microbiome which has 2 been associated with a number of different issues, 3 including drug-resistant infection, Clostridium 4 Difficile, and really restricted microbiome diversity, 5 and increased mortality in patients with acute 6 leukemia, as well as an increased risk of 7 graft-versus-host disease. 8       Next slide. 9       I want to move back to the treatment of 10 febrile neutropenia. This is the NCCN guidance, and 11 you will see slides similar to this, and I just want 12 to just generally bring up what is done in the setting 13 of febrile neutropenia. 14       The general approach is you consider 15 the history. You do an exam. You try to localize the 16 site of infection. And you generally start an 17 antibiotic which is usually taken from an 18 institutional protocol based on published guidelines 19 such as this, and hopefully taking into account the 20 epidemiology of your area and your 21 antibiotic-resistant patterns. 22       Next slide.</p>	<p>1 strategy that a number of guidelines, including NCCN 2 and a number of other guidelines, have advocated the 3 consideration of clinical de-escalation in a patient 4 who is otherwise stable. 5       Next slide. 6       Finally, I want to complete the 7 scenario by talking about the patient, and we've all 8 seen these patients where the fever did not resolve, 9 and the patient remained febrile. Antibiotics were 10 escalated to Meropenem. No infectious agent was 11 found, but the patients continued on Meropenem because 12 maybe they had a little pneumonia. 13       Fever resolved, ultimately, but 14 retrogressed and then the patient grew Meropenem 15 multidrug-resistant klebsiella. Patient was placed on 16 Ceftazidime-tazobactam but with prolonged hypotension, 17 multiorgan failure, the patient was made DNR, and 18 passed away. And this is a scenario that we see all 19 too often. 20       Next slide. 21       And just as we are aware, you know, 22 bacteremia's changed. Initially, they were dominated</p>
<p>1       So, again, back to this case, I just 2 want to go to scenario one, which is patient is 3 febrile neutropenic on Cefepime, but the fever 4 resolves. No infectious agent identified. The 5 patient does great. So what do we do in that setting? 6       Next slide. 7       And I wanted to briefly mention 8 de-escalation, which is kind of a follow-up approach 9 to high-risk patients with febrile neutropenia. A 10 number of studies have now led to a growing 11 recognition that de-escalation of the antibiotic can 12 be safe and decrease the burden of antibiotic use and 13 its attendant risks. 14       Here, I am showing one, which I'm not 15 going to go through it in detail, but this is one 16 potential approach to de-escalation, where you -- in a 17 patient who is otherwise doing well, you can change 18 your antibiotic either to prophylaxis or to no 19 antibiotic, or if you've identified a pathogen, you 20 can modify your antibiotic based on susceptibility 21 patterns. 22       And this is, you know, this is a</p>	<p>1 by gram-negatives, and then in recent studies, we've 2 seen a more equal distribution of gram-negatives and 3 gram-positives. But one of the things that we're also 4 seeing is a concerning rise in drug-resistant 5 pathogens, including Carbapenem-resistant organisms. 6       And these are, you know, listed some of 7 the organisms where we are seeing of these 8 drug-resistant patterns in. And just two factors I 9 want you to keep in mind, that colonization with 10 multidrug-resistant organisms has been shown to lead 11 to worse outcomes, including higher non-relapse 12 mortality. 13       And infections, not just colonization, 14 but infections with MDROs, with limited treatment 15 options, are also associated with increased morbidity, 16 mortality, and health care costs, a decrease in 17 microbiota diversity, and then increase in GVHD as 18 well as a decrease in overall survival. 19       Next slide. 20       So where are we today? And I think 21 what I wanted to end with is, just to make clear, that 22 in addition to increased drug-resistant organisms,</p>

<p style="text-align: right;">Page 26</p> <p>1 we're also seeing just a change in the complexity of  2 our patients. We're now treating patients with  3 increased age, a lot of comorbidities, and with an  4 expansion of therapeutic cancer drugs with on-target  5 and off-tumor toxicities.</p> <p>6 For this reason, it is even more  7 important to consider not just neutropenia, but the  8 next state of immunosuppression and even immune  9 activation in the patient. And that is really what  10 are the vulnerabilities that make our patients at risk  11 for infection and make us really need, you know, more  12 anti-infective options in this setting.</p> <p>13 I'd also say we still think in terms of  14 prevention, you know, maybe some preemptive therapy  15 treatment, de-escalation, or escalation. I think we,  16 to some degree, need to change our thinking about this  17 and modernize.</p> <p>18 And my final slide, I believe -- next  19 slide. Yes.</p> <p>20 I'd just like to leave you with a final  21 consideration of the potential of the future with a  22 more refined risk assessment, or what I like, you</p>	<p style="text-align: right;">Page 28</p> <p>1 And as Dr. Taplitz mentioned, we are  2 still trying to develop an adequate scoring and  3 predictor system for individual patients and the  4 individual diseases and treatments, but, in general,  5 this is a way that we can broadly organize patients or  6 broadly think of patients in terms of their risk for  7 developing febrile neutropenia and bacterial  8 infections.</p> <p>9 We've known for a long time that the  10 duration of neutropenia does directly correlate with  11 risk for febrile neutropenia and subsequent bacterial  12 infections. And so breaking these patients into high,  13 intermediate, and low-risk categories, the  14 highest-risk patients are going to be those that have  15 an anticipated neutropenia of ten days or more.</p> <p>16 This includes patients who are  17 receiving cytotoxic chemotherapy for acute leukemias,  18 as well as those undergoing allogeneic stem cell  19 transplantation. Intermediate risk also includes  20 patients with other hematologic malignancies,  21 typically with an anticipated neutropenia period of  22 seven to ten days.</p>
<p style="text-align: right;">Page 27</p> <p>1 know, what we like to call precision infectious  2 diseases, which is developing a risk score for  3 patients which would take into account a lot of  4 factors.</p> <p>5 And it allowed us to individualize  6 treatment and are based on their history, their  7 genetics, what drugs they've been on, and all of these  8 other features, which would really allow us to give  9 the appropriate antimicrobial in the appropriate  10 setting to improve outcome and limit adverse events  11 from antibiotics.</p> <p>12 So I will stop there and thank you very  13 much for your attention.</p> <p>14 DR. ZIMMER: Next slide, please.</p> <p>15 Again, I'm Dr. Andrea Zimmer from the  16 University of Nebraska Medical Center, and I will be  17 talking about the current treatment options for  18 empiric therapy of febrile neutropenia.</p> <p>19 Next slide, please.</p> <p>20 This is a brief outline of the topics I  21 will cover.</p> <p>22 Next slide, please.</p>	<p style="text-align: right;">Page 29</p> <p>1 The depth of neutropenia also directly  2 influences the risk for infection. And the  3 intermediate risk category includes patients with  4 lymphomas, chronic lymphocytic leukemias, multiple  5 myeloma, or those receiving autologous hematopoietic  6 cell transplantation, or CAR T cell therapy.</p> <p>7 And then the lowest category includes  8 those with much shorter durations of neutropenia, less  9 than seven days, primarily solid tumor patients.</p> <p>10 Next slide, please.</p> <p>11 And these two scores have been around  12 for twenty -- ten to twenty years but are still  13 utilized today to help us determine or to predict who  14 is at high risk for morbidity and mortality with  15 episodes of febrile neutropenia.</p> <p>16 These are weighted scoring systems.  17 The mass score is a weighted score using  18 comorbidities, age, underlying disease factors, and a  19 higher score, above 21 or higher, predicts low risk  20 for morbidity and mortality following febrile  21 neutropenia.</p> <p>22 Likewise, the CISNE score uses</p>



<p style="text-align: right;">Page 30</p> <p>1 different variables but also stratifies patients into  2 low risk if they have a CISNE score of zero,  3 intermediate risk if they have a score of one to two,  4 or high risk if they have a score of three or more.  5       Next slide, please.  6       So when we are evaluating somebody  7 who's received chemotherapy within the past six weeks  8 and presents with a fever, this is treated as a  9 medical emergency. We want to presume they have a  10 bacterial infection or bacterial sepsis with  11 bacteremia and get them evaluated and started on  12 antibiotics very rapidly.  13       And so as soon as they're walking in  14 the door, we want to get blood cultures and obtain  15 other blood work, including a comprehensive metabolic  16 panel and a complete blood count to determine whether  17 they are neutropenic.  18       And then we want to do a fairly rapid  19 assessment, including history, physical exam, and  20 order any symptom-directed workup. Cultures from  21 specific sites based on underlying, you know,  22 symptoms. If they're having urinary symptoms, sending</p>	<p style="text-align: right;">Page 32</p> <p>1 using our clinical judgment and some of our scoring  2 tools to determine if patients fall into a high or  3 low-risk category.  4       High-risk patients, those with  5 anticipated neutropenia periods that are longer or  6 that are higher risk score by the MASCC or CISNE or  7 clinically unstable or have an organ disease at  8 presentation, are generally admitted to the hospital  9 and treated with empirical IV or intravenous  10 antibiotics.  11       Whereas patients that are determined to  12 be low-risk and are clinically stable after being  13 monitored for at least four hours can sometimes be  14 sent home with oral antibiotic therapy if they are not  15 already receiving oral antibiotics for prophylaxis  16 that are included in the treatment regimen.  17       Next slide, please.  18       These are the current empirical  19 therapies recommended for febrile neutropenia by the  20 most recent U.S. Guidelines. And so the only agent on  21 this list that is actually a labeled indication or  22 FDA-approved for treatment of febrile neutropenia is</p>
<p style="text-align: right;">Page 31</p> <p>1 urine cultures, as well as symptom-directed  2 radiography.  3       And then within an hour of  4 presentation, we want to be administering their first  5 dose of empiric antibiotic therapy. And this first  6 dose is usually an IV antibiotic, and the preference  7 is generally for a broad-spectrum antipseudomonal  8 beta-lactam antibiotic.  9       The choice of antibiotics will be  10 directed by their underlying clinical signs and  11 symptoms, history of prior infections, and prior  12 susceptibility profiles.  13       We know that once patients are  14 colonized or have had an infection with a specific  15 organism with a particular susceptibility profile,  16 they are at risk for recurrent infections due to gut  17 and skin colonization, allowing translocation of those  18 organisms, as well as we want to pay attention to the  19 local and institutional antibiograms.  20       Next slide, please.  21       And then after their first dose of  22 antibiotics, we're able to make our risk assessments</p>	<p style="text-align: right;">Page 33</p> <p>1 IV Cefepime.  2       The other agents, both in the IV and  3 oral categories, are recommended and utilized  4 frequently but do not currently carry an indicated  5 label for treatment of febrile neutropenia. And if  6 you notice that IV antibiotic regimens are frequently  7 dosed at least three to four times a day and so are  8 cumbersome to do as outpatients.  9       In terms of the oral antibiotic  10 therapy, it's typically recommended to be a  11 combination of an oral Fluoroquinolone that has  12 antipseudomonal coverage such as Ciprofloxacin or  13 Levofloxacin plus Amoxicillin/clavulanate. And the  14 intention is to cover for the Enterobacterales  15 antipseudomonal coverage as well as broad  16 gram-positive coverage.  17       Next slide, please.  18       There's been a lot of controversy and  19 look at whether we need to be adding empiric coverage  20 for resisting gram-positive organisms. And there's  21 been several studies, including this one, that do not  22 show benefit in addition of Vancomycin empirically for</p>

<p style="text-align: right;">Page 34</p> <p>1 febrile neutropenia unless patients have certain  2 characteristics including hemodynamic instability, a  3 suspected catheter, or skin and soft-tissue infection,  4 or concern for MRSA pneumonia.  5       Next slide, please.  6       These are some of the newer therapies  7 that have come to market or come to availability for  8 treatment of resisting gram-negatives. None of these  9 have been specifically studied for use in febrile  10 neutropenia, but they are starting to be used more  11 commonly clinically for these organisms.  12       Again, none of these agents actually  13 have a labeled indication for treatment of bacteremia.  14 Most have been studied in the context of treatment of  15 pneumonia, complicated UTIs, or intraabdominal  16 infections, but we do need to broaden our tool kit.  17       And so antibiotics that can be used for  18 treatment of Carbapenem-resistant Enterobacterales,  19 which is a rising problem across the U.S. and is  20 certainly worldwide, include Ceftazidime-avibactam,  21 Imipenem-cilastatin-relebactam, Meropenem-vaborbactam,  22 and Cefiderocol.</p>	<p style="text-align: right;">Page 36</p> <p>1 Cefepime is by far and away the most commonly utilized  2 agent for empirical treatment of febrile neutropenia  3 followed by Piperacillin-tazobactam and then  4 Meropenem. Additional gram-positive coverage with  5 either Vancomycin, Daptomycin, or Linezolid was  6 included empirically in about half of the cases of  7 patients with Aminoglycosides combination utilizing  8 about 6 percent.  9       Next slide, please.  10       A broad look at susceptibility  11 profiles. On these 343 organisms isolated across  12 these U.S. Cancer Centers demonstrated variables  13 susceptibility patterns. Meropenem was their most  14 reliable agent to cover all gram-negatives,  15 particularly the Enterobacterales, but had less  16 coverage or less reliable coverage against Pseudomonas  17 compared to Cefepime or Piperacillin-tazobactam.  18       Next slide, please.  19       And that concludes my materials. It is  20 my pleasure to introduce our next speaker.  21       Next slide, please.  22       So our next speaker is Dr. Kimberly</p>
<p style="text-align: right;">Page 35</p> <p>1       And then, likewise, treatment of  2 difficult-to-treat Pseudomonas multidrug-resistant  3 include the following organisms. And then there are  4 some combination therapies recommended including some  5 of the newer agents for the Carbapenem-resistant  6 Acinetobacters and Stenotrophomonas.  7       Next slide, please.  8       The epidemiology of febrile neutropenia  9 and the bacteremia associated with this syndrome  10 varies across the U.S. according to centers, and also  11 varies worldwide. And so focusing on U.S. data, there  12 is a contemporary study that looked at positive  13 organisms of bacteremia across U.S. Cancer Centers.  14       The breakdown of gram-positive and  15 gram-negative organisms are relatively equal, and so  16 about half and half caused by gram-negative as by  17 gram-positive. The most common gram-negative organism  18 is E. coli, and the most common gram-positive organism  19 is Viridans Group strep with a small number of  20 anaerobes.  21       Next slide, please.  22       Practice patterns across the U.S.,</p>	<p style="text-align: right;">Page 37</p> <p>1 Hanson who will be discussing diagnostic testing in  2 febrile neutropenia. Dr. Hanson is a Professor of  3 Medicine and Pathology at the University of Utah.  4 Administratively, Dr. Hanson serves as the Director of  5 the Immunocompromised Host Infectious Diseases  6 Service, and she is the Section Chief for Clinical  7 Microbiology within ARUP Laboratories.  8       Thank you, Dr. Hanson.  9       DR. HANSON: Thanks, Dr. Zimmer.  10       Good morning, everybody.  11       Next slide, please.  12       So what I'll be talking about today is  13 trying to provide just a very high-level broad  14 overview of current diagnostic approaches for  15 bacterial infections in the setting of febrile  16 neutropenia. And along the way, I also want to  17 highlight three recent diagnostic utility studies that  18 included neutropenic participants.  19       Next slide.  20       So febrile neutropenia is a very common  21 complication of current cytotoxic chemotherapeutic  22 regimens, much more common in the treatment of</p>

<p style="text-align: right;">Page 38</p> <p>1 hematologic malignancies than solid tumors. But I'll  2 note that despite, you know, very aggressive and  3 multiple attempts at diagnostic testing, we only  4 identify a proven infection in about half of patients  5 who present with febrile neutropenia.  6       Looking across studies, bacterial  7 infections tend to be more common than fungal or viral  8 infections, but risk for an individual type of  9 infection really varies by host. It depends on the  10 duration of neutropenia, what prophylaxis may have  11 been received, and it takes a lot of combination of  12 thinking, looking at an individual patient to assess  13 their risk for any given invasive infection.  14       Next slide.  15       So making the microbiologic diagnosis  16 though of bacterial infection in the setting of  17 febrile neutropenia is really important because it  18 allows us then to prescribe and target infection and  19 pick the right antibiotic for the right patient at the  20 right time. But as I mentioned, we often don't  21 identify infection.  22       There are multiple diagnostic</p>	<p style="text-align: right;">Page 40</p> <p>1 presents to the emergency department with new onset  2 febrile neutropenia. As was mentioned in previous  3 presentations for current guidelines, the goal really  4 is to identify neutropenic patients and collect blood  5 cultures, and then initiate empiric antibiotics really  6 within 60 minutes of that first documentation of fever  7 and no neutropenia.  8       Next slide. And one more, next slide.  9       So along the arrow here, I've listed  10 the diagnostic timeline and tried to group current  11 diagnostics in terms of when we might expect to  12 receive results from these tests. So first up would  13 be point-of-care viral tests that are nucleic acid  14 amplification tests or antigen tests for viruses. We  15 can get that answer in about 30 minutes.  16       Next would be a group of molecular  17 diagnostic tests that could be applied directly to  18 clinical samples like blood or respiratory specimens,  19 and we can get results from these assays on the order  20 of hours. One hour, two, three, four hours. But that  21 really assumes that the clinical laboratory can  22 perform testing in real-time or on-demand and that the</p>
<p style="text-align: right;">Page 39</p> <p>1 challenges. These include the fact that the clinical  2 signs and symptoms of infection in neutropenic  3 patients are often nonspecific. The infectious  4 differential diagnosis is quite broad. It includes  5 common organisms, rare organisms, multidrug-resistant  6 organisms.  7       And invasive testing also may not be  8 possible in the setting of critical illness or  9 coagulopathy that can come along with recent receive  10 of chemotherapy. We also know that standard  11 diagnostics that are culture-based are relatively  12 insensitive and slow.  13       And so one of the major advances, I  14 think, in the clinical microbiology laboratory in  15 recent years is the broad availability of molecular  16 diagnostic testing that has really improved our  17 ability to identify bacterial infections, to do it  18 more sensitively and more quickly relative to standard  19 approaches that are culture-based.  20       Next slide.  21       So this schematic kind of illustrates a  22 hypothetical patient at high risk, let's say, who</p>	<p style="text-align: right;">Page 41</p> <p>1 testing is performed near the patient.  2       Next up would be our more advanced  3 sequencing-based assays which tend to take days to  4 generate results. And then finally, that's followed  5 by culture-based testing and phenotypic susceptibility  6 testing, again, which is essential for targeted  7 therapy, but that takes days.  8       So I show this to point out that none  9 of our current diagnostic tests are really going to be  10 able to inform that first dose of empiric therapy for  11 neutropenic patients. However, the hope is after  12 several hours, we may be able to begin to modify our  13 regimens to be more targeted to an infection that an  14 individual patient may have.  15       Next slide.  16       So I've mentioned that culture-based  17 diagnostics have major limitations, but it's important  18 to remember that standard blood cultures obtaining two  19 sets from separate sites, really does remain the  20 cornerstone of the diagnostic approach to neutropenic  21 fever. And we know all comers included will identify  22 bacteremia in about 10 to 30 percent of cases of</p>

<p style="text-align: right;">Page 42</p> <p>1 new-onset febrile neutropenia.  2 Next slide.  3 One of the major advances though, I  4 think, in the clinical microbiology lab now is the use  5 of test methods that can be applied to positive blood  6 culture bottles. So taking an aliquot from a bottle  7 that is flagged positive for an organism and applying  8 a rapid diagnostic test to quickly identify what  9 organism is growing in that blood culture.  10 And many of these assays then are also  11 linked to downstream assessments of antibiotic  12 susceptibility or resistance which can be done either  13 genotypically by detecting resistance genes or through  14 newer methods that are able to generate rapid  15 phenotypic susceptibility results.  16 Next slide.  17 A number of studies have looked at the  18 clinical impact of rapid diagnostics from positive  19 blood culture bottles. I show one of the studies here  20 which I think was one of the more well-done studies  21 because it was multicenter and is actually randomized  22 to include several interventions.</p>	<p style="text-align: right;">Page 44</p> <p>1 recommendations for targeted antimicrobial therapy."  2 You can see the results of the study  3 here listed to the right. And not surprisingly, with  4 the use of the rapid multiplex PCR, organism ID  5 displayed by the red boxes was much quicker in the  6 intervention arm versus the control. So they  7 identified organisms about a day faster. And this  8 really did allow more rapid escalation of antibiotics.  9 So escalation in a setting where the  10 organism that was detected was predicted not to have  11 been covered by empiric selection of antibiotics  12 upfront in advance of the culture. The rapid testing  13 also enabled a more rapid de-escalation, but I'll  14 point out that was only possible with the support of  15 antibiotic stewardship.  16 And most de-escalation events included  17 dropping that extended gram-positive coverage, for  18 instance, stopping the Vancomycin, Linezolid, or  19 Daptomycin when a resistant gram-positive organism was  20 not identified in the blood culture.  21 Next slide.  22 I also want to highlight another</p>
<p style="text-align: right;">Page 43</p> <p>1 So the control group got the standard  2 workup of positive blood cultures. We take an aliquot  3 from that blood culture bottle, inoculate it onto  4 standard solid media, incubate it for an additional  5 period of time, and then identify that organism using  6 methods like MALDI-TOF and perform phenotypic  7 susceptibility testing.  8 But in this study, they also assessed  9 use of a rapid multiplex PCR panel applied to the  10 positive blood culture aliquot. That panel also  11 included a limited amount of resistance determinants,  12 and there were two intervention arms then.  13 One group randomized to receive the  14 rapid PCR and an enhanced report from the clinical  15 lab. So the lab issued a result that said, "This is  16 what was detected by the rapid PCR, and here's some  17 suggestions of what antibiotics would be recommended."  18 In the third arm, they used the rapid  19 PCR, their enhanced report, and they included  20 real-time antibiotic stewardship, where a steward  21 called the clinical provider to say, "Hey, the test is  22 positive, this is what was present, and here's some</p>	<p style="text-align: right;">Page 45</p> <p>1 molecular method that can be applied directly to  2 blood, so without the need for culture up front to  3 amplify organisms. And the method I'll discuss today,  4 although there are multiple that exist, is the use of  5 unbiased metagenomic next-generation sequencing to  6 detect and identify circulating microbial cell-free  7 DNA that is present in plasma or in serum of patients  8 who may have a bloodstream infection or potentially an  9 infection at a site distant to the bloodstream.  10 Next slide.  11 So this was a study looking at the use  12 of metagenomic next-generation sequencing for that  13 microbial cell-free DNA in a small group of  14 neutropenic patients. And what they did was compared  15 the MGS result to standard of care microbiology, and  16 then they also adjudicated with a panel of three  17 experts, these 55 subjects who had febrile neutropenia  18 to compare the results of the metagenomics to standard  19 of care and then whether or not they thought the  20 patient actually had an infection.  21 And high-level results I've shown here  22 across the bottom of the slide, I want to point out</p>

<p style="text-align: right;">Page 46</p> <p>1 first that the metagenomic sequencing was able to  2 detect the majority of bloodstream infections. So,  3 again, a small sample size, but nine of ten bacteremia  4 patients were identified with the metagenomic assay.  5 But what the metagenomic test really  6 did was in patients who were thought to have an  7 infection identified many more potential pathogens.  8 So standard of care microbiology identified potential  9 pathogens in 42 percent of patients, whereas the  10 metagenomic sequencing was able to identify organisms  11 in 85 percent.  12 And the vast majority of these  13 additional detections were polymicrobial infections  14 and also detection of normal, endogenous GI or oral  15 flora, many of which were anaerobes. And that made  16 sense in a neutropenic population which had recently  17 received chemotherapy may have significant mucositis  18 and translocation of these organisms into the  19 bloodstream.  20 Although this metagenomic test was a  21 send-out test to a reference lab, they were able to  22 get the metagenomic sequencing back before standard of</p>	<p style="text-align: right;">Page 48</p> <p>1 patients.  2 Next slide.  3 And then the last study I want to  4 mention is colonization microbiome study which is  5 really fascinating and hypothesis-generating, I think.  6 But what this study did was look at the frequency and  7 predictive value of colonic colonization with  8 Fluoroquinolone-resistant Enterobacteriaceae.  9 So it was a single-center study. It  10 enrolled 234 patients who were being admitted to the  11 hospital for a stem cell transplant and they were  12 planned to undergo Levofloxacin prophylaxis during  13 neutropenia.  14 So at the time of admission and then  15 weekly, they collected stool samples or rectal swabs  16 from these patients to look for colonization with  17 Fluoroquinolone-resistant Enterobacteriaceae  18 organisms, and they tracked bacteremia.  19 What they found was in their cohort  20 about 23 percent of patients were colonized with  21 Fluoroquinolone-resistant Enterobacteriaceae. And  22 when they compared development of bacteremia between</p>
<p style="text-align: right;">Page 47</p> <p>1 care microbiology for the majority of patients, and  2 they hypothesized that this would have changed  3 antimicrobial management in about 50 percent of the  4 cases.  5 I should have mentioned that the  6 metagenomic sequencing result was not provided to the  7 providers, so they were blinded to the results. So  8 this observational study doesn't really tell us  9 whether or not those possible antibiotic changes would  10 have impacted clinical outcome, although it would have  11 been possible for more rapid changes in antimicrobial  12 therapy.  13 Next slide.  14 There are a variety of molecular  15 diagnostics out there, many of which can be applied to  16 sample types other than blood. And these are  17 potentially useful for neutropenic patients where a  18 clinical syndrome or anatomic site of infection is  19 suspected.  20 I'll say that there have not been many  21 studies looking at the performance of these tests or  22 the clinical utility of these tests in neutropenic</p>	<p style="text-align: right;">Page 49</p> <p>1 those who were colonized as denoted in the gray bars  2 to the right here versus those who were not colonized,  3 bloodstream infections were seen in a statistically  4 significantly increased proportion of patients who  5 were colonized.  6 And interestingly, when infection did  7 develop, the organism was the same one that was  8 identified on the colonization cultures when they  9 compared the two using whole genome sequencing.  10 Next slide.  11 So in summary then, I've tried to show  12 the current kind of molecular diagnostic landscape to  13 show you that we're able to identify organisms more  14 quickly, and it can enable more rapid changes in  15 targeted antibiotic therapy.  16 However, there have been few studies  17 that have really shown that that change in therapy  18 translates into improved mortality of their patient-  19 important outcomes. I think those studies are needed.  20 And lastly, I've tried to show the  21 colonization status and potentially the gut microbiome  22 can be useful for guiding potentially prophylaxis or</p>

<p style="text-align: right;">Page 50</p> <p>1 no-prophylaxis, as well as prediction of bloodstream                  2 or other invasive infections.                  3           So with that, I'll stop, and I'll thank                  4 you for your attention.                  5           DR. PEASE: Great. Thank you.                  6           Next slide.                  7           Our next speaker is Dr. Anita Sheoran.                  8 Dr. Sheoran is a health scientist in an antimicrobials                  9 program at the Center of Biomedical Advanced Research                  10 Development Authority, BARDA. She also serves as a                  11 steering committee member of Military Infectious                  12 Diseases Research Program in the wound infection                  13 prevention and management area.                  14           DR. SHEORAN: Thanks, Dr. Pease, for                  15 the introduction.                  16           And hello, everyone.                  17           So looking at the names of these                  18 agencies, I thought, you know, I'll start off with a                  19 brief description of the agency that I represent and                  20 then go from there to why the focus of this workshop                  21 is of importance to us.                  22           Next slide, please.</p>	<p style="text-align: right;">Page 52</p> <p>1           So this brings to my program, which is                  2 an antimicrobial program, and we fund both antifungals                  3 and antibacterials. But on the antibacterial side, we                  4 work towards providing our first responders and                  5 clinicians with options to treat not only -- pathogens                  6 but also for the opportunistic and secondary bacterial                  7 infections that can occur during the treatment course                  8 of the patients after any public health emergency.                  9           Next slide, please.                  10           So that brings me to the focus of this                  11 workshop and that aligns very well with our mission to                  12 have medical countermeasures available to our patients                  13 after a radiological or a nuclear event. And as you                  14 can imagine that radiation exposure, you know, it                  15 leads to complex injuries, and if there's a nuclear                  16 detonation, then we are looking at a more complex                  17 injury.                  18           So when we are looking at the                  19 countermeasures that we need to focus on, we have to                  20 look at not only the clinical spectrum of injury but                  21 also the systems that are affected. And with respect                  22 to that, the hemopoietic system is the most sensitive.</p>
<p style="text-align: right;">Page 51</p> <p>1           So my organization, as Dr. Pease said,                  2 is BARDA. It falls under ASPR, and ASPR stands for                  3 Administration for Strategic Preparedness and                  4 Response. It is a lead federal health agency that                  5 prepares the -- that helps the nation for preparing,                  6 responding, and recovering from disasters or public                  7 health emergencies that can affect our healthcare                  8 system.                  9           Next slide, please.                  10           And under ASPR is BARDA, which is the                  11 largest organization under ASPR. We support advanced                  12 research and development of countermeasures against                  13 multiple threats. They can be chemical, biological,                  14 radiological, or nuclear events, or flu, influenza.                  15           We also procure products of strategic                  16 value for national security so that, you know, if                  17 needed, ASPR can respond in a timely manner. And we                  18 do all this through our public-private partnerships                  19 providing non-dilutive funding, providing technical                  20 support, core facilities to advance the product in a                  21 faster manner.                  22           Next slide, please.</p>	<p style="text-align: right;">Page 53</p> <p>1           So we -- considering, you know, the                  2 turnover of the cells, it is so fast which makes                  3 sense, so we would expect in the case of any Rad/Nuc                  4 event, we will see the majority of the patients with                  5 these injuries.                  6           And the typical acute radiation                  7 syndrome, you know, characteristics are, of course,                  8 neutropenia. Then, you know, hemorrhage, multiorgan                  9 failure, infection, sepsis, and might lead to death.                  10 So the products and the supportive care therapeutics                  11 that I have listed on the right here, as I mentioned                  12 earlier, the focus of my group is antibiotics and                  13 antifungals.                  14           Next slide, please.                  15           So I'm not going to spend any time on                  16 the antimicrobial resistance. We all heard about it,                  17 we all know about it. And antimicrobial resistance                  18 being, you know, a moving target, we do expect an                  19 increase in the rate of treatment failure in patients                  20 both for the hemopoietic acute radiation syndrome as                  21 well as the severe neutropenia in the oncology                  22 patient.</p>

<p style="text-align: right;">Page 54</p> <p>1 The other factor that we had to really 2 look into when we are evaluating the 3 antimicrobial -- the countermeasures are that we lack 4 robust clinical data in patients with hemopoietic 5 acute radiation system. And so most of the data that 6 we have are from our neutropenic cancer patients. So 7 we've done some animal studies, and we have seen some 8 similarities.</p> <p>9 For example, the non-human primate 10 acute radiation syndrome study showed that if the 11 non-human primates are not treated in time, and what 12 does that mean? That means if they're not treated 13 with a broad-spectrum antibiotic prior to the -- of 14 neutrophil decrease, then these hemopoietic ARS and 15 the bloodstream infection and sepsis, more than 50 16 percent of these NHPs die.</p> <p>17 And from the literature of what we have 18 seen that the neutropenic cancer patients, the death 19 rate from sepsis has been reported about 36 percent. 20 In fact, the ASCO/IDSA 28 referenced takes this number 21 to up to 50 percent. So kind of at par what we are 22 seeing in the NHP study.</p>	<p style="text-align: right;">Page 56</p> <p>1 Looking at the pipeline of the 2 antibiotics, there are limited choices for an oral 3 broad-spectrum antibiotic that we think we really need 4 for this indication. And plus, there's no clear path 5 for the product developers to develop a product for 6 febrile neutropenia. So we certainly need more 7 diagnostics as well as the antibacterials for this.</p> <p>8 Next slide, please.</p> <p>9 So looking at the gaps that I just, you 10 know, talked about, from our perspective, we see that 11 we can approach this by taking two treatment 12 approaches at the same time.</p> <p>13 One is making sure that we have 14 antibacterial treatment options available to the 15 patients that are febrile neutropenia. Secondly, we 16 have to have a better understanding of the role of 17 prophylaxis in patients that are at higher risk of 18 neutropenia.</p> <p>19 So what we need is the clinical 20 consensus among different groups for both these, you 21 know, treatment approaches. And the questions, of 22 course, will be -- we have a better understanding of</p>
<p style="text-align: right;">Page 55</p> <p>1 The other observation was that the 2 pattern of bacterial infection that we saw in this 3 model in the NHPs was the same as that has been 4 reported in the oncology neutropenic patients, the 5 usual suspect, staph aureus, enterococcus species, 6 Viridans Group streptococci. So we do see some 7 similarities.</p> <p>8 And next slide, please.</p> <p>9 So where are we with respect to 10 treating these neutropenic patients which have been 11 neutropenic for a long period of time? And I'm 12 talking about more than 30 days, putting them at 13 higher risk of getting secondary bacterial infections. 14 These neutropenic patients may be febrile, may not be 15 even febrile.</p> <p>16 So as Peter said, there are only two 17 antibiotics that have been approved for febrile 18 neutropenia. We are using off-label, and the ones 19 that are approved, we have seen the resistance against 20 them. We lack the robust clinical data for the 21 neutropenic patients, including the hemopoietic ARS 22 patients.</p>	<p style="text-align: right;">Page 57</p> <p>1 the clinical need for such an indication in daily 2 practice, the feasibility of the design of the 3 clinical development plan for these both approaches, 4 as well as what would be the ideal type target product 5 profile based on the clinician's experience.</p> <p>6 Next slide, please.</p> <p>7 So with that, I thank you for your time 8 and look forward to discussions today.</p> <p>9 DR. PEASE: Thank you.</p> <p>10 Next slide.</p> <p>11 And our next speaker is Dr. Douglas 12 Girgenti. Dr. Girgenti is an internist and 13 pediatrician with more than 25 years of clinical and 14 industry experience. He currently serves as Vice 15 President, Head of Development at Malinta Therapeutics 16 overseeing clinical pharmacovigilance and regulatory 17 functions.</p> <p>18 Thank you, Dr. Girgenti.</p> <p>19 DR. GIRGENTI: Hi, thank you.</p> <p>20 And good morning and good afternoon and 21 good evening to colleagues joining elsewhere. 22 If we could advance to the next slide.</p>

<p style="text-align: right;">Page 58</p> <p>1 As noted on the slide here, I am a  2 full-time employee of Malinta Therapeutics where I  3 lead clinical development, as well as  4 pharmacovigilance and regulatory functions. However,  5 the views and opinions I'll express today are solely  6 my own, and I have no other conflicts to disclose.  7 Okay, next slide. Thank you.  8 Okay. So thank you for the opportunity  9 to be here for this really important event. And as  10 noted from our earlier speakers that really, despite  11 being quite frankly the most serious complications of  12 chemotherapy-induced neutropenia, and what is truly a  13 key driver of dose delay and reduction and perhaps  14 survival in patients receiving chemotherapy.  15 And despite the existence of numerous  16 guidance regarding the use of antibiotics for empiric  17 treatment of febrile neutropenia, there really is no  18 standardized agreed-upon study designed for clinical  19 trial development. And this is the way I really tried  20 to approach this discussion today.  21 So there are a few antibiotics that are  22 currently recommended and even fewer licensed for</p>	<p style="text-align: right;">Page 60</p> <p>1 safety events that might be incurred in a clinical  2 trial.  3 And, perhaps, most importantly,  4 outcomes where, you know, as Dr. Taplitz earlier  5 described, that this disease has really evolved over  6 the last even 50 years, where at one point the  7 mortality perhaps was greater than 50 percent and is  8 essentially now down to 5 to 10 percent in most  9 clinical trials that have evaluated the disease.  10 Okay, next slide.  11 So to date there are really only one or  12 perhaps two antibacterial agents that are approved,  13 and a small handful of drugs which are recommended for  14 the empiric treatment of FN. Approved drugs include  15 Cefepime and Ciprofloxacin, but only in combination  16 with Piperacillin.  17 Yet, despite a lack of label  18 indication, the antibiotics that are recommended by  19 IDSA as well as ESMO and ASCO for empiric treatment  20 includes Ceftazidime, Piperacillin-tazobactam,  21 Imipenem-cilastin, and Meropenem. And, of course,  22 none of these are really novel antibiotics, and, in</p>
<p style="text-align: right;">Page 59</p> <p>1 empiric treatment, and these are largely based on, as  2 we've seen earlier, randomized clinical trials which  3 have been conducted in some cases more than 20 years  4 or more prior to now.  5 And since that time, we've really seen  6 great advances in the treatment of malignancy which  7 have impacted the course of disease, microbiological  8 considerations, and overall the course of FN, and I've  9 highlighted some of them here.  10 Particularly, the microbiology, which  11 has evolved largely due to the increased use of  12 indwelling lines, and we also see emerging resistance  13 patterns in both gram-negative and gram-positive  14 populations. With regard to the population itself, a  15 wider breadth of tumor types that are being treated,  16 and certainly an aging population.  17 Treatment recommendations which are now  18 risk-based stratified in terms of high risk and low  19 risk. Really important ancillary treatments of  20 chemotherapy, particularly, and most importantly, I  21 would say, the use of G-CSF, which has had a  22 substantial impact on outcomes as well as potential</p>	<p style="text-align: right;">Page 61</p> <p>1 fact, these recommendations are largely based on  2 multicenter trials that were conducted more than 20  3 years ago. And the field has become, you know,  4 somewhat stagnant.  5 While endpoints have not necessarily  6 been consistent from trial to trial, in each of the  7 cases I've shown here, the antibiotics have largely  8 been evaluated primarily based on head-to-head  9 clinical trials, evaluating clinical response which  10 includes defervescence, resolution of signs and  11 symptoms.  12 And if identified, clearance of the  13 cultured organism, plus or minus the need for  14 modification of the original antibiotic therapy chosen  15 for empiric treatment.  16 So, you know, immediately evident, I  17 think, are the challenges -- some of the challenges  18 that we face in a randomized clinical trial design.  19 Where looking at the clinical responses that have  20 achieved, you know, they're not particularly robust,  21 and really demonstrate small, if any, margin between  22 the test and the comparative antibiotics in each</p>



<p style="text-align: right;">Page 62</p> <p>1 trial.</p> <p>2           Okay, next slide.</p> <p>3           So this is current as of about maybe</p> <p>4 two weeks ago, where I did a search of</p> <p>5 clinicaltrials.gov based on febrile neutropenia or</p> <p>6 fever plus neutropenia which revealed in total about</p> <p>7 162 posted trials. And merely 10 of these really</p> <p>8 represent antibiotic trials which are evaluating</p> <p>9 empiric treatment of FN. And even more importantly,</p> <p>10 only two are either ongoing or planned.</p> <p>11           And yet, you know, as I really tried to</p> <p>12 lay out on the bottom of the slide, there are numerous</p> <p>13 beta-lactam, as well as non-beta-lactam class</p> <p>14 antibiotics, that could potentially be considered as</p> <p>15 candidates for empiric treatment.</p> <p>16           Okay, next slide.</p> <p>17           So where I've really started this</p> <p>18 discussion in terms of, you know, what I would do when</p> <p>19 considering whether to develop a drug for really any</p> <p>20 potential indication? You know, hypothetically, how</p> <p>21 would I address clinical development as a sponsor?</p> <p>22 What would I need to consider with regard to both</p>	<p style="text-align: right;">Page 64</p> <p>1 would really only entertain the potential to develop a</p> <p>2 drug for febrile neutropenia if the cost of</p> <p>3 development would at least be offset by</p> <p>4 commercialization.</p> <p>5           Okay, next slide.</p> <p>6           So where I'd like to start then, you</p> <p>7 know, in considering how to design or how I would</p> <p>8 approach clinical development. For any hypothetical</p> <p>9 drug in designing a clinical development strategy, my</p> <p>10 first step would be to understand the population and</p> <p>11 the disease as thoroughly as possible.</p> <p>12           And really to anticipate the unique</p> <p>13 challenges that each would represent. Thus, to design</p> <p>14 a clinical efficacy trial best designed not only for</p> <p>15 success but the best potential in a label indication.</p> <p>16           So, importantly, with regard to the FN</p> <p>17 population, we know that despite important advances in</p> <p>18 this field, there is still a substantial unmet need</p> <p>19 for novel and improved therapies. And in considering</p> <p>20 whether our previous randomized clinical trials would</p> <p>21 remain valid, despite the changes over the last two</p> <p>22 years, I think is really important.</p>
<p style="text-align: right;">Page 63</p> <p>1 clinical and economic impacts of development?</p> <p>2           So first of all, on the clinical side,</p> <p>3 you know, what is really to be gained by a clinical</p> <p>4 development strategy? Is there clinical value to be</p> <p>5 added by the drug that we'd like to bring to market?</p> <p>6           So does the drug clinically</p> <p>7 differentiate from existing therapy, either with</p> <p>8 regard to efficacy and outcomes or perhaps with</p> <p>9 improved safety and tolerability, as was seen, you</p> <p>10 know, 20 to 30 years ago with going from combination</p> <p>11 therapy to the rationale for monotherapy?</p> <p>12           And will the results of the clinical</p> <p>13 development influence the treatment paradigm? Whether</p> <p>14 this is really top-down with respect to guidance and</p> <p>15 recommendations or even locally at the formulary</p> <p>16 level? And then, very importantly, on the economic</p> <p>17 side, you know, what impact is anticipated that could</p> <p>18 either add or detract from a value from the current</p> <p>19 treatment?</p> <p>20           And finally, you know, realistically</p> <p>21 from a sponsor perspective, there is cost to consider.</p> <p>22 Antibiotic development is costly and realistically, we</p>	<p style="text-align: right;">Page 65</p> <p>1           What we see are that there are an</p> <p>2 increased breadth of diseases which are being treated</p> <p>3 with chemotherapy and particularly late-stage diseases</p> <p>4 which were not previously treated. So the overall</p> <p>5 impact of this has been to age the population at risk.</p> <p>6 However, the breadth of diseases makes this much more</p> <p>7 disease-specific.</p> <p>8           With regard to the breadth of solid</p> <p>9 tumors which are now being treated sometimes in</p> <p>10 combination with radiation therapy, as well as the</p> <p>11 increased use of central venous access and</p> <p>12 Fluoroquinolone prophylaxis, what used to be a disease</p> <p>13 predominated by gram-negative pathogens, this is</p> <p>14 perhaps precipitated a predominance of gram-positive</p> <p>15 pathogens responsible for febrile neutropenia.</p> <p>16           However, we also know that patients</p> <p>17 that have hematological malignancies are generally</p> <p>18 older, more morbid, and at higher risk of febrile</p> <p>19 neutropenia, as well as poor outcomes. So the age,</p> <p>20 the morbidity, the healthcare exposures are certainly</p> <p>21 drivers of morbidity and particularly gram-negative</p> <p>22 and multidrug-resistant organisms predominating in</p>

<p style="text-align: right;">Page 66</p> <p>1 this population.</p> <p>2           And all of these really contribute to</p> <p>3 the inclusion/exclusion criteria that we might</p> <p>4 consider in a clinical trial which could potentially</p> <p>5 impact both efficacy and safety and inevitably impact</p> <p>6 what the label looks like at the conclusion of this.</p> <p>7           Multidrug resistance and a rise of</p> <p>8 novel healthcare-associated infections, as well as</p> <p>9 fungal infections, also are to be considered pretty</p> <p>10 substantially in this population.</p> <p>11           And really in terms of relying on</p> <p>12 historical data, the important changes in supportive</p> <p>13 care, most notably the introduction of G-CSF and</p> <p>14 prophylactic antibiotic use, have certainly</p> <p>15 contributed substantially to incidents as well as</p> <p>16 outcomes in this population. And risk-based treatment</p> <p>17 and short step-down therapy have further impacted how</p> <p>18 we might consider clinical development in the</p> <p>19 population.</p> <p>20           So what we know at this point is that</p> <p>21 the FN population will include a substantial age</p> <p>22 range, including a substantial patient range well</p>	<p style="text-align: right;">Page 68</p> <p>1 opportunity to refine the population based on more</p> <p>2 recent microbiologic techniques that could either</p> <p>3 reduce a fungal -- identify those that are likely to</p> <p>4 be a fungal or a viral origin or more likely to be a</p> <p>5 bacterial origin?</p> <p>6           And I'll move to the next slide.</p> <p>7           Okay. So I'd like to present what I'm</p> <p>8 calling an enigma here, which is that, you know, how</p> <p>9 do we address what may be existing versions or</p> <p>10 improvements upon existing beta-lactams, beta-lactam,</p> <p>11 beta-lactamase combinations, which could certainly</p> <p>12 serve as an improvement upon existing -- the backbone</p> <p>13 beta-lactam drug.</p> <p>14           Yet, these drugs are in the two</p> <p>15 examples I've identified here, Cefepime-enmetazobactam</p> <p>16 and Meropenem-vaborbactam, that are, in fact,</p> <p>17 indicated only for urinary tract infection due to</p> <p>18 gram-negative pathogens.</p> <p>19           So, you know, while we know that, in</p> <p>20 fact, that these newer beta-lactam, beta-lactamase</p> <p>21 inhibitor combinations, which are only approved for</p> <p>22 gram-negative pathogens, could be a substantial</p>
<p style="text-align: right;">Page 67</p> <p>1 above 65 and above, which is important to the label</p> <p>2 indication. On average, the patient population</p> <p>3 remains somewhat morbid. The average mass score would</p> <p>4 represent high-risk patients.</p> <p>5           Depending on the disease, most, if not</p> <p>6 all, patients will have central venous access. Most</p> <p>7 of patients will be prophylactically treated with</p> <p>8 Fluoroquinolones. This may be disease-specific. And</p> <p>9 we can anticipate that a large proportion of subjects</p> <p>10 will be on G-CSF therapy which may alter the natural</p> <p>11 course of neutropenia, particularly the time of</p> <p>12 neutropenia.</p> <p>13           Okay. Let's move to the next slide.</p> <p>14           Okay. So important for us to</p> <p>15 understand is what the microbiology looks like. This</p> <p>16 is very important to the disease, where more than half</p> <p>17 of our subjects may never declare a site of infection.</p> <p>18 And the remainder will be split evenly between those</p> <p>19 that are microbiologically defined and those that are</p> <p>20 just clinically defined based on site.</p> <p>21           So this is really important with regard</p> <p>22 to endpoint evaluation. And does this offer us the</p>	<p style="text-align: right;">Page 69</p> <p>1 improvement upon the existing beta-lactam drug, could</p> <p>2 this be considered in a more broad-spectrum incidence</p> <p>3 of febrile neutropenia, where the majority of bugs are</p> <p>4 anticipated to be gram-positive?</p> <p>5           And furthermore, if we were to succeed,</p> <p>6 particularly in, say, a non-inferiority trial, what</p> <p>7 would be the value-added, particularly considering</p> <p>8 antibiotic stewardship as well as substantially higher</p> <p>9 cost?</p> <p>10           And then finally, you know, in terms of</p> <p>11 considering everything, if I can move to the next</p> <p>12 slide with regard to clinical trial design. I've</p> <p>13 included a quote here which is now 29 years old, and I</p> <p>14 thought it was particularly relevant considering it</p> <p>15 could really well be the topic of today's workshop.</p> <p>16 So we empirically treat FN to, in fact, prevent poor</p> <p>17 outcomes in patients with regard to morbidity and</p> <p>18 mortality.</p> <p>19           And, you know, with regard to what we</p> <p>20 should evaluate, I think it's been noted earlier</p> <p>21 whether to evaluate outcomes, potentially, say,</p> <p>22 mortality versus clinical response. And, you know,</p>

Page 70	Page 72
<p>1 what we've seen is a disease which has progressed from  2 having perhaps a 50 percent or more mortality, to now  3 in most clinical trials 5 to 10 percent.</p> <p>4 And in most cases where the majority of  5 mortality is not attributable to infectious causes,  6 which really makes this perhaps untenable as a primary  7 outcome evaluation which really leaves us with what I  8 believe to still be the most responsible approach to  9 evaluate clinical and microbiologic endpoints as a  10 primary outcome of the study.</p> <p>11 However, you know, as for additional  12 design considerations, we also want to consider  13 whether to stratify based on what we know are a very  14 heterogeneous population. For instance, solid versus  15 hematologic malignancies, whether there's been G-CSF  16 usage or prophylactic antibiotics. Okay.</p> <p>17 And further considerations are, you  18 know, really, now that we're in an environment where  19 de-escalation to a narrow spectrum or oral treatment  20 can be permitted relatively early in the course, where  21 does that leave our endpoint for evaluation earlier or  22 later in the time course?</p>	<p>1 may introduce another four years and approximately ten  2 to twelve million dollars to conduct -- to achieve  3 approval in the pediatric indication.</p> <p>4 So in total, I would assume that for a  5 pediatric development program for a drug which is  6 based on a single Phase 3 trial which has already been  7 approved in an additional indication, that this would  8 roughly cost forty to fifty million dollars in total.  9 And in total about a decade or so for five years of  10 adult followed by another five years of pediatric  11 approval.</p> <p>12 And finally, last slide.</p> <p>13 And really what I've shown here is that  14 the clinical development for antibiotics treatment for  15 febrile neutropenia presents a lot of challenges from  16 the sponsor perspective with regard to population,  17 disease, and microbiology, and endpoints. And it's a  18 lengthy and costly path to licensure. So I would  19 propose here that there are additional opportunities  20 that could be pursued.</p> <p>21 These could include evaluating  22 pragmatic trials or real-world experience. And</p>
<p>Page 71</p> <p>1 Okay. And I'll move on in the interest  2 of time to the next slide.</p> <p>3 So here I've really just laid out what  4 a clinical trial design might look like, and I've  5 really tried to highlight most of my considerations,  6 most of the questions I've raised at the bottom of the  7 slide here, so I won't reiterate those.</p> <p>8 And I can move on to the next slide  9 where here I've really hypothetically mapped out what  10 this would look like. This is very hypothetical but  11 really based on a lot of clinical trial experience.</p> <p>12 So looking at a clinical trial  13 response, I've assumed that for crude assumptions in a  14 one-to-one randomized trial, that this would roughly  15 require approximately two years to enroll at a cost of  16 about eighty to one hundred thousand dollars per  17 subject. And therefore, thirty to forty million  18 dollars in total. And really in total, this would  19 take four to five years for approval.</p> <p>20 And in all likelihood, this would be  21 required for -- it would be required to conduct as a  22 post-marketing requirement, a pediatric trial, which</p>	<p>Page 73</p> <p>1 really, is there an opportunity to evaluate  2 antibiotics rather than in the traditional clinical  3 trial in more of a platform trial design where  4 multiple antibiotics could be evaluated head-to-head  5 against additional therapies?</p> <p>6 Really, all of these are intended to  7 look at ways that we can leverage and improve upon  8 existing clinical trial designs to facilitate  9 development and make this more attractive from the  10 industry perspective.</p> <p>11 Okay. Next slide, finally.</p> <p>12 So it does take a village, and I'm  13 grateful to my team and my colleagues who make work  14 every day a pleasure and particularly for their  15 contributions to this presentation. And thank you all  16 for listening.</p> <p>17 DR. PEASE: Thank you, Dr. Girgenti.  18 Next slide. Thank you. We'll now  19 break for five minutes. Please be back at -- it's,  20 like, 10:22 for the start of session two. Thank you.</p> <p>21 (Off the record.)  22 DR. BOTGROS: It's 10:22. So I would</p>

<p style="text-align: right;">Page 74</p> <p>1 like to welcome you back.</p> <p>2 THE REPORTER: Are we back?</p> <p>3 DR. BOTGROS: Sorry?</p> <p>4 THE REPORTER: Are we starting? This</p> <p>5 is the court reporter.</p> <p>6 DR. BOTGROS: Yeah -- yeah. We are</p> <p>7 starting indeed.</p> <p>8 So again, welcome back to this</p> <p>9 workshop. My name is Radu Botgros, and I'm a</p> <p>10 physician specializing in infectious diseases. I work</p> <p>11 at the European Medicines Agency as a senior</p> <p>12 scientific officer in the Department of Public Health</p> <p>13 Threats. And I take the opportunity to thank the FDA</p> <p>14 for having invited me both to present and to moderate</p> <p>15 this session together with Dan Rubin from the FDA.</p> <p>16 So I think, Dan, if you want to say a</p> <p>17 few words as well?</p> <p>18 DR. RUBIN: Hello, my name is Daniel</p> <p>19 Rubin, and I'll be a co-moderator for this session.</p> <p>20 I'm from the Office of Biostatistics, CDER, FDA.</p> <p>21 Next slide, please.</p> <p>22 Our first speaker will be my colleague,</p>	<p style="text-align: right;">Page 76</p> <p>1 for related indications when their sponsor</p> <p>2 subsequently performed clinical trials showing benefit</p> <p>3 in the treatment of patients with febrile neutropenia.</p> <p>4 Cefepime monotherapy, which is</p> <p>5 administered intravenously, was the first approved</p> <p>6 antibacterial for this indication in 1997. Cefepime</p> <p>7 was approved for this indication based on the pooled</p> <p>8 results of two adequate and well-controlled trials</p> <p>9 with additional supportive studies.</p> <p>10 Shortly following Cefepime's approval</p> <p>11 for this indication, intravenous Ciprofloxacin in</p> <p>12 combination with Piperacillin sodium was also approved</p> <p>13 for the empiric therapy of febrile neutropenia, also</p> <p>14 in 1997, based on one adequate and well-controlled</p> <p>15 trial with additional supportive studies.</p> <p>16 So it has now been more than 25 years</p> <p>17 since the two currently approved antibacterials were</p> <p>18 approved for this indication. Additionally, there</p> <p>19 have been no oral antibacterials approved for this</p> <p>20 indication.</p> <p>21 Next slide, please.</p> <p>22 The statutory standards are that a</p>
<p style="text-align: right;">Page 75</p> <p>1 Dr. Robert Pease, who introduced himself during the</p> <p>2 first session. At this point, I will turn it over to</p> <p>3 Dr. Pease.</p> <p>4 DR. PEASE: Thank you, Dr. Rubin.</p> <p>5 Hello. My name is Robert Pease. I am</p> <p>6 a medical officer at the FDA here in the Division of</p> <p>7 Anti-Infectives. In the next ten minutes or so, I</p> <p>8 will give you a very high-level overview of regulatory</p> <p>9 pathways that are relevant for febrile neutropenia</p> <p>10 drug development.</p> <p>11 Next slide, please.</p> <p>12 This is an outline for my talk today.</p> <p>13 I'll start with an overview of the approved</p> <p>14 antibacterials for the empiric treatment of febrile</p> <p>15 neutropenia and then discuss regulatory programs,</p> <p>16 pathways and designations, or incentive programs that</p> <p>17 are available.</p> <p>18 Next slide, please.</p> <p>19 Two antibacterial drugs have been</p> <p>20 approved for the empiric treatment of febrile</p> <p>21 neutropenic patients. Briefly summarizing, both</p> <p>22 products were available on the market with approvals</p>	<p style="text-align: right;">Page 77</p> <p>1 drug's effectiveness must be established by</p> <p>2 substantial evidence defined as evidence consisting of</p> <p>3 adequate and well-controlled investigations, including</p> <p>4 clinical investigations. Historically, this was</p> <p>5 generally interpreted as requiring two adequate and</p> <p>6 well-controlled trials, each convincing on its own to</p> <p>7 establish effectiveness.</p> <p>8 However, Section 115(a) of the</p> <p>9 Modernization Act amended the provision to make clear</p> <p>10 that FDA may consider data from one adequate and</p> <p>11 well-controlled clinical investigation and</p> <p>12 confirmatory evidence to constitute substantial</p> <p>13 evidence of effectiveness.</p> <p>14 Next slide, please.</p> <p>15 This slide lists the types of</p> <p>16 confirmatory evidence which are described in the</p> <p>17 reference guidance document. This includes clinical</p> <p>18 evidence from a related indication which we think is</p> <p>19 going to be the most pertinent for the indication of</p> <p>20 empiric treatment of febrile neutropenia.</p> <p>21 Next slide.</p> <p>22 Under certain circumstances, evidence</p>

<p style="text-align: right;">Page 78</p> <p>1 of effectiveness of a drug from a clinical  2 investigation for a particular indication can provide  3 confirmatory evidence of effectiveness to support  4 approval of a drug in a different but closely related  5 indication.</p> <p>6 An example of this approach is the  7 submission of a new drug application or a new  8 indication or an already approved therapy, where one  9 adequate and well-controlled clinical investigation of  10 the drug where the new indication is supported by the  11 results from the clinical investigations that form the  12 basis of the previous approval.</p> <p>13 An example of this would be if a drug  14 was previously approved for, say, the indication of  15 health care or ventilator-associated bacterial  16 pneumonia, then a single Phase 3 trial for the empiric  17 treatment of febrile neutropenia could be supported  18 with confirmatory evidence coming from the results  19 formed for the basis of the previous approval and the  20 HABP/VABP development program.</p> <p>21 Next slide.</p> <p>22 An overview of regulatory pathways.</p>	<p style="text-align: right;">Page 80</p> <p>1 to the LPAD guidance document.</p> <p>2 Next slide.</p> <p>3 Expedited programs are designations  4 which are designed to facilitate the development, and  5 a review of new drugs that address unmet medical needs  6 in the treatment of a serious or life-threatening  7 condition.</p> <p>8 The programs include fast track,  9 breakthrough therapy, and priority review. A drug  10 development program may qualify for more than one of  11 these expedited programs.</p> <p>12 Fast track designation is intended to  13 facilitate development and expedite review of drugs to  14 treat serious and life-threatening conditions so that  15 an approved product can reach the market  16 expeditiously.</p> <p>17 Fast track designation allows for  18 frequent interaction with the review team, and the  19 agency may consider a rolling review in which portions  20 of a marketing application are reviewed before the  21 sponsor submits the complete application.</p> <p>22 Breakthrough therapy designation</p>
<p style="text-align: right;">Page 79</p> <p>1 Traditional approval is based on a clinical endpoint  2 which measures how a patient feels, functions, or  3 survives. There's an accelerated approval pathway  4 based on a surrogate endpoint.</p> <p>5 Given endpoints in febrile neutropenia  6 occur relatively quickly, we currently think that the  7 accelerated approval pathway would not be a viable  8 option for a febrile neutropenia drug development  9 program.</p> <p>10 But if you have a drug for which you  11 would like to use a surrogate endpoint, please talk to  12 us about it.</p> <p>13 The LPAD pathway is for drugs that are  14 intended to treat a serious and life-threatening  15 infection in a limited population of patients with  16 unmet needs. Given that treatment of febrile  17 neutropenia is most likely to be empiric, we think  18 that the LPAD pathway is less likely to apply for the  19 indication of empiric treatment of febrile  20 neutropenia.</p> <p>21 But if you have a population in mind,  22 we are available to help. I've included a reference</p>	<p style="text-align: right;">Page 81</p> <p>1 requires preliminary clinical evidence that the drug  2 may demonstrate a substantial improvement over  3 available therapy on a clinically significant  4 endpoint.</p> <p>5 Breakthrough therapy designation  6 usually means that the drug -- that the effect of the  7 drug will be large compared with available therapies,  8 and the development program could be considerably  9 shorter than for other drugs intended to treat the  10 disease being studied.</p> <p>11 The FDA will seek to ensure that a  12 sponsor of a product designated as breakthrough  13 therapy receives timely advice and interactive  14 communications to help the sponsor design and conduct  15 a drug development program beginning as early as  16 Phase 1.</p> <p>17 Breakthrough therapy designation is an  18 organizational commitment from FDA, including the  19 involvement of senior management, and it also includes  20 all of the benefits of fast track designation,  21 including eligibility for rolling review, and may be  22 eligible for priority review. What priority review</p>

<p style="text-align: right;">Page 82</p> <p>1 does is that it allows a shorter clock for the review  2 of marketing application.  3           Next slide.  4           Regarding incentives for the  5 development of drugs for febrile neutropenia, one set  6 of incentives is the Qualified Infectious Disease  7 Product Designation which is available for  8 antibacterial or antifungal human drugs that are  9 intended to treat serious or life-threatening  10 infections.  11           FDA generally intends to consider a  12 drug to be intended to treat a serious or  13 life-threatening infection if it is intended to  14 diagnose, prevent, or treat such an infection. The  15 QIDP designation applies to a specific indication,  16 meaning more than one designation may be granted for  17 the same active ingredient.  18           For example, one sponsor may receive  19 QIDP designation for multiple dosage forms of the same  20 active ingredient or for multiple indications. QIDP  21 provides a five-year extension for any marketing  22 exclusivity that the application qualifies for upon</p>	<p style="text-align: right;">Page 84</p> <p>1 treatment of febrile neutropenia, including sources of  2 confirmatory evidence, such as clinical evidence from  3 a related indication. I've also reviewed regulatory  4 pathways that are available to expedite drug  5 development and designations or incentive programs.  6           We have had no new approved  7 antibacterials for this indication in more than 25  8 years, and there are no oral antibacterials which have  9 been approved for febrile neutropenia.  10           If you are embarking on a program for  11 the empiric treatment of febrile neutropenia, we  12 highly recommend that you come talk to us, so at the  13 end of the day, we have a development program that has  14 a high likelihood of success.  15           Thank you. Next slide.  16           DR. BOTGROS: Thank you very much, Rob,  17 for this nice presentation as well for keeping time.  18           We are now having our next speaker,  19 which is Dr. Rama Kapoor, who is currently a senior  20 medical officer in the Division of Anti-Infectives at  21 the FDA. Dr. Kapoor completed her internal medicine  22 residency training from George Washington University,</p>
<p style="text-align: right;">Page 83</p> <p>1 approval.  2           And for the first application that's  3 submitted to us, it's an automatic priority review  4 even if you don't necessarily meet other criteria for  5 priority review, and the products are also eligible  6 for fast track designation. We have now had more than  7 35 QIDP-designated products approved.  8           Next slide.  9           An additional consideration is orphan  10 drug designation for rare diseases or conditions that  11 affect fewer than 200,000 people in the United States.  12 Benefits of orphan drug designation include tax  13 credits for qualified clinical trials, exemption from  14 user fees, and the potential for seven years of market  15 exclusivity after approval.  16           Orphan drugs may also use expedited  17 programs during their development or after a review  18 should they qualify.  19           Next slide.  20           In summary, I have provided a  21 high-level overview for the key regulatory  22 considerations for drug development in the empiric</p>	<p style="text-align: right;">Page 85</p> <p>1 and she had a fellowship in infectious diseases from  2 the University of Louisville.  3           So, Rama, over to you.  4           DR. KAPOOR: Thank you, Radu.  5           Hello. Can you hear me?  6           DR. BOTGROS: Yes, we can.  7           DR. KAPOOR: Thank you.  8           My name is Rama Kapoor, and I'm a  9 medical officer at the FDA. In the next 15 to 20  10 minutes, I'll discuss regulatory perspective on the  11 clinical trial design for empiric antibacterial  12 therapy in febrile neutropenia.  13           Next slide.  14           Let's start with the roadmap of our  15 discussion today. I'll begin by addressing general  16 regulatory considerations for febrile neutropenia  17 indication, delve into the challenges presented by  18 heterogeneity, discuss primary efficacy and point  19 considerations, comment on the unmet need in the  20 treatment of febrile neutropenia, and conclude with  21 the summary of our discussion.  22           Next slide.</p>

<p style="text-align: right;">Page 86</p> <p>1 To support an indication for febrile</p> <p>2 neutropenia, one adequate and well-controlled trial is</p> <p>3 acceptable, and, as Dr. Pease noted, usually these are</p> <p>4 the situations when the test drug is already approved</p> <p>5 for another serious bacterial infection.</p> <p>6 The FDA acknowledges unique challenges</p> <p>7 for designing an interpretable and feasible trial</p> <p>8 posed by heterogeneity among FN patients. These</p> <p>9 challenges impact both enrollment criteria and choice</p> <p>10 of the primary analysis population. Discussing ideas</p> <p>11 that may address these challenges is the focus of this</p> <p>12 workshop.</p> <p>13 Next, I'm going to discuss</p> <p>14 characteristics of an adequate and well-controlled</p> <p>15 trial.</p> <p>16 Next slide, please.</p> <p>17 An adequate and well-controlled trial</p> <p>18 clearly states its objectives, methods of analysis,</p> <p>19 permits valid comparisons with a control to provide a</p> <p>20 quantitative assessment of drug effect, and ensures</p> <p>21 that the selected subjects have the disease being</p> <p>22 studied are susceptible to the condition being</p>	<p style="text-align: right;">Page 88</p> <p>1 by definitive evidence of infection, either through</p> <p>2 the detection of bacteremia without a localized site</p> <p>3 of infection, or through the identification of</p> <p>4 specific site of infection with or without concurrent</p> <p>5 bacteremia.</p> <p>6 Patients with clinically defined</p> <p>7 infection presents with signs and symptoms indicative</p> <p>8 of an infection such as pneumonia or cellulitis but</p> <p>9 lack confirmatory microbiologic evidence. Unexplained</p> <p>10 fever or possible infection includes patients with</p> <p>11 fever without clinical or microbiologic evidence of</p> <p>12 infection, and fever should not be attributed to</p> <p>13 non-infectious cause. Whereas non-infectious fever</p> <p>14 includes patients with fever that can be attributed to</p> <p>15 non-infectious causes.</p> <p>16 Now let's look at the distribution of</p> <p>17 FN categories in previously conducted trials in next</p> <p>18 slide.</p> <p>19 Next slide.</p> <p>20 This slide illustrates the distribution</p> <p>21 of FN categories in previously conducted trials with</p> <p>22 consistent finding of a considerable proportion of</p>
<p style="text-align: right;">Page 87</p> <p>1 prevented.</p> <p>2 Methods of assignment to study arms in</p> <p>3 the trial should ensure comparability between the</p> <p>4 study groups. Ordinarily, in a concurrently</p> <p>5 controlled study, assignment is by randomization.</p> <p>6 Measures to minimize bias on the part of the subject,</p> <p>7 observers, and analysts of the data, such as blinding</p> <p>8 should be taken, and methods of assessing treatment</p> <p>9 response must be well-defined and reliable.</p> <p>10 Finally, the trial must employ</p> <p>11 statistical methods that are robust and appropriate</p> <p>12 for the data collected. This includes not just the</p> <p>13 primary analysis, but also handling any interim</p> <p>14 analysis, missing data, subgroup analysis to ensure</p> <p>15 that the conclusions drawn from the trial are valid</p> <p>16 and reliable.</p> <p>17 With these considerations in mind,</p> <p>18 let's delve deeper into the heterogeneity challenge.</p> <p>19 Next slide.</p> <p>20 Based on the clinical course, FN</p> <p>21 episodes are divided into four categories.</p> <p>22 Microbiologically defined infection is characterized</p>	<p style="text-align: right;">Page 89</p> <p>1 patients falling into the unexplained fever category</p> <p>2 to the right, almost the rightmost column.</p> <p>3 This confirms the heterogeneity</p> <p>4 highlighting the challenges with establishing the</p> <p>5 ideology of fever in FN patients. The resulting</p> <p>6 heterogeneity of the trial population impacts the</p> <p>7 efficacy analysis.</p> <p>8 Also, in one study, a notable</p> <p>9 proportion of patients were categorized as having</p> <p>10 doubtful infections underscoring the difficulties in</p> <p>11 establishing the ideology of fever in febrile</p> <p>12 neutropenia.</p> <p>13 Next, I am going to discuss further an</p> <p>14 impact of heterogeneity on efficacy analysis starting</p> <p>15 with general description of trial design in next</p> <p>16 slide.</p> <p>17 Next slide.</p> <p>18 In terms of an efficacy assessment, a</p> <p>19 clinical trial may aim to demonstrate that the test</p> <p>20 drug is superior or not inferior to active control. A</p> <p>21 superiority trial seek to demonstrate that the test</p> <p>22 drug is significantly better than the active control</p>

<p style="text-align: right;">Page 90</p> <p>1 or standard treatment.</p> <p>2 In general, a superiority trial</p> <p>3 provides the strongest evidence of effectiveness. A</p> <p>4 non-inferiority trial aims to show that the new</p> <p>5 treatment is not significantly worse than the</p> <p>6 established therapy by more than a pre-specified</p> <p>7 margin, which is a non-inferiority margin.</p> <p>8 NI trials relies upon an assumption of</p> <p>9 an anticipated effect of a control based on the data</p> <p>10 from historic trials, which is the basis for NI</p> <p>11 margin. Either trial can utilize an active</p> <p>12 comparator.</p> <p>13 Next slide.</p> <p>14 The inclusion of patients with</p> <p>15 unexplained fever in primary analysis population will</p> <p>16 impact interpretability of superiority and a</p> <p>17 non-inferiority trial in a different way. For</p> <p>18 superiority trial, including subjects in the primary</p> <p>19 analysis population were ultimately classified as</p> <p>20 having unexplained fever does not compromise trial</p> <p>21 interpretability if superiority is demonstrated.</p> <p>22 However, demonstrating superiority of</p>	<p style="text-align: right;">Page 92</p> <p>1 Next slide.</p> <p>2 To improve the feasibility of FN</p> <p>3 trials, enrichment strategies may be considered to</p> <p>4 select the population in which the intervention is</p> <p>5 expected to have most significant effect thereby</p> <p>6 increasing the trials efficiency and power.</p> <p>7 These strategies may include the use of</p> <p>8 clinical characteristics and risk factors in selecting</p> <p>9 inclusion and exclusion criteria. And as Dr. Hanson</p> <p>10 noted, use of rapid diagnostic tools such as</p> <p>11 polymerase chain reaction for bacterial DNA or</p> <p>12 advanced imaging techniques can be considered to</p> <p>13 identify patients more likely to have bacterial</p> <p>14 infection.</p> <p>15 Today's discussion is an invitation to</p> <p>16 explore these strategies and other ideas during the</p> <p>17 panel discussion.</p> <p>18 Next slide.</p> <p>19 Another key consideration for efficacy</p> <p>20 analysis is the selection of an appropriate endpoint.</p> <p>21 Trial endpoints serve as predefined outcomes used to</p> <p>22 evaluate the efficacy and safety of a therapeutic</p>
<p style="text-align: right;">Page 91</p> <p>1 an antibacterial drug may become more challenging if</p> <p>2 efficacy analysis includes patients not having a</p> <p>3 bacterial infection. For a non-inferiority trial,</p> <p>4 inclusion of patients not having a bacterial infection</p> <p>5 in the efficacy analysis population may bias the trial</p> <p>6 towards non-inferiority.</p> <p>7 Importantly, for the trial to be</p> <p>8 interpretable, the characteristics of the patients in</p> <p>9 the primary analysis population of current trial needs</p> <p>10 to be sufficiently similar to patients in the historic</p> <p>11 placebo-controlled trials that support NI margin.</p> <p>12 Thus, the treatment effect of the</p> <p>13 active control in FN patients with confirmed</p> <p>14 bacteriaemia seen in historically placebo-controlled</p> <p>15 trials, may not be applicable to the efficacy analysis</p> <p>16 that includes patients with unexplained fever.</p> <p>17 This backdrop underscores the</p> <p>18 importance of precise patient selection and clear</p> <p>19 definition of primary endpoints that are robust and</p> <p>20 sensitive enough to detect differences in the mixed</p> <p>21 population. One approach to address this challenge is</p> <p>22 through the use of enrichment strategies.</p>	<p style="text-align: right;">Page 93</p> <p>1 intervention.</p> <p>2 The chosen endpoints must be</p> <p>3 well-defined and clinically meaningful. A clinical</p> <p>4 endpoint is a variable that directly measures</p> <p>5 therapeutic benefit that is how a patient feels,</p> <p>6 functions, and survives.</p> <p>7 Microbiologic outcomes are not</p> <p>8 considered as clinical endpoints. For non-inferiority</p> <p>9 trials, the primary endpoint should be sufficiently</p> <p>10 similar to historic trials that justify the</p> <p>11 non-inferiority margin. For instance, in febrile</p> <p>12 neutropenia, most historic trials demonstrated</p> <p>13 mortality advantage.</p> <p>14 Next slide.</p> <p>15 Delving into the primary endpoint</p> <p>16 considerations further, each option presents its own</p> <p>17 set of challenges. Potential endpoints of FN trials</p> <p>18 includes all-cause mortality, primary</p> <p>19 infection-related mortality, and clinical success.</p> <p>20 Each endpoint has its advantages and limitations.</p> <p>21 All-cause mortality endpoint is</p> <p>22 objective, reliably measurable, and unequivocally</p>



<p style="text-align: right;">Page 94</p> <p>1 relevant. The limitations of all-cause mortality is                  2 that mortality in FN may not be related to an                  3 infection. Also, patients who survived after                  4 modification of study therapy due to poor clinical                  5 response or adverse events may be considered success                  6 because they survived.                  7         Furthermore, decreasing mortality rates                  8 necessitates larger sample sizes to detect any                  9 potential improvement over standard of care. The                  10 endpoint of primary infection-related mortality more                  11 directly measures the efficacy of an antibacterial                  12 therapy.                  13         However, the challenge here lies in                  14 accurately determining the cause of death. Moreover,                  15 as compared to all-cause mortality, the use of this                  16 endpoint further lowers event rate resulting in an                  17 increase in trial sample size.                  18         So the endpoint of clinical success, on                  19 the other hand, includes other outcomes of interest                  20 such as resolution of fever, absence of recurrent                  21 febrile episodes, eradication of the infection, or                  22 discontinuation of study therapy due to adverse</p>	<p style="text-align: right;">Page 96</p> <p>1           This slide looks at the different                  2 outcomes used in FN trials. Most FN trials used a                  3 composite endpoint to evaluate the response to                  4 therapy. However, the definition and timing of the                  5 assessment of these endpoints vary leading to                  6 challenges in interpreting the trial results.                  7           Success was generally characterized by                  8 a combination of clinical and microbiologic criteria,                  9 primarily the resolution of the FN symptoms, and the                  10 eradication of infecting organism without modification                  11 of the initial treatment regimen. Failure was                  12 generally defined as death, persistence of symptoms or                  13 causative pathogens, or modification of study therapy.                  14           Patients with fungal or viral                  15 infections or non-infectious fever, protocol                  16 violations, study drug discontinuations due to adverse                  17 events, are classified as non-accessible for response                  18 and were excluded from the primary analysis in some                  19 trials. That poses additional challenges in                  20 interpreting the trial results.                  21           So, in general, a trial for regulatory                  22 approval purposes would be expected to use an ITT or a</p>
<p style="text-align: right;">Page 95</p> <p>1 reactions. However, it introduces variables that may                  2 be subjective or influenced by the external factors                  3 such as -- modified therapy.                  4         Blinding and other strategies such as                  5 establishment of objective criteria could be used for                  6 assessing treatment outcomes to address the observer                  7 bias.                  8         Now, let's examine the mortality rates                  9 observed in historic and recent trials.                  10         Next slide.                  11         The table here displays mortality rates                  12 observed in old and recent trials. The timing of the                  13 mortality assessment varied, but overall mortality                  14 rates in recent trials are lower as compared to                  15 historical trials.                  16         For instance, as you can see, the                  17 studies conducted by the International Antimicrobial                  18 Therapy Cooperative Group in 1987, had a mortality                  19 rate of 26 percent which gradually went down to                  20 8 percent by 2006. In more recent trials, mortality                  21 rate is down to as low as 2 percent.                  22         Next slide.</p>	<p style="text-align: right;">Page 97</p> <p>1 modified ITT for analyzing the trial data.                  2         Next slide.                  3         We are interested in discussing areas                  4 of unmet need in treatment of febrile neutropenia and                  5 would appreciate if the panel could comment on the                  6 need for novel outpatient therapies in febrile                  7 neutropenia.                  8         For instance, in the setting of                  9 prevalence of quinolone-resistant and ESBL-producing                  10 pathogens, clinicians might be reluctant to use                  11 currently recommended oral therapies for outpatient                  12 empiric use in FN patients.                  13         Could an oral drug with activity                  14 against drug-resistant pathogen a suitable option for                  15 developing an antibacterial drug for the outpatient                  16 management in febrile neutropenia?                  17         Next slide.                  18         So, in summary, a major goal of this                  19 workshop is to discuss the ideas in addressing                  20 challenges in designing FN trials. A major challenge                  21 impacting the feasibility of all trials and                  22 interpretability for an FN-NI trial is the</p>

<p style="text-align: right;">Page 98</p> <p>1 heterogeneity of the population of patients with FN,  2 and strategies to enrich the trial population with  3 bacterial infections are needed to overcome this  4 challenge.  5         With the decreasing mortality rate,  6 choosing a primary efficacy endpoint is also  7 challenging. While there is a greater flexibility for  8 superiority trial designs, clinical meaningfulness of  9 measured outcomes, strategies to address observer  10 bias, and an ITT or a modified ITT analytic approach  11 are important considerations.  12         Another goal of this workshop is to  13 understand unmet need in the treatment of febrile  14 neutropenia and discuss strategies to develop drug  15 products to address these needs.  16         That completes my presentation. Thank  17 you so much for your interest and attention.  18         DR. RUBIN: Thank you very much,  19 Dr. Kapoor.  20         This is Dan Rubin, and, again, I will  21 give the next talk on statistical considerations in  22 clinical trials in febrile neutropenia.</p>	<p style="text-align: right;">Page 100</p> <p>1 which all patients in both arms receive background  2 standard of care, but patients in the treatment arm  3 additionally receive the experimental drug.  4         If ethically acceptable, a superiority  5 trial could restrict the inclusion/exclusion criteria  6 or analysis population to patients in whom superiority  7 may be more achievable. An example could be patients  8 with greater certainty of bacterial infections due to  9 resistant pathogens.  10         The main challenge with superiority  11 trials relates to feasibility because it may be  12 difficult to enroll large numbers of patients for whom  13 a new experimental drug could greatly improve upon an  14 optimized standard of care control antibacterial  15 regimen in the comparator arm.  16         Next slide, please.  17         In a non-inferiority trial, the  18 objective is to determine whether the new drug is  19 unacceptably worse than the control according to some  20 margin. For instance, as shown in the figure at the  21 bottom of the slide, if the margin is 10 percent, then  22 the trial would need to provide statistical evidence</p>
<p style="text-align: right;">Page 99</p> <p>1         Next slide, please.  2         I will first discuss considerations  3 related to superiority trial. I will then discuss  4 non-inferiority trials and the problem of justifying a  5 non-inferiority margin for a febrile neutropenia  6 trial.  7         Next, I will describe the statistical  8 trade-offs involved in selecting the analysis  9 population primary endpoint and non-inferiority  10 margin. And finally, I will discuss sample size  11 considerations.  12         Next slide, please.  13         Suppose a sponsor plans to conduct a  14 randomized trial to evaluate an experimental  15 antibacterial drug by comparing it to a control  16 antibacterial drug. In a superiority trial, the  17 objective is to determine whether the new drug is  18 better than the control drug.  19         Next slide, please.  20         This could be a head-to-head comparison  21 between the experimental drug and control drug. A  22 superiority trial could also use an add-on design in</p>	<p style="text-align: right;">Page 101</p> <p>1 to rule out a difference in success rates between the  2 new drug and active control that is 10 percent or  3 larger in favor of the control drug.  4         Next slide, please.  5         So how should the non-inferiority  6 margin be selected? Well, the margin should not be  7 any larger than a value that is often called M1. This  8 is the difference in response rates between the active  9 control and hypothetical placebo.  10         The reason why the non-inferiority  11 margin should not be larger than M1 is because  12 otherwise demonstrating that the new drug is within M1  13 as the active control would not provide indirect  14 evidence that the new drug is actually better than  15 what could be achieved with a hypothetical placebo.  16         Ideally, M1 should be quantified by  17 meta-analyzing previous placebo-controlled trials of  18 the drug that will be used as the active comparator in  19 the prospective trial. And the hypothetical example  20 in this slide, the confidence limit from the  21 meta-analysis supports an M1 of 20 percent.  22         Next slide, please. Next slide,</p>

<p style="text-align: right;">Page 102</p> <p>1 please.</p> <p>2           Once quantifying the M1, two additional</p> <p>3 steps are often applied to reduce the margin to a</p> <p>4 value term M2, which is the non-inferiority margin</p> <p>5 that will be used in the prospective non-inferiority</p> <p>6 trial.</p> <p>7           The first step is that the value could</p> <p>8 be discounted based on subjective judgment if the</p> <p>9 setting of the historical data used to determine M1</p> <p>10 was different from the expected setting of the</p> <p>11 prospective non-inferiority trial.</p> <p>12           The second step is to reduce the</p> <p>13 margins that preserve a clinically acceptable fraction</p> <p>14 of the treatment effect to ensure that a new drug</p> <p>15 found to be non-inferior to an active control does not</p> <p>16 have clinically unacceptable efficacy compared to this</p> <p>17 control.</p> <p>18           For example, if the non-inferiority</p> <p>19 margin M2 is 10 percent, an efficacy decrement of 10</p> <p>20 percent or more would be clinically unacceptable.</p> <p>21           Next slide, please.</p> <p>22           The challenge we have encountered</p>	<p style="text-align: right;">Page 104</p> <p>1 within 72 hours of drawing a first positive blood</p> <p>2 culture. After instituting empiric treatment, the</p> <p>3 survival rate and a subsequent cohort increased to 69</p> <p>4 percent. Further, the rate of complete improvement</p> <p>5 increased to 62 percent.</p> <p>6           Another study published in the same</p> <p>7 year found that in cancer patients treated with</p> <p>8 Polymyxin, the survival rate within 10 days from the</p> <p>9 onset of septicemia was only 28 percent. After</p> <p>10 introducing empiric treatment with Carbenicillin, that</p> <p>11 survival rate increased to 81 percent.</p> <p>12           Further, the complete response in</p> <p>13 Pseudomonas aeruginosa bacteremia episodes increased</p> <p>14 to 71 percent.</p> <p>15           Next slide, please.</p> <p>16           Despite the small sample sizes, you can</p> <p>17 see from the -- circles in bold that if meta-analyzing</p> <p>18 the study, there is evidence that the difference in</p> <p>19 clinical response rates between empiric treatment with</p> <p>20 an active antibacterial drug and a hypothetical</p> <p>21 placebo would be at least 30 percent.</p> <p>22           However, when considering the</p>
<p style="text-align: right;">Page 103</p> <p>1 applying this framework to margin justification for</p> <p>2 febrile neutropenia trials is that we are not aware of</p> <p>3 any previous placebo-controlled randomized trials of</p> <p>4 antibacterial drugs.</p> <p>5           Nevertheless, there is evidence that</p> <p>6 empirical antibacterial therapy would have a very</p> <p>7 large treatment effect compared to a hypothetical</p> <p>8 placebo. However, the magnitude of the treatment</p> <p>9 effect over a hypothetical placebo may depend on the</p> <p>10 analysis, population, and endpoint.</p> <p>11           Next slide, please.</p> <p>12           The studies from shortly after the</p> <p>13 introduction of empirical antibacterial treatment</p> <p>14 provide evidence that effective antibacterial drugs</p> <p>15 would have a large effect on key outcomes compared to</p> <p>16 a hypothetical placebo.</p> <p>17           One study from 1971 found that in the</p> <p>18 year before use of empiric treatment with</p> <p>19 Carbenicillin and Gentamicin for leukemia patients,</p> <p>20 the survival rate for patients with Pseudomonas</p> <p>21 aeruginosa bloodstream infections was only 9 percent.</p> <p>22           Moreover, half of the deaths were</p>	<p style="text-align: right;">Page 105</p> <p>1 non-inferiority margin that would be used in a</p> <p>2 prospective trial to evaluate a new drug, this may</p> <p>3 need to be discounted to account for several</p> <p>4 limitations. These were non-randomized study. The</p> <p>5 studies were conducted in settings with different</p> <p>6 background standards of care than would be present</p> <p>7 today.</p> <p>8           And additionally, patients with</p> <p>9 Pseudomonas bacteremia had a higher certainty of</p> <p>10 lethal bacterial infections than many patients with</p> <p>11 fever of unexplained origin who might be enrolled in</p> <p>12 more asthmatic trials.</p> <p>13           Next slide, please.</p> <p>14           I will now discuss several trade-offs</p> <p>15 that should be considered when deciding upon the</p> <p>16 analysis population endpoint and non-inferiority</p> <p>17 margin.</p> <p>18           The trial will need to determine which</p> <p>19 categories of fever should be included in the primary</p> <p>20 analysis population among fevers of unexplained</p> <p>21 origin, clinically documented infections,</p> <p>22 microbiologically documented infections, and</p>

<p style="text-align: right;">Page 106</p> <p>1 bloodstream infections.</p> <p>2           As the analysis population becomes more</p> <p>3 restrictive to ensure bacterial infections, the trial</p> <p>4 likely becomes more sensitive for differentiating</p> <p>5 antibacterial drugs. And a non-inferiority trial, the</p> <p>6 margin justification would likely be on surer footing,</p> <p>7 but a drawback is that trial feasibility likely</p> <p>8 decreases.</p> <p>9           And in addition, it would become harder</p> <p>10 to generalize results to an all-comer target</p> <p>11 population.</p> <p>12           Next slide, please.</p> <p>13           There are also trade-offs when deciding</p> <p>14 upon the primary endpoint. Consider use of a</p> <p>15 composite endpoint defined by components such as</p> <p>16 all-cause mortality, development of serious medical</p> <p>17 complications, or failure to respond to empiric</p> <p>18 antibacterial therapy as defined by persistent fever,</p> <p>19 worsening of clinical signs of infection, or the need</p> <p>20 to escalate or change the antibacterial regimen due to</p> <p>21 lack of efficacy.</p> <p>22           As the endpoint becomes more</p>	<p style="text-align: right;">Page 108</p> <p>1 feasibility would become more challenging.</p> <p>2           Next slide, please.</p> <p>3           I will now discuss sample size</p> <p>4 consideration. The slide displays sample sizes for</p> <p>5 superiority trials. The calculations assume a</p> <p>6 standard statistical significance level, 90 percent</p> <p>7 power, and one-to-one randomization. The evaluability</p> <p>8 rate is the proportion of randomized subject expected</p> <p>9 to be included in the analysis.</p> <p>10           And this may depend on whether the</p> <p>11 trial uses an intent to treat population or is more</p> <p>12 restricted to ensure bacterial infections, such as</p> <p>13 excluding subjects without clinically or</p> <p>14 microbiologically documented infections.</p> <p>15           The table shows evaluability rates at</p> <p>16 100 percent, two-thirds, and one-third. The table</p> <p>17 also displays sample sizes assuming a success rate and</p> <p>18 the control arm of 65 percent, and success rates in</p> <p>19 the experimental arm that correspond to being 15</p> <p>20 percent better, 10 percent better, or 5 percent</p> <p>21 better.</p> <p>22           For instance, suppose the evaluability</p>
<p style="text-align: right;">Page 107</p> <p>1 restrictive to only include major events with the most</p> <p>2 extreme example being an all-cause mortality endpoint,</p> <p>3 then the endpoint may become more meaningful. The</p> <p>4 endpoint also likely would be defined more</p> <p>5 objectively.</p> <p>6           And a non-inferiority trial, the</p> <p>7 non-inferiority margin would likely be on surer</p> <p>8 footing because the historical data I described mostly</p> <p>9 related to survival. However, with an endpoint driven</p> <p>10 by mortality or serious complications, the study</p> <p>11 population may need to be enriched to ensure</p> <p>12 participants are at high risk for major events, and</p> <p>13 this would likely decrease trial feasibility.</p> <p>14           Next slide, please.</p> <p>15           Finally, in a non-inferiority trial,</p> <p>16 there are important statistical trade-offs when</p> <p>17 deciding upon the non-inferiority margin. As the</p> <p>18 margin is decreased, the trial reduces the potential</p> <p>19 efficacy decrements allowed for the new</p> <p>20 investigational drug.</p> <p>21           The margin justification would also</p> <p>22 likely be on surer footing. However, the trial</p>	<p style="text-align: right;">Page 109</p> <p>1 rate is 100 percent as might occur if the primary</p> <p>2 analysis population was an intent to treat population.</p> <p>3 If the treatment arm is 10 percent better than the</p> <p>4 control arm, so that success rates in the two arms are</p> <p>5 75 percent and 65 percent, then a total sample size of</p> <p>6 879 participants would be needed to power the trial or</p> <p>7 approximately 440 subjects per arm.</p> <p>8           The sample size increases if the</p> <p>9 evaluability rate is lower or if the treatment effect</p> <p>10 is smaller.</p> <p>11           Next slide, please.</p> <p>12           My final slide shows sample sizes for</p> <p>13 non-inferiority trials. The sample size calculations</p> <p>14 assume success rates for the primary endpoint are</p> <p>15 equal in the control arm and experimental arm.</p> <p>16           The table displays sample sizes for</p> <p>17 success rates of 70 percent, 65 percent, and 60</p> <p>18 percent. The table also shows sample sizes for</p> <p>19 margins of 15 percent, 12.5 percent, or 10 percent,</p> <p>20 assuming that there would be justifications for these</p> <p>21 margins for that trial population and endpoint</p> <p>22 definitions chosen.</p>

<p style="text-align: right;">Page 110</p> <p>1 You can see that, in general,  2 non-inferiority trials for febrile neutropenia may  3 require relatively large sample sizes. For instance,  4 suppose the evaluability rate is 100 percent, the  5 success rate in each arm is 70 percent, and the  6 non-inferiority margin is 10 percent.</p> <p>7 The table shows that the trial would  8 need a sample size of approximately 881 total subjects  9 or approximately 440 subjects per arm. The sample  10 size would increase if evaluability was lower, the  11 success rate was closer to 50 percent, or the  12 non-inferiority margin was decreased.</p> <p>13 Thank you very much.</p> <p>14 DR. BOTGROS: Thank you very much, Dan,  15 for this very nice presentation.</p> <p>16 And the next two presentations will be  17 actually from the EMA and the Japanese PMDA for which  18 there will be Katsuhiko Ichimaru, who is currently a  19 review director in the anti-infectives area at the  20 Pharmaceuticals and Medical Devices Agency in Japan.</p> <p>21 He works at the regulatory agency for  22 about 20 years and has extensive experiences in review</p>	<p style="text-align: right;">Page 112</p> <p>1 this was addressed previously by speakers. So I will  2 get to the regulatory side of it as we see it in the  3 European Union.</p> <p>4 Next slide, please.</p> <p>5 As in the United States, some of the  6 product information of what we call old antibiotics,  7 that is antibiotics that have been approved some of  8 them a long while ago, still retain the indication in  9 period treatment of febrile neutropenia.</p> <p>10 And you see here as a comparison, the  11 U.S. label and one of the labels for Cefepime in the  12 European Union, actually it's a Romanian one, and you  13 see that -- or you can trust me that actually the  14 indication is empiric therapy for febrile neutropenic  15 patients.</p> <p>16 Next slide, please.</p> <p>17 At the EMA, we have been conducting and  18 harmonizing product information of old antibiotics.  19 And around 10 years ago, it was agreed that granting  20 of the wording of the indication for an antibacterial  21 agent for febrile neutropenia was not supported any  22 longer.</p>
<p style="text-align: right;">Page 111</p> <p>1 in anti-infectives and psychology. But first, as per  2 the order of the slides, I will talk to you about the  3 regulatory considerations that we have in the European  4 Union about this indication.</p> <p>5 Next slide, please.</p> <p>6 As we heard today a number of times,  7 and I won't enter into details again, febrile  8 neutropenia is a coined entity and obviously is an  9 entity that, you know, needs and also benefits from  10 treatment or either preemptive treatment, prophylaxis,  11 or real treatment.</p> <p>12 You see here on the slide that the  13 infections, most of them are bacterial caused by both  14 gram-negatives and gram-positives, and we heard today  15 what is the balance between the two. Obviously, there  16 can be also other agents like fungal or viral, less  17 frequent.</p> <p>18 The next slide, please.</p> <p>19 And in any case, we heard that  20 mortality is much lower if the condition is treated  21 with -- is managed with antibiotics. Obviously, I  22 won't be telling you about, you know, what -- because</p>	<p style="text-align: right;">Page 113</p> <p>1 And our approval committee, the CHMP,  2 agreed to replace the outdated indication at the time  3 of harmonization to the product, so the antibiotic may  4 be used in the management of neutropenic patients with  5 fever that is suspected to be due to bacterial  6 infection.</p> <p>7 Obviously, this is more of a wording  8 change rather than anything else, and actually it has  9 been recognized that this condition needs to be  10 treated with antibiotics.</p> <p>11 What we also notice is that  12 prospectively we had an extremely limited number of  13 applications that were received in the European Union  14 and, therefore, any further meaningful discussion on  15 the design of clinical trials that would underpin such  16 an indication has not taken place.</p> <p>17 It was acknowledged, as I said, that  18 the institution of antibacterial agents prior to or at  19 the time of onset of expected neutropenia is common  20 practice. And in some patients population center, it  21 is done so that the rates through infections may be  22 comparatively low compared to other patient groups.</p>

<p style="text-align: right;">Page 114</p> <p>1 Next slide, please.</p> <p>2 The study population enrolled with</p> <p>3 acute bacterial infections during neutropenia</p> <p>4 comprises, as we heard before, some ratio of patients</p> <p>5 with breakthrough infections despite prophylaxis,</p> <p>6 patients who have not received routine prophylaxis.</p> <p>7 So you see there are at least these two</p> <p>8 subgroups which we believe may be substantially</p> <p>9 different in terms of their underlying conditions and</p> <p>10 are likely to be enrolled also at different centers</p> <p>11 with variable routine management protocols.</p> <p>12 So on this basis, at the very least,</p> <p>13 stratification according to prior or no prophylaxis</p> <p>14 may be appropriate. The protocol should also provide</p> <p>15 clear criteria to be met in terms of neutropenia, and</p> <p>16 so what is the cutoff value? What is the expected</p> <p>17 duration of the neutropenia?</p> <p>18 You saw that there are different risk</p> <p>19 categories and also neutropenia is, you know,</p> <p>20 undivided in a number of categories. Also, the</p> <p>21 definition of fever will require alignment across</p> <p>22 sites.</p>	<p style="text-align: right;">Page 116</p> <p>1 discussing all these in the panel discussion, but, you</p> <p>2 know, one may wonder if, for instance, for prophylaxis</p> <p>3 and for, you know, treatment of breakthrough</p> <p>4 infections, we need only to stratify or maybe we can</p> <p>5 think even about different endpoints.</p> <p>6 I'll stop here. I thank you very much.</p> <p>7 And I give the floor now to our colleague from Japan.</p> <p>8 Thank you.</p> <p>9 DR. ICHIMARU: Thank you for your kind</p> <p>10 introduction, Dr. Radu.</p> <p>11 I'm Katsuhiko Ichimaru, Review Director</p> <p>12 in Anti-Infectives Area, PMDA. Today, I would like</p> <p>13 to -- share review of therapeutic or febrile</p> <p>14 neutropenia, etcetera, with you.</p> <p>15 Next slide.</p> <p>16 At first, I will touch the definition</p> <p>17 of FN in Japan and recommended -- they were developed</p> <p>18 by Japanese Society of Medical Oncology. The latest</p> <p>19 version was published in 2024. The U.S. IDSA</p> <p>20 published FN Guideline in 1990 and revised in 1997.</p> <p>21 We find the IDSA Guideline -- Japanese</p> <p>22 FN Guideline was developed in 1998. Therefore, the</p>
<p style="text-align: right;">Page 115</p> <p>1 Next slide.</p> <p>2 So if the test agent needs to be</p> <p>3 co-administered due to its spectrum of activity, then</p> <p>4 the additional agents should be specified in the</p> <p>5 protocol, including the dose regimen and any dose</p> <p>6 adjustments. And if possible, the range of agents</p> <p>7 allowed should be standardized.</p> <p>8 But there should be clear criteria for</p> <p>9 stopping therapy in the trial protocol pertaining to</p> <p>10 susceptibility data, clinical progress, cultural</p> <p>11 results, recovery of the granulocyte count at the very</p> <p>12 least, and also the criteria for failure need to be</p> <p>13 specified.</p> <p>14 Next slide.</p> <p>15 To agree on the key elements of any</p> <p>16 clinical trial which would underpin this indication,</p> <p>17 we highly recommend you to come to the EMA to discuss</p> <p>18 with us these during development. We have a number of</p> <p>19 processes and procedures that we offer to developers.</p> <p>20 I think the most important of which scientific advice</p> <p>21 and the innovation task force discussions.</p> <p>22 And, you know, we will definitely be</p>	<p style="text-align: right;">Page 117</p> <p>1 Japanese definition of FN is very similar with the</p> <p>2 U.S. one. However, body temperature is usually</p> <p>3 measured in the armpit in Japan. Actually,</p> <p>4 temperature is approximately 0.5 degrees lower than</p> <p>5 oral temperature.</p> <p>6 In Japanese Guideline, the criteria is</p> <p>7 written in both measurement sites. Neutrophil count</p> <p>8 is same with IDSA definition. Bottom lines are</p> <p>9 recommended empiric therapy in Japan. The upper line</p> <p>10 is approved antibiotics for FN in Japan. Bottom line</p> <p>11 is recommended antibiotics but not approved for FN in</p> <p>12 Japan. These recommended antibiotics are also similar</p> <p>13 with U.S., I think.</p> <p>14 Next slide.</p> <p>15 This slide shows approved</p> <p>16 anti-infectives for FN in Japan. Two antifungals and</p> <p>17 four microbials agents were approved. Right front are</p> <p>18 dosage for adult and pediatric of each drugs. I will</p> <p>19 share the data on which these are depicted and</p> <p>20 obtained regulatory approval in the next slides.</p> <p>21 Next slide.</p> <p>22 The first drug is Cefepime. It is the</p>

<p style="text-align: right;">Page 118</p> <p>1 first antimicrobial agent approved for FN in Japan.  2 And that product was approved in 1995 as a new active  3 ingredient. FN was additionally approved in 2004.  4 When the product is approved for FN in Japan, it has  5 been already approved for FN in U.S., Sweden, and  6 Germany.  7 In Japan, the product was prescribed to  8 FN patient as off-label use before regulatory  9 approval. Such data was published as scientific  10 articles. Such off-label use, the data, and the  11 clinical trial data which were submitted to U.S. FDA  12 to obtain regulatory approval were utilized for  13 regulatory approval in Japan.  14 Because Japan has a unique regulatory  15 system that the administration of the drug or the  16 indication is medically and pharmaceutically known,  17 and the drug's indication is approved in a country  18 with the same regulatory levels as Japan.  19 If these two conditions are met, the  20 company can skip to conduct clinical trials to obtain  21 regulatory approval. It means that the company can  22 obtain an additional indication based on existing</p>	<p style="text-align: right;">Page 120</p> <p>1 approval in Japan. This is a summary of my talk. In  2 some cases, the definition is different region by  3 region. However, the definition of FN is the same  4 between U.S. and Japan. Foreign data was utilized to  5 obtain regulatory approval. So far, foreign data was  6 utilized as kind of a separation.  7 However, it means possibility of  8 multi-regional clinical trial. MRCT is one of the  9 useful tools to obtain regulatory approval for FN. I  10 wish that MRCT can be used efficiency obtain approval.  11 Thank you.  12 DR. RUBIN: Thank you very much to all  13 of the session two speakers. We will now break for  14 ten minutes and then return for a moderated panel  15 discussion at 11:26.  16 (Off the record.)  17 DR. TAPLITZ: Hello. It's 11:26, so I  18 think we'll go ahead and get restarted on the panel  19 discussion. I have met you earlier. I'm Randy  20 Taplitz from City of Hope National Medical Center  21 joined by my co-moderator, Dmitry Iarikov, and by this  22 august group of panelists whose affiliations you can</p>
<p style="text-align: right;">Page 119</p> <p>1 data. By utilizing the system, Cefepime obtained FN  2 indication in Japan.  3 Next slide.  4 Next case is Meropenem. The  5 antimicrobial agent was approved as a new active  6 ingredient in 1995 in Japan. FN is approved as new  7 indication in 2009. The data package is described  8 here. Phase 1 and the Phase 3 trials were conducted  9 in Japan. For pediatric indication, PK/PD analysis  10 was utilized.  11 Next slide.  12 This slide shows clinical data package  13 for other products. You can see most of the products  14 utilized for clinical trial data to obtain regulatory  15 approval in Japan. In addition to the following data,  16 small scale of clinical trials were conducted to  17 confirm the similarities in effectiveness between  18 overseas and the Japanese.  19 Regarding the Vancomycin, FN indication  20 was approved based on published scientific articles.  21 Next slide.  22 So far, I shared Japanese -- of FN</p>	<p style="text-align: right;">Page 121</p> <p>1 see listed on this slide.  2 So in order to kick off this  3 discussion, what we will do is, you know, read the  4 questions and ask for certain individuals to sort of  5 start a response, and then what we'll do is, we'll  6 take comments from the panelists group. We would  7 appreciate if you could raise your virtual hands, and  8 we will call on you in turn from the panelists group.  9 Also, I know that we have, well, I saw  10 it previously one question in the Q&amp;A. But I think if  11 there are questions that you specifically would like  12 answered, please put them in the Q&amp;A, and we can take  13 a look at those as well.  14 So without further ado, why don't we  15 move to the first -- the next slide which has the  16 discussion questions. So the first question is  17 "Please discuss the greatest unmet needs for empiric  18 treatment of febrile neutropenia," and "comment on an  19 ideal drug profile."  20 And to start us off, we thought we  21 would ask Dr. Zimmer to make some comments on this.  22 DR. ZIMMER: Thank you, Dr. Taplitz.</p>

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<p>1 Well, to start off with, an ideal drug 2 for empirical treatment of febrile neutropenia would 3 have to be broad-spectrum in nature. It would need to 4 include coverage against particularly 5 Enterobacteriales, Pseudomonas. 6 Ideally, those with different resistant 7 mechanisms, ESBLs and Carbapenem resistance, to be 8 able to most adequately treat these infections in the 9 age of increasing antimicrobial resistance. We would 10 also want it to have excellent coverage against 11 gram-positive organisms, particularly the sensitive 12 streptococcus and staphylococcus. 13 And then as alluded to in earlier 14 talks, it would be very ideal if this agent -- if we 15 had options to, apart from the oral Fluoroquinolones, 16 to use for outpatient therapy either a novel oral 17 antibiotic or a long-acting intravenous antibiotic 18 that could be amenable to be arranged for outpatient 19 transition, either to avoid admission to the hospital 20 or to enable patients to be discharged early once 21 they're clinically stable and improving. 22 And then, of course, we would want the</p>	<p>1 reading -- while watching the presentations today, is 2 that we have shifted somehow in our way of approaching 3 the problem because with the definition of the ideal 4 drug, why isn't Imipenem-relebactam the ideal drug as 5 Dr. Zimmer just described? 6 It got great coverage against resistant 7 organism, including resistant Pseudomonas, resistant 8 Enterobacteriales, gram-positives. We don't need to do 9 anything else; right? And the reason is that we now 10 are more aware of the consequences for other patients 11 of using drugs with too broad of a spectrum. That 12 consideration wasn't there; right? 13 Originally, when the first big paradigm 14 shift was empirical treatment against Pseudomonas, no 15 one was saying, "Well, but most people don't have 16 Pseudomonas." No one said, "You're overtreating a lot 17 of people who don't need this antibiotic." 18 Everybody said, "Yeah, we have a drug 19 that covers the most dangerous things, and so we'll 20 give it to everybody." And that is the way we are in 21 the current standard of care that we are on. 22 And so the question about the unmet</p>
<p>1 agent to be well-tolerated from a side-effect profile. 2 One of the questions that has come up sometimes in the 3 management of febrile neutropenia, particularly with 4 Cefepime use, is the risk of neurotoxicity or 5 neuro-side effects with Cefepime. 6 And so if I'm picking my wish list, I 7 also want it to be well-tolerated with minimal side 8 effects. 9 DR. TAPLITZ: Great, thank you. 10 Other comments from the panelists? 11 Okay. Juan, and please introduce 12 yourself if you haven't already been a speaker here 13 today. 14 DR. GEA-BANACLOCHE: Yeah. My name is 15 Juan Gea-Banacloche. I work in the infectious 16 diseases consult service at the NIA Clinical Center, 17 and which probably contributes to my biases because 18 this is the place where cytotoxicity monotherapy was 19 introduced 40 years ago or so, and we, interestingly 20 enough, keep doing the same thing that Dr. Pitchell 21 [ph] was doing back then. 22 So one thing that came to mind while</p>	<p>1 need in the neutropenia is really the key question. 2 What is the problem that we need to solve? Is the 3 problem that many patients are dying of resistant 4 gram-negative rods? 5 Because if that is the problem, then 6 the solution is we either identify the patients who 7 need empirical treatment against those better, or we 8 give empirical treatment against those MDR 9 gram -- rods drugs to everybody. 10 But maybe that is not the problem. And 11 I think that that is the problem that too many 12 patients are getting exposed to too many antibiotics 13 for too long because then the solution for that 14 problem is a different kind of trial. We need to know 15 how to de-escalate. And so I think that that is what 16 we need to define. 17 What is the problem in the empirical 18 management of febrile neutropenia that we need to fix? 19 What is harming our patients, or what is harming our 20 non-patients, future patients, our hospitals in terms 21 of resistance? And I think that until we nail that 22 down, it's very difficult to get anywhere.</p>



<p style="text-align: right;">Page 126</p> <p>1 DR. TAPLITZ: Okay. So basically what 2 you're saying is that we maybe need to nuance and 3 define what the questions we need answered are, and 4 it's not necessarily going to be go broad or go home. 5 DR. GEA-BANACLOCHE: Exactly. 6 DR. TAPLITZ: Dr. Liu from -- well, you 7 can introduce yourself, Doctor. 8 DR. LIU: Good morning, everyone. My 9 name is Catherine Liu from the Fred Hutchinson Cancer 10 Center. So I fully agree with the comments that were 11 just made. I do think in terms of unmet need, we need 12 to address the growing threat of antimicrobial 13 resistance. 14 But in that context really thinking 15 about how we can move from a one-size-fits-all empiric 16 approach to management of neutropenia fever, which I 17 think is what we're, you know, kind of what we're 18 doing right now, but can we move towards a more 19 tailored approach to empiric therapy? 20 Really identifying those patients who 21 are at risk for MDROs, who are at risk for 22 colonization with ESBLs and CREs, so that we can</p>	<p style="text-align: right;">Page 128</p> <p>1 older people here, we have to remind ourselves that 2 fever neutropenia was classified as an indication for 3 antibiotic therapy based on these observations, right, 4 in the 1970s. 5 And what have we done in the last 6 50-plus years? We have incrementally decreased the 7 risks that fever during neutropenia actually is an 8 indicator or a reliable indicator for a bacterial 9 infection. 10 And that's what we've done by choosing 11 the hosts, our treatments even, when we use the broad 12 categories of -- B&amp;T, we now know that -- and we're 13 using drugs that are really minimizing that duration 14 and depth of risk. So we have to start thinking about 15 fever during neutropenia as exactly what it is. It's 16 a symptom. It's not a syndrome. 17 And then get to the place, in my 18 opinion, where we define what the syndrome is, and we 19 can do that iteratively with our multiple different 20 kinds of diagnostics. There's limitations of 21 diagnostics here too because the prevalence of 22 infection is so exceedingly low.</p>
<p style="text-align: right;">Page 127</p> <p>1 provide a more nuanced approach to empiric therapy. 2 And I think, you know, to some degree, we are doing 3 this on a pragmatic level. We are sort of identifying 4 patients in the clinical setting whom we think may 5 need something other than Cefepime for empiric 6 therapy. 7 But how do we study this in a 8 randomized control trial? Can we take a more 9 pragmatic design where patients might be risk stratified 10 based on their, you know, risk of colonization? Can 11 we screen folks to identify those who might be at risk 12 for these MDROs to provide a more targeted approach 13 with some of these broader spectrum agents? 14 DR. TAPLITZ: Dr. Marr? 15 DR. MARR: Hey, good morning, everyone. 16 Kieren Marr here. I'm a retired prior director of 17 Transplant and Oncology ID at Johns Hopkins and now 18 currently affiliated with Elion Therapeutics, an 19 antifungal company. 20 I want to build on the comments by my 21 prior colleagues, and I agree with them completely, 22 but just kind of to go back. As probably one of the</p>	<p style="text-align: right;">Page 129</p> <p>1 So, you know, it becomes very complex 2 trial design. But in my opinion, the first thing we 3 need to do is to acknowledge that this is a symptom. 4 It's not a syndrome as it may have been 50 years ago. 5 And that puts it in a very different context for 6 studying and whether that becomes a feasible 7 indication from my point of view. 8 I'll stop there for now. 9 DR. TAPLITZ: Kieren, how would you 10 define a syndrome that needs to be -- 11 DR. MARR: So what do we do? I mean, 12 we've -- we're all on these guidelines, right? You've 13 got fever during neutropenia, you do a CT scan, blood 14 cultures. You do the standard diagnostics, the 15 physical exam. Clinically, we kind of understand or 16 have in our minds an understanding of where that 17 infection is likely to be coming from. 18 If that person has a nondescript, 19 infiltrate, nodule, etcetera, we think it's maybe an 20 early pulmonary infection. Or if they don't, maybe we 21 think that it's kind of an early sepsis, especially 22 with the GI source. We can iteratively then say this</p>

<p style="text-align: right;">Page 130</p> <p>1 is a presumed bacterial infection from the lung or  2 presumed bacterial infection from the gut.  3 I tend towards kind of taking the  4 approach now that our European regulators are kind of  5 inching towards, and that fever during neutropenia  6 itself needs to be kind of further defined in a  7 syndromic fashion, both so that we can understand what  8 drugs would be most important, and so that we can  9 design a trial where there's a prevalence estimate for  10 outcomes that will enable the feasibility of a trial  11 design.  12 DR. TAPLITZ: So I think there's a  13 question in the Q/A which I'm going to read and ask  14 for comments on. An anonymous attendee is asking to  15 comment on the potential role of non-small molecule  16 products such as phage or antibodies for febrile  17 neutropenia, and what consideration should be  18 considered in developing such products?  19 Anybody want to make a comment?  20 DR. BOTGROS: Yeah, maybe I can start.  21 I mean, phages, talking about phages,  22 so alternatives to antibiotics. I think the current</p>	<p style="text-align: right;">Page 132</p> <p>1 Union and some Eastern European countries.  2 So while I cannot exclude that they may  3 play a role in the future, I think we first need to  4 have the proof of concept that would reassure us that  5 this kind of products really do work and do provide  6 added value to the antibiotic treatment.  7 Thank you.  8 DR. TAPLITZ: Yeah. I mean, I will  9 make a comment and then Andrea also.  10 So I do think that there will be work  11 on phage therapy in the future. I know that there's  12 some work looking at it for even for sort of  13 preventive therapy for, you know, patients colonized  14 with multidrug-resistant organisms, etcetera. But I  15 agree, I'm not sure that it's necessarily ready for  16 primetime.  17 Andrea, did you want to make a comment?  18 DR. ZIMMER: I was going to say the  19 same thing, Dr. Taplitz, and add on to, I think this  20 kind of crosses that border of, you know, targeted  21 therapy versus empirical therapy. And so phage  22 therapy most commonly has been utilized when there's</p>
<p style="text-align: right;">Page 131</p> <p>1 picture is that actually phages, even for standard  2 indications as add-ons to antibiotics, have not yet  3 shown efficacy from, you know, well-controlled  4 randomized clinical trials.  5 Actually, the trials that have been  6 conducted have rendered negative results due to a  7 number of issues from stability issues of  8 manufacturing and stability and sort -- in this kind  9 of -- but also, due to, you know, to the fact that  10 what has been studied was most of the time a cocktail,  11 which from the very beginning was not active for all  12 the strains on the infection.  13 So when it comes to phages, while  14 obviously if they do work, because I think safety is a  15 bit less of an issue with phages. It's, you know, it  16 could depend on the way they are administered and for  17 what indication, but most of the time they are deemed  18 to be fairly safe.  19 While, again, on efficacy what we have,  20 to the best of my knowledge, are anecdotal evidence  21 like, you know, case reports. We know that, you know,  22 they have been used in the former space of the Soviet</p>	<p style="text-align: right;">Page 133</p> <p>1 an identified organism with a specific profile and  2 susceptibility, you know, genetic profile.  3 Once that is a known organism either  4 colonized previously and concerned to be, you know,  5 causing reinfection or identified from a clinical  6 isolate, that's when the phage therapy kind of comes  7 into play.  8 When we're talking about empirical  9 therapy of febrile neutropenia, we're sort of starting  10 from that patient that is presenting in the ER or in  11 clinic day one. And you don't know if they're going  12 to have a bacteremia or if they're going to have, you  13 know, develop a positive culture. You just have the  14 data on, you know, the exam and the radiographic  15 findings that you're working with that day.  16 Once we're changing therapy, once we  17 have identified, you know, a source or a culprit  18 organism, then we kind of move into a different  19 category of treating a known infection or process.  20 DR. TAPLITZ: So we have another  21 question that I actually think fits better into  22 question number two. So is there any further comments</p>

<p style="text-align: right;">Page 134</p> <p>1 on unmet needs from empiric treatment of febrile  2 neutropenia from the group?  3           If not, then maybe what we'll do is  4 move to the second question which is "Discuss  5 strategies for enrichment of the study population in  6 patients most likely to have a bacterial etiology for  7 their fever (e.g., clinical characteristics,  8 diagnostics, etc.)."  9           And I'd like to call on Dr. Hanson  10 first for her comments.  11           DR. HANSON: Yeah, sure. Thanks,  12 Dr. Taplitz.  13           So I'm interested in thoughts of the  14 panelists on this as well. When I've reviewed the  15 literature on this, there actually have been a number  16 of studies that have looked at risk prediction models  17 trying to look at an individual patient and assess  18 what's the likelihood that this person with  19 neutropenia fever actually has an invasive bacterial  20 infection.  21           Most of those models have been  22 validated in pediatric patients actually, and I</p>	<p style="text-align: right;">Page 136</p> <p>1 those in various models have been more suggestive of  2 bacterial infection, but pro-calcitonin is a little  3 more controversial. Some studies suggest it's  4 suggestive, others not.  5           But many analysts have said that  6 elevated levels may be more suggestive of the presence  7 of a bacterial infection. Elevated lactate, another  8 marker. So again, thinking about enrollment in  9 clinical trials, wanting to potentially stratify for  10 some of these findings like hypotension and lactate as  11 markers of people who are more severely ill and making  12 sure arms are balanced.  13           And then the last thing I mentioned  14 during my talk is assessments of the microbiome and  15 how it's perturbed or is the patient known to be  16 colonized with multidrug-resistant organisms, either  17 in the gut or have a prior infection with a  18 drug-resistant pathogen, might allow you then to  19 identify individuals who are more at risk and more  20 likely to have a bacterial infection as the cause of  21 their fever.  22           Maybe I'll pause there, as some of the</p>
<p style="text-align: right;">Page 135</p> <p>1 haven't seen as much work done on the adult side. But  2 the risk models tend to factor in a variety of things.  3 Host factors like what is the underlying malignancy  4 with heme malignancies, especially leukemia is being  5 at higher risk, and relapsed leukemia is being at  6 higher risk.  7           Clinical science and symptoms. So how  8 high is the fever? Is the patient hypotensive?  9 Hypotension is another one that tends to fall out in  10 various models as being predictive of an invasive  11 bacterial infection.  12           Also, certain findings on physical  13 exam. Like, skin findings that are suggestive of  14 cellulitis, for instance, is one that tends to  15 potentially be more predictive of bacterial infection.  16 And then this whole question about diagnostics and how  17 might diagnostics help us.  18           In my talk, I really focused on  19 pathogen directed tests, but there are a number of  20 studies looking at host directed tests. Markers of  21 inflammation that are non-specific. For instance,  22 C-reactive protein, pro-calcitonin, elevations of</p>	<p style="text-align: right;">Page 137</p> <p>1 things that have fallen out in models, especially for  2 kids that are suggestive and see what others think.  3           Thanks.  4           DR. TAPLITZ: I might actually since  5 I'm a moderator, I get to ask a question first before  6 going to some of the other questions, but what about  7 other biomarkers? So if using proteomics, I mean, I  8 think, you know, as you kind of commented, it's not  9 all about the pathogen. It's about the response to  10 the pathogen.  11           DR. HANSON: Yeah.  12           DR. TAPLITZ: I just wondered if you  13 had any comments on --  14           DR. HANSON: You know, I'll mention a  15 couple of --  16           DR. TAPLITZ: -- future technologies,  17 genomics, proteomics, etcetera, in order --  18           DR. HANSON: Yeah.  19           DR. TAPLITZ: -- to have biomarkers to  20 look at that.  21           DR. HANSON: I think in the future a  22 number of things are being looked at. One is</p>

<p style="text-align: right;">Page 138</p> <p>1 different cytokine profiles potentially. IL-10  2 falling out in models being more predictive. And then  3 this whole kind of era of the genetic host response.  4 So immune response profiles that may be more  5 suggestive of, is this fever due to an infection or  6 not?  7       If it's infection, is it bacterial  8 versus viral versus fungal? A lot of that work is  9 being done mostly in immunocompetent patients with  10 neutrophils because they're looking at the signals in  11 the gene expression profiling in neutrophils. So in a  12 neutropenic patient that might not be as predictive or  13 useful.  14       However, there's some newer work  15 looking at gene expression profiling in plasma that  16 may be totally separate from the neutrophil response  17 that will be interesting to see down the road. Is  18 this predictive for immunocompromised patients?  19       So I think, yeah, the wave of the  20 future for me in terms of diagnostics is some  21 combination of pathogen directed testing and host  22 stress directed testing to say responding to an</p>	<p style="text-align: right;">Page 140</p> <p>1       So this brings us to the issue of how  2 do we identify those patients who are at greatest risk  3 from FN and make sure that they're not being missed  4 and potentially could be enriched in the studies of  5 new drugs or even some of the old drugs.  6       And things I'm thinking of are  7 particularly things like age, older age, or  8 comorbidities. And I can't overemphasize enough how  9 important major comorbidities are, such as diabetes,  10 cardiopulmonary disease, cardiovascular disease, and  11 so forth. And, of course, patients with overt sepsis  12 and tissue invasion with infection, so, and  13 unfortunately, there are exceptions.  14       Many of these factors often become the  15 exclusion factors we've used in the prospective  16 studies. So what we need, it's challenging, but we  17 need more pragmatic approach to the -- not only the  18 inclusion but the exclusion criteria and make sure  19 that the patients we're excluding aren't the ones who  20 are most likely to benefit from the therapies that  21 we're testing.  22       So I think there are opportunities</p>
<p style="text-align: right;">Page 139</p> <p>1 infection or not. If so, what's the broad category  2 and can we be more targeted in our empiric approaches?  3       Thanks for that.  4       DR. TAPLITZ: Yes, thank you.  5       Dr. Lyman?  6       DR. LYMAN: Yes, thanks. Dr. Hanson  7 already touched on this, but clearly we're victims of  8 our own success here in the sense that with better  9 drugs, better supportive care, better preventive  10 measures, there's a need to, as this question has  11 highlighted, to identify enriched population for  12 trials moving forward.  13       And here, again, we run into a dilemma.  14 There are distinctions. You know, the models that we  15 have and that we've mentioned during this program,  16 have their limitations. And, in fact, the test  17 performance is not terribly good with any of them.  18       And we've distinguished factors that  19 enriched for the risk of FN which appears to have gone  20 down, but also for the serious medical complications  21 and potential mortality from FN which is still real.  22 Patients are still dying, as we know, from FN.</p>	<p style="text-align: right;">Page 141</p> <p>1 here, better risk models, as Dr. Hanson said, I think  2 are really needed. But we know enough that I think we  3 can find ways to better enrich the eligibility for  4 these trials.  5       DR. TAPLITZ: Yes. Thank you.  6       Yeah. So, you know, again, not  7 necessarily excluding the better risk stratification  8 in the inclusion group, maybe a larger inclusion  9 group. And I think we'll probably talk a little bit  10 more about that in trial design as well.  11       Kieren?  12       DR. MARR: Yeah. Great conversation,  13 great questions. You know, all of our risk  14 stratifications have, in my opinion, been too high up  15 to the things that we can identify that we don't  16 really understand. They have not been validated as  17 Dr. Hanson points out.  18       And really what we need in order to  19 really deploy these risk strategies is to identify the  20 population that with fever would have a pre-test  21 probability of bacterial infection that exceeds 30  22 percent.</p>

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<p>1 And the reason that I'm bringing up</p> <p>2 that number is straight up Bayesian statistics, which</p> <p>3 is you cannot have a reliable positive predictive</p> <p>4 value of any diagnostic or any symptom or any risk</p> <p>5 criteria with a prevalence or pre-test probability</p> <p>6 that is less than 30 percent.</p> <p>7 And what we can know is that we can</p> <p>8 deploy all of these diagnostics and with the risks</p> <p>9 that we're currently in the zero to 10 percent, 20</p> <p>10 percent is our high-risk category right now. With</p> <p>11 that, we can rely on negative predictive values and</p> <p>12 not positive predictive values just because of that</p> <p>13 driver alone.</p> <p>14 And so I think this is the absolute</p> <p>15 bottom line on the problem of fever during neutropenia</p> <p>16 trials. You can be fever, and all clinicians on this</p> <p>17 call can and will honestly say that we can pick out of</p> <p>18 a group of ten people with fever neutropenia, the two</p> <p>19 people who are likely to have it based on things that</p> <p>20 are not going to register necessarily in our</p> <p>21 inclusion/exclusion criteria.</p> <p>22 And the flip side, which are all of</p>	<p>1 DR. TAPLITZ: Juan?</p> <p>2 DR. GEA-BANACLOCHE: Yeah. So one</p> <p>3 thing that I want to mention, I put it on the chat.</p> <p>4 But I think that the data on cell-free DNA suggests</p> <p>5 that most cases of fever during neutropenia reflect</p> <p>6 either active or impending bacterial infection.</p> <p>7 And so I don't know that we're ever</p> <p>8 going to be out of the first empirical dose of</p> <p>9 antibiotic. So no matter what, the first dose of</p> <p>10 antibiotic, the patient comes with neutropenic fever,</p> <p>11 there's no way I'm going to not give them antibiotics.</p> <p>12 And so I think that the way the thing</p> <p>13 will evolve is, how early can I de-escalate? How</p> <p>14 early can I stop my antibiotic? And I think that that</p> <p>15 may be a path forward because if we have changed from</p> <p>16 the old paradigm of, you know, keep the antibiotic</p> <p>17 until the neutropenia resolves and the fever resolves,</p> <p>18 which would be 14 days of Ceftazidime, and now you</p> <p>19 say, "Well, maybe now it's three days of</p> <p>20 Ceftazidime-lactam."</p> <p>21 You know, I think that something like</p> <p>22 that may be helpful, because you say, you come, I get</p>
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<p>1 those predictors of, you know, when those neutrophils</p> <p>2 are going to come back. And one of the other issues</p> <p>3 that we should be hitting home, is that these criteria</p> <p>4 also impact overall mortality more so than the</p> <p>5 infection does. Relapse malignancy, the outcome of</p> <p>6 death, you just can't include those people in a trial,</p> <p>7 whether there's a documented infection or not because</p> <p>8 that's the driver.</p> <p>9 So, with all of this said, there are</p> <p>10 some important new ways that people are approaching</p> <p>11 that. I'll just draw out the work of Carol</p> <p>12 Garcia-Vidal in Barcelona, where she's using machine</p> <p>13 learning models to validate actual risks in the</p> <p>14 setting of fever during neutropenia.</p> <p>15 And probably, in my opinion, it's going</p> <p>16 to take a lot more data and a lot of that kind of</p> <p>17 analytic approach to actually derive a population or</p> <p>18 agreement where there's a studiable population that we</p> <p>19 can identify and to try and simulate what, as</p> <p>20 clinicians, have been looking at and labeling as high</p> <p>21 risk, low risk, because our current risk strategies</p> <p>22 aren't adequate in my opinion.</p>	<p>1 the carrier test, the carrier's test is back in 50</p> <p>2 hours. So after three days, the patient is in</p> <p>3 febrile, there's no evidence of bacterial DNA in the</p> <p>4 blood, I stop my antibiotic and watch.</p> <p>5 And overall, I am doing a service to my</p> <p>6 patient because I'm not undertreating him, and I'm</p> <p>7 being a service to the world because I'm not overusing</p> <p>8 antibiotics and creating resistance. I think that is</p> <p>9 a potential strategy to be explored. I don't know</p> <p>10 that is the thing, and that is not what I'm doing.</p> <p>11 What I'm doing is, I'm screening all</p> <p>12 the patients to look for ESBLs and so on, but I don't</p> <p>13 know how good my screening is. You know, but the idea</p> <p>14 that I'm going to, at some point, say, "Oh, I know</p> <p>15 that you don't have a bacterial infection." I don't</p> <p>16 know that is going to be reliable enough -- that any</p> <p>17 prediction model is going to be reliable enough for me</p> <p>18 to say that.</p> <p>19 DR. TAPLITZ: But you're talking about</p> <p>20 the concept of using the negative predictive value of</p> <p>21 certain cell-free DNA type tests in order to</p> <p>22 de-escalate and use shorter-term antibiotics.</p>

<p style="text-align: right;">Page 146</p> <p>1 I see a lot of head nods for the 2 concept here, so definitely something worth 3 considering. Although, as you say, I'm not sure that 4 anyone is using it in clinical practice, and nor 5 should they without it being studied. 6 Yeah, Andrea, you had a comment? 7 DR. ZIMMER: I was just going to tag on 8 to the last comment, is when can I stop antibiotics, 9 and then when can I send the patient home from the 10 hospital? When do I feel comfortable that they can go 11 out into the world and they're not going to come back 12 worse off than they were when they came in? Because 13 that's, I think, a big question among our oncology 14 colleagues too. 15 DR. TAPLITZ: Absolutely. 16 Kim, you had a comment? 17 DR. HANSON: Yeah. Just as it relates 18 to de-escalation. I mean de-escalating potentially 19 back to prophylaxis versus de-escalating from a broad 20 empiric therapy to a more targeted therapy to complete 21 a course of treatment. I think an unmet diagnostic 22 need for the latter, though, is more rapid detection</p>	<p style="text-align: right;">Page 148</p> <p>1 regards to probabilities. 2 But this isn't really what most 3 commercial entities are going to be interested in with 4 regards to developing a drug; right? Yeah. That's 5 all I wanted to say. That's a real clinically 6 relevant algorithm. 7 But, you know, you've got to then ask 8 the question of it. This is our answer, is it 9 feasible to be developing a drug for fever during 10 neutropenia? So I'm going to go back to that. 11 DR. TAPLITZ: Catherine? 12 DR. LIU: This has all been a great 13 discussion. And I just wanted to go back to sort of 14 this question about enriching patients who are more 15 likely to have a bacterial etiology as we think about 16 outpatient, sort of, oral antibiotics, particularly 17 for those low-risk patients or, perhaps in the context 18 as was presented from BARDA, of a nuclear detonation 19 event. 20 If we think about developing oral 21 antibiotics, identifying those patients who are more 22 likely -- or more likely to have bacterial etiologies</p>
<p style="text-align: right;">Page 147</p> <p>1 of antimicrobial resistance. 2 So right now, cell-free DNA, they're 3 little pieces, and they may not, depending on how deep 4 the sequencing is or how much of the genome is 5 covered, give you information about antimicrobial 6 resistance. 7 So additional diagnostic studies kind 8 of linking the genotype to the phenotype and looking 9 for platforms that can give us more in terms of, you 10 know, targeted treatment for individuals who do need 11 to continue a course of therapy for neutropenic fever. 12 So I wanted to make a plug for that. 13 DR. TAPLITZ: Yeah. And those 14 platforms are actively being developed; right? 15 DR. HANSON: Yes. 16 DR. TAPLITZ: Yes. 17 Kieren? 18 DR. MARR: I agree with all of this. 19 And I just want to say out loud, though, that, you 20 know, de-escalating is absolutely essential and 21 probably more statistically valid in an approach for 22 all of the reasons that we're pointing out with</p>	<p style="text-align: right;">Page 149</p> <p>1 may be more challenging in these lower risk 2 populations. So how do we sort of enrich for this in 3 a lower risk population that may be less likely to 4 have microbiologic diagnoses? 5 This is really sort of, I think, a 6 question, you know, do we have studies for these lower 7 risk patients as far as bacterial etiologies? How can 8 we enrich for those folks? These are low risk 9 patients with -- who are younger, who have less 10 comorbidities, less exposure to health care. 11 And so that, I guess, if we're trying 12 to develop an oral antibiotic option for outpatient 13 management, I think it's maybe a challenge at least to 14 get sort of a group that has microbiologic 15 confirmation of infection. 16 DR. TAPLITZ: I think I'm going to 17 move -- we have a couple of questions. Number one, if 18 anybody would like to answer, what about Citrulline as 19 a biomarker for GI epithelial? Anybody have 20 experience or want to comment on the use of Citrulline 21 as a biomarker? 22 Yeah. Yeah. I'm not sure we have any</p>

<p style="text-align: right;">Page 150</p> <p>1 takers here. I don't personally have experience with  2 it as a biomarker. I'm not aware of the studies  3 so --  4 And then I can't really, the other  5 question is, it looks like it says, "I integrity?"  6 Which I'm not sure what that means. I don't know,  7 Helga, if you wanted to type in a revision of that  8 comment or question, we'd be happy to answer it.  9 Okay. Dr. Hanson?  10 DR. HANSON: Yeah. I was just going to  11 say looking at that question, I wonder if Citrulline  12 is a biomarker of GI epithelial integrity got carried  13 over onto --  14 DR. TAPLITZ: Yes, yes, yes --  15 epithelial integrity. You got it.  16 DR. HANSON: It's an interesting  17 question; right? I guess it's after cytotoxic  18 chemotherapy, you have marker of, you know, mucositis  19 that's not clinically apparent, are you more likely to  20 have translocation of bacterial DNA or entire  21 organisms?  22 I think that's an interesting question,</p>	<p style="text-align: right;">Page 152</p> <p>1 Dr. Girgenti, the floor is yours.  2 DR. GIRGENTI: Sure. Thank you,  3 Dr. Iarikov.  4 So addressing the first point, you  5 know, in terms of the appropriate primary endpoint,  6 you know, and maybe this is kind of bleeding a little  7 bit into question two as well. You know,  8 historically, I'm a pediatrician as well as an  9 internist, you know.  10 I kind of look at this population as  11 probably, quite frankly, the closest thing to sort of  12 the rule out sepsis protocol in newborns, you know,  13 for a lot of very parallel reasons, in terms of a very  14 vulnerable, susceptible population in pediatrics and a  15 very susceptible population here in adults, where the  16 intention, the goal of treatment, empiric treatment is  17 really to prevent a really catastrophic outcome in a  18 population that can succumb very quickly.  19 You know, so having said that, in terms  20 of the most appropriate primary endpoint, I would  21 normally suggest that this should, as original trials  22 have been designed many, many years ago, you know,</p>
<p style="text-align: right;">Page 151</p> <p>1 and it would be cool to kind of compare that biomarker  2 along with all the stuff that the metagenomic  3 cell-free DNA test is detecting in blood, which is  4 often anaerobes from the gut. So a couple ways to get  5 at that question.  6 DR. TAPLITZ: All right. Any more  7 questions, comments regarding question number two? I  8 think we've gotten the questions from the Q&amp;A. And  9 we're actually right on time, 40 minutes, almost 40  10 minutes into our discussion.  11 So maybe we'll move on to question  12 three, Dmitri?  13 DR. IARIKOV: Hi, again. It's Dmitri  14 Iarikov, Deputy Director in the Division of  15 Anti-Infectives at FDA. And for question three, it's  16 "Regarding trial design consideration in febrile  17 neutropenia."  18 And I would ask Dr. Girgenti to start  19 the discussion. And there are three sub-bullets under  20 this question related to primary endpoint, primary  21 efficacy population, and potential strategies to make  22 these trials feasible.</p>	<p style="text-align: right;">Page 153</p> <p>1 looked at outcomes, particularly in mortality and  2 other outcomes that would reflect, you know, the true  3 treatment effect and the intended prevention of poor  4 outcomes in this population.  5 Unfortunately, for clinical trial  6 design, very fortunate for patients, but very  7 unfortunate for clinical trial design, this is very  8 challenging now to evaluate mortality and morbidity in  9 patients that are being treated empirically for FN.  10 Particularly, considering where the  11 mortality rate is probably somewhere between 5 and 10  12 percent overall in this population, and more so, where  13 the mortality is in the majority of cases, not  14 infection-related, but more related to the tumor or  15 other non-infectious reasons.  16 So to the first question, I would  17 insist that probably still we are looking at, for  18 better or for worse, clinical along with  19 microbiological response to truly be the most  20 appropriate primary endpoint to be evaluated.  21 Still, you know, as I got into in my  22 talk and a few others did as well, it's an endpoint</p>

<p style="text-align: right;">Page 154</p> <p>1 that's certainly fraught with concern in terms of                  2 clinical trial development.                  3           You have a population which is                  4 naturally inclined so that the rule rather than the                  5 exception will be natural improvement and resolution                  6 with or without antibiotics which creates a bias                  7 towards non-inferiority, you know.                  8           So in terms of considering type 1 and                  9 type 2 error of a clinical trial design, while in                  10 terms, you know, of the most important being type 1,                  11 that a drug is considered more efficacious than truly                  12 deserving in the clinical trial setting.                  13           If we're looking at clinical response,                  14 there is a bias towards non-inferiority which makes                  15 it, quite frankly, a low bar to achieve                  16 non-inferiority in this case. And likewise, at the                  17 same time, makes it really challenging to achieve                  18 superiority.                  19           So to this point in, you know, again,                  20 dialing back to question number two, how can we best                  21 refine the population? I think it really becomes                  22 hand-in-glove to refine the population in such a way</p>	<p style="text-align: right;">Page 156</p> <p>1 restricted to hematologic malignancy and not include                  2 or limit that the drug has not been evaluated in                  3 additional tumor types for instance?                  4           And there are a number of other ways                  5 that that could play out in terms of what you study in                  6 the trial is what you get in the label. But                  7 nonetheless, I think it is truly important to refine                  8 the study population in such a way that it is far more                  9 specific what is evaluated in the clinical trial that                  10 would potentially improve the likelihood of                  11 demonstrating superiority and not just demonstrating                  12 what is, quite frankly, a relatively low bar, that                  13 being non-inferiority.                  14           And then to the third point in terms of                  15 strategies to make this more feasible, as I alluded to                  16 at the end of my talk, you know, we've heard a number                  17 of times, I think in various talks, the term                  18 "heterogeneity." And this is a disease which is truly                  19 heterogeneous. I like Dr. Marr's reference to this as                  20 more of a symptom than a syndrome in that, you know,                  21 this is truly heterogeneity.                  22           The heterogeneity really is not in</p>
<p style="text-align: right;">Page 155</p> <p>1 that this primary endpoint makes sense.                  2           You know, are we really looking at a                  3 primary endpoint of clinical response which is                  4 attributable to the antibiotic effect rather than the                  5 natural course of disease? So that's my response thus                  6 far in terms of the first bullet.                  7           With regard to the primary efficacy                  8 population, again, you know, what I reflected on                  9 earlier, I think in any way that we can refine the                  10 population to make this a more specific endpoint would                  11 truly benefit the clinical trial population and the                  12 likelihood of demonstrating a meaningful clinical                  13 response.                  14           Of course, you know, coming from the                  15 sponsor perspective, when I look at refining a                  16 clinical trial population, I always look at, you know,                  17 the mantra of what you evaluate in the study is what                  18 you get in the label.                  19           And this becomes really important that                  20 if you refine a population, let's say you refine it                  21 to, you know, in extreme terms to hematologic                  22 malignancy. Will you have a label indication which is</p>	<p style="text-align: right;">Page 157</p> <p>1 favor of conducting clinical trials. Clinical trials                  2 are intended to be as homogenous as possible, minimize                  3 the variability. And in many ways, this is, quite                  4 frankly the, you know, contrary to that.                  5           So are there opportunities for us to                  6 really kind of think outside the box from the really                  7 traditional, if you will, explanatory randomized                  8 clinical trial design to looking at more pragmatic                  9 trials?                  10           More real-world evidence outside of the                  11 traditional inclusion/exclusion criteria in terms of                  12 how the drugs are truly being used in the clinic to                  13 evaluate both clinical and outcome efficacy endpoints.                  14           And likewise, I think the last point                  15 that I got to in my talk was, you know, could we                  16 evaluate, again, outside of the traditional model of                  17 looking at perhaps something like a platform-based                  18 design where multiple antibiotics could be evaluated                  19 in head-to-head fashion against existing standard of                  20 care.                  21           So I think there are a number of ways                  22 that we could look at, you know, another would be can</p>



<p style="text-align: right;">Page 158</p> <p>1 we model, can we utilize, can we leverage more than we  2 are currently doing. Modeling and simulation efforts  3 to look at probability of target attainment in this  4 population against these particular pathogens,  5 extrapolating from, perhaps, an existing license  6 indication for UTI or HABP/VABP in an existing  7 antibiotic.</p> <p>8 So all of these, I think, you know,  9 potentially represent ideas that could look at  10 clinical trial designs which are outside of the  11 traditional randomized clinical pivotal Phase 3 design  12 that would not only facilitate development, make it  13 less costly and less labor intensive, time intensive,  14 in terms of reaching licensure, the intended outcome,  15 but also, quite frankly, generate more meaningful  16 results.</p> <p>17 DR. IARIKOV: Thank you. It's been  18 very helpful and informative. I have a question as we  19 got to primary endpoints. What do you think about the  20 timing of assessment considering effort to de-escalate  21 stopped earlier? What do you believe would be the  22 optimal timing for the endpoint?</p>	<p style="text-align: right;">Page 160</p> <p>1 point, primary efficacy time point, really needs to be  2 positioned fairly early.</p> <p>3 And I would strongly propose that if a  4 primary efficacy endpoint of a clinical response, an  5 early clinical response in a traditional clinical  6 trial setting, should probably be sitting at about the  7 72-hour time point.</p> <p>8 Now, going back on what I said earlier  9 in terms of, well, what if we explored less  10 traditional clinical trial, you know, more novel  11 clinical trial approaches such as pragmatic trials?</p> <p>12 Well, a pragmatic trial would not -- an  13 endpoint for a pragmatic trial would not necessarily  14 fit to say a, you know, given percent response of 72  15 hours, would be more appropriate as a generalized  16 response that can be easily evaluated outside of the,  17 you know, typical Phase 3 setting.</p> <p>18 So in a more pragmatic sense of  19 evaluating the disease, then you would perhaps want to  20 position this at a later time point. But I think at  21 least with the traditional typical pivotal Phase 3  22 one-to-one randomized clinical trial, really</p>
<p style="text-align: right;">Page 159</p> <p>1 DR. GIRGENTI: Sure. I think, you  2 know, traditionally, and again, if we're looking at  3 this from an outcomes perspective, if we're looking at  4 what we're truly trying to prevent, which is the  5 morbidity and mortality of the disease, then it would  6 make sense to evaluate a later time point.</p> <p>7 But as has also been discussed pretty  8 extensively during this workshop, there is, of course,  9 a trend towards the disease itself changing, where  10 particularly with the introduction of ancillary  11 treatments like G-CSF, the expectation is that  12 neutropenia will respond a lot faster.  13 Hospitalizations will be shorter.</p> <p>14 Given the anticipation that we will  15 have a bug in hand within two or three days or an  16 indication of whether the patient is improving or not,  17 whether step-down therapy or more narrow antibiotic  18 therapy, you know, de-escalation could be introduced  19 earlier.</p> <p>20 You know, taking into account where we  21 are in 2024 and where the disease is heading, I would  22 suggest that the primary efficacy endpoint, the time</p>	<p style="text-align: right;">Page 161</p> <p>1 considering all of the dynamics at play, including  2 G-CSF, including the likelihood of de-escalation  3 therapy, that at much like, say, UTI, that the primary  4 efficacy endpoint should probably be positioned early  5 in therapy. Probably at 72 hours.</p> <p>6 DR. IARIKOV: Thank you so much.  7 Dr. Marr?</p> <p>8 DR. MARR: Yeah. I want to say that we  9 can't answer the question that you asked. How  10 long -- when should the primary endpoint be because  11 fever during neutropenia is not a disease? And then  12 it's a few risks for bad infections and bad outcomes.  13 And then beyond that, if we're using the most  14 objective outcomes, survival, that's subjective.</p> <p>15 These are driven by other host  16 variables that we're not controlling by the  17 antibiotics that we're giving or any antimicrobials.  18 And so, you know, it's like there are far too many.  19 We don't have a syndrome defined, so we don't even  20 know what to measure.</p> <p>21 And, you know, God knows how many  22 editorials have been written about this. I've</p>

<p style="text-align: right;">Page 162</p> <p>1 contributed several of them. This is why we came up  2 with this five-point endpoint to be, you know, and  3 antifungal studies to begin with, which was completely  4 driven by tolerability and safety.  5         And the reason is that we're enrolling  6 people that don't have a defined syndrome. They have  7 a lot of different biases towards the outcomes we're  8 trying to measure. And the one that we're trying to  9 either prevent or treat is rare. And so, you know,  10 there's, I think, no more uniquely nurturing place to  11 have a bias towards non-inferiority because we don't  12 even know what we're treating in that setting.  13         And I would even go to the point where  14 we don't know if we're preventing the infection or  15 treating it. And as has been absolutely indicated  16 here, a lot of this is because of our diagnostic  17 limitations. There's a lot of data using the more  18 sensitive tests that are not clinically used that says  19 that there is an infection. It's just not otherwise  20 clinically apparent.  21         And so, I think that we need to roll  22 back and say, is this feasible as an indication for a,</p>	<p style="text-align: right;">Page 164</p> <p>1 Dr. Iarikov.  2         You know, obviously I won't be able to  3 provide definite answers to the questions, but just a  4 few reflections. First of all, from what I heard  5 today, you know, I don't think mortality can be a  6 reasonable endpoint for such a trial. I think it's so  7 low that, you know, it would be probably possible to  8 demonstrate what needs to be demonstrated in terms of  9 efficacy.  10         Now, the other thing that I was  11 thinking about because I think in one of the  12 presentations, I think the Melinta one, there was, and  13 actually during more than one presentation, there was  14 this concept of looking into those patients that have  15 documented microbiology at baseline. So, you know,  16 where the pathogen can be identified.  17         Now to me, that one is a bit of a  18 different indication actually. It's not about empiric  19 therapy. Actually, this is bacterium. So, you know,  20 once you can isolate the pathogen, you know, and  21 appreciated that it's just 15 to 30 percent, I think  22 was the -- this is a bit of a different situations.</p>
<p style="text-align: right;">Page 163</p> <p>1 you know, current drug development? That's one  2 question that still is looming in my mind. And then  3 start with, what are we treating with fever during  4 neutropenia? Because I think that we can iteratively  5 make this a more feasible environment for us to  6 measure objective and meaningful outcomes with  7 antibiotics.  8         It's not to say that they're not  9 needed. They are absolutely needed. It's just to say  10 that given the complexity in enrollment,  11 heterogeneity, is host heterogeneity, and now it's  12 been pointed out that we're enrolling a heterogeneous  13 bag of people who have infections at different time  14 points.  15         I think about the host more. We have  16 to really re-emphasize what that's doing to the  17 feasibility of our clinical trials as well.  18         DR. IARIKOV: Thank you.  19         Dr. Botgros, and let's make it the last  20 question, comment for this question, and we'll move on  21 to question four next.  22         DR. BOTGROS: Thank you very much,</p>	<p style="text-align: right;">Page 165</p> <p>1 We are not talking anymore in a certain sense about  2 empiric therapy, or we shouldn't at the very least.  3         And then the other thing with regard to  4 a time of collection of the endpoint and what the  5 endpoint, the clinical endpoint could be, I was  6 wondering if, and, you know, here I want to hear more  7 from you.  8         You know, I'm wondering how far  9 something like, you know, documented breakthrough  10 infection after a certain period of time from start  11 of, well, we say therapy, but actually it's preemptive  12 therapy, I would imagine for most patients.  13         If such an endpoint collected maybe,  14 and this particular one could be collected at a later  15 time point from the start of therapy, if this could be  16 something that developers could think about. I don't  17 know. It's just my own reflection based on what I  18 heard today.  19         Thank you.  20         DR. IARIKOV: Thank you.  21         Dr. Gea-Banacloche, I noticed that they  22 all raised their hands. Please comment.</p>

<p style="text-align: right;">Page 166</p> <p>1 DR. GEA-BANACLOCHE: Yeah. I just put 2 it on the chat. You know, when -- studied 3 Ceftazidime, things were all very complicated. He had 4 a very simple design in which the patients were 5 assessed at 72 hours and at the end of the 6 neutropenia. 7 And so every episode of neutropenia 8 could be classified as failure when the patient had 9 died or a success with modification. If they had to 10 modify the antibiotic or success without modification, 11 which meant that the patient had survived without 12 changing the antibiotic. 13 And that is a very pragmatic way of 14 looking at things and avoids the issue of very slow 15 mortality because mortality was not the key thing. 16 And, in fact, there was no difference in mortality. 17 But the key issue is that there was no difference 18 either in success without modification overall. 19 Although, clearly, when there was a 20 documented infection, people had to modify the 21 Ceftazidime alone half the time. But as pragmatic 22 studies go, there was a pragmatic study that changed</p>	<p style="text-align: right;">Page 168</p> <p>1 DR. FARLEY: Yeah. Sorry to make you 2 late, Dmitri. I just kind of wanted to follow up on a 3 point that Kieren had brought up. 4 So we're doing a fair amount of 5 collaboration with ARLG on door endpoint development. 6 And just to clarify, you know, for the agency, we're 7 not at the point for a new molecular entity accepting 8 a door endpoint as a primary endpoint, but there's a 9 lot of utility. 10 And I'm just wondering if there are 11 unanswered questions for this sort of empiric period 12 of treatment where you have a lot of options, some of 13 which have adverse events associated with it, whether 14 you thought that would be helpful or not to explore 15 further. Thanks. 16 DR. MARR: Can I speak? I actually 17 think it's a great idea as more exploratory endpoints. 18 And, you know, a lot of that has been said is really 19 very relevant. We've got a really reposition what 20 we're trying to do. Are we preventing an early 21 infection from establishing? 22 Because as Juan says, there's ways to</p>
<p style="text-align: right;">Page 167</p> <p>1 the management of neutropenia fever. 2 If you want to think of what happened 3 that -- the paradigmatic changes in neutropenic fever, 4 one was empirical management of neutropenic fever. 5 That was number one. Number two was monotherapy and 6 everything after that has been incremental and trying 7 to do it a little bit better. But those are the two 8 things that really set the field the way the field it 9 is right now. 10 And I think that, you know, trial 11 designers can look at this, which, you know, of 12 course, is a 40-year-old design. But, you know, think 13 about if the answers of -- if a sponsor could 14 consider, "Oh, maybe I can put my drug against the 15 standard of care, and if I have to change my drug less 16 often than the standard of care, maybe that is good 17 enough for me to get approval." 18 So I don't think that is particularly 19 crazy, but I wouldn't know. 20 DR. IARIKOV. Thank you. Very helpful. 21 Thank you. 22 Dr. Farley?</p>	<p style="text-align: right;">Page 169</p> <p>1 measure that with our classical microbiology, 2 infection-free survival. I absolutely agree that we 3 can't rely on survival alone because it's driven by 4 too many things. 5 Survival in all of our infection 6 endpoints also causes bias in this population because 7 they die too, as well the toxicities of the drug which 8 we've seen in these early treatment studies before. 9 But, and as Catherine points out in the chat, I think 10 absolutely appropriately, there's other ways to do it. 11 Adaptive platforms. She brings up 12 pragmatic outcomes such as store. Absolutely. But, 13 you know, I think that some of the framework in which 14 we're working here is that we need to redefine what 15 we're approaching given the contemporary population 16 that we're dealing with. 17 The differences that have evolved and 18 the lessons that we've learned based on the problems 19 with measuring these outcomes in our historical 20 trials. And with all of that, I think that we can 21 probably come up with a better strategy. 22 For me, we're sitting in the early</p>

<p style="text-align: right;">Page 170</p> <p>1 therapy land and labeling it as fever during                  2 neutropenia is not encompassing enough because that                  3 early therapy can also be someone who doesn't have a                  4 fever but has a pulmonary syndrome that is consistent                  5 with early pulmonary.                  6         So I think that I'd like to be starting                  7 to move towards more syndromic approaches and                  8 inclusion and labeling the indication so that we can                  9 use some of these new tools and some of these new                  10 measures as you're pointing out.                  11         DR. IARIKOV: Sorry. I was on mute.                  12 Any more comments on question three before we move to                  13 the next one? Okay, hearing none. So question four.                  14 Actually, it's not that directly related to febrile                  15 neutropenia, but as an M.D. we're very interested in                  16 discussing this subject.                  17         So we know the data -- limited on the                  18 use of new antibacterial drugs, recently approved                  19 drugs, in your neutropenic patients, and we would                  20 greatly appreciate the discussion about the need,                  21 utility, and visibility of obtaining efficacy and                  22 safety data on new drugs in neutropenic patients with</p>	<p style="text-align: right;">Page 172</p> <p>1             Do you have data gaps for use of this                  2 drug, recognizing, of course, you're also working to                  3 increase the patient's neutrophil count while all of                  4 this is going on?                  5             We have provided you as much data that                  6 we can in terms of optimizing the exposure in the                  7 setting of comorbidities like renal failure, renal                  8 compromise. We've tried -- we worked really hard                  9 during development to do that. We haven't                  10 necessarily, because of just the practicalities of                  11 getting these trials done, given you everything that                  12 you need.                  13             And so the question is, what do you                  14 need and are there ideas for us to provide that                  15 information?                  16             So, thanks.                  17             DR. IARIKOV: Dr. Marr?                  18             DR. MARR: I'll just jump out there                  19 with my answer. I think that adding neutropenic                  20 patients to other indications makes the trials more                  21 complicated and difficult to interpret. We treat for                  22 different periods of time. The diseases occur through</p>
<p style="text-align: right;">Page 171</p> <p>1 defined systemic bacterial infection.                  2         Dr. Farley, please start the                  3 discussion.                  4         DR. FARLEY: Yeah. So I just wanted to                  5 provide a little framing because actually as I've                  6 heard the discussion today, I think, in some prep for                  7 this Kieren sort of accused me of tangential thinking,                  8 which I sometimes am guilty of. But I think this is                  9 less tangential really as I learn more about sort of                  10 the state of the art from you experts.                  11         Because my sense is that one of the                  12 possibilities during this -- after this sort of                  13 empiric period of treatment is that you're going to                  14 realize that the patient, either based on diagnostic                  15 testing fairly early, or maybe syndromic presentation                  16 clinically, really warrants treatment.                  17         And you also have a high probability of                  18 needing to use one of a number of antibacterial drugs                  19 that have been approved during the last decade. And                  20 kind of speaking as a regulator and working with the                  21 pharmaceutical industry, the question to you all is                  22 have we given you the data that you need?</p>	<p style="text-align: right;">Page 173</p> <p>1 a different pathobiology frequently. The example is,                  2 you know, CAP versus HAP is really irrelevant in this                  3 patient population.                  4             And then to add to that, if you do a                  5 study in an artfully chosen population of people with                  6 community-acquired pneumonia or hospital-acquired                  7 pneumonia with the pathogen profile that we can                  8 understand, and you tell me that an antibiotic works                  9 for that pathogen profile, that's what I need to use                  10 it in my neutropenic population.                  11             I don't need the data necessarily. I                  12 need it to be shown to be safe and effective in a                  13 population in which it can be measured. Now, if                  14 they're, you know, and you put it into a different                  15 population, we can have an endless discussion about                  16 who those other patients are. But we don't need to do                  17 studies in each of them, especially as they become                  18 more complicated.                  19             That's my opinion.                  20             DR. IARIKOV: So you believe that                  21 specific data on neutropenic host in a neutropenic                  22 population might not be needed because you don't</p>

<p style="text-align: right;">Page 174</p> <p>1 expect any significant differences in terms of PK/PD  2 or any other host factors that might change the  3 efficacy, so to speak, plus-minus safety of the drug?  4 Okay.  5 DR. MARR: Or at least let me clarify  6 not due to neutropenia alone.  7 DR. IARIKOV: Got you.  8 DR. MARR: You know, other reasons that  9 impact the PK are apparent and apply to my population  10 as well. But neutropenia alone is another variable  11 that we're managing that doesn't necessarily have to  12 do with the antimicrobial. It may not work as much  13 because the immune system is really driving so much.  14 But that's not going to take away from my enthusiasm  15 in translating the data that are derived from a  16 different population.  17 DR. IARIKOV: Right. So basically,  18 it's not special population as would be reflected in  19 our labeling like, you know, geriatric patients,  20 pregnant patients, pediatric patients, not neutropenic  21 patients?  22 DR. MARR: No. Because as you've heard</p>	<p style="text-align: right;">Page 176</p> <p>1 that's approved for complicated urinary tract  2 infection or that really isn't relevant either. It's  3 more about bacterial spectrum.  4 I don't know if you've got comments on  5 it.  6 DR. MARR: I don't mean to speak for  7 everyone and there's some tremendous clinicians and  8 minds on this call. I will just -- I brought up the  9 issue, and I'll give you my opinion. We don't have  10 data that is approved in febrile neutropenic patients  11 to guide our neutropenic syndromes.  12 We have neutropenic patients with  13 pneumonia or UTIs, and we interpret the data that has  14 been given to us with the appropriate indications  15 anatomically and microbiologically based on what we  16 think that our patients have.  17 And so I don't necessarily need to know  18 how any -- I don't need the specific data in a  19 neutropenic patient as much as I need that specific  20 data in someone with my severe lung disease. It's  21 interpreting it in the context of more clinical  22 variables that we have to go through.</p>
<p style="text-align: right;">Page 175</p> <p>1 today that neutropenic population isn't even  2 homogeneous enough to know what we're modeling for.  3 DR. IARIKOV: Got you. Thanks. Very  4 helpful.  5 Any comments on question four?  6 Dr. Peter, please, and then  7 Dr. Girgenti. Sorry, I might miss the order.  8 DR. KIM: Please, Dr. Girgenti, your  9 hand was up first.  10 DR. GIRGENTI: Oh, by all means.  11 That's okay.  12 DR. KIM: Okay. So my question is  13 actually kind of like an add-on to what Dr. Marr was  14 discussing and Dr. Iarikov. So of the indications  15 that we typically grant and indications that drug  16 developers typically conduct studies in, are there any  17 of those indications that allow for more confidence in  18 an antibacterial drug for use in febrile neutropenia?  19 Such as, if drug X has a HABP/VABP  20 indication, then I'm more likely to use it in my  21 febrile neutropenia patients. I have more confidence  22 given the level of acuity of HABP/VABP versus a drug</p>	<p style="text-align: right;">Page 177</p> <p>1 I mean that's great ancillary data for  2 outcomes and to understand some of the other  3 complications that can occur. But I don't think it's  4 necessary for -- to have that as an indication for the  5 use of these drugs, and we currently don't. I'd be  6 very interested in hearing other -- like Randy's  7 opinion on this too.  8 DR. IARIKOV: Dr. Girgenti, you were  9 next.  10 DR. GIRGENTI: Sure. Okay. I don't  11 know -- did we want to let Dr. Taplitz respond to that  12 first or I'd be happy to defer.  13 DR. TAPLITZ: Yeah. I just wanted to  14 say, you know, again, I think the sort of the concept  15 of the syndrome, you know, the febrile neutropenia  16 syndrome is sort of, I think, it's just too simplistic  17 now for what we're dealing with on a clinical level.  18 And so we kind of need to, you know, what I think what  19 we're sort of moving towards is we need to rethink  20 that.  21 You know, again, patients have a  22 variety of risk factors, and I think people have</p>

<p style="text-align: right;">Page 178</p> <p>1 pointed out that, you know, again, it's not just  2 neutropenia. It's, you know, everything from, you  3 know, age to comorbidities to, you know, immunogenic  4 or genetic risk factors to, you know, treatments.  5       And, you know, as ID physicians, we  6 keep up on exactly what our immune system is being  7 altered by the drug that they're currently, the drug  8 du jour, and not only immune deficiency but immune  9 activation we have to deal with and steroids.  10       And so I guess, you know, that's not to  11 really answer the question, but just to sort of point  12 out how complicated treatment of these patients has  13 become and, you know, maybe to move past the concept  14 of febrile neutropenia.  15       DR. FREIFELD: I'd like to follow up on  16 some of this discussion. I'm sorry that I'm late.  17 This is Dr. Alison Freifeld. And like so many  18 clinicians, I've seen the last 40 years of this  19 evolve.  20       And first of all, I'd like to agree  21 with Kieren Marr that we don't need any specific data,  22 I think, in answer to Peter Kim's question on these</p>	<p style="text-align: right;">Page 180</p> <p>1 pointed out in the chat, that would be the right point  2 to make an evaluation as to whether or not a drug is  3 effective or not.  4       I mean, clearly, no drug is going to be  5 able to cover pneumonia or UTI sepsis. You know,  6 that's simply not possible given the array of  7 pathogens and syndromes and things that we have to  8 deal with.  9       So, I guess, I just wanted to throw  10 those two things out, and that the primary endpoints  11 clearly are no longer going to be death. Mortality is  12 simply not an appropriate endpoint as it might have  13 been 40 or 50 years ago. So we have to certainly come  14 up with better clinical and laboratory endpoints that  15 are reflective of how a certain drug or regimen does  16 in the first few days.  17       So sorry to be late and hope that I  18 didn't backtrack a little too much.  19       DR. IARIKOV: Thank you so much. It  20 was really helpful.  21       And Dr. Girgenti, thank you for waiting  22 so patiently, please.</p>
<p style="text-align: right;">Page 179</p> <p>1 documented infections in neutropenic patients.  2 Because, honestly, it's not the drugs that we use as  3 much as it is the recovery from neutropenia that's  4 going to really affect outcomes.  5       So that is yet another variable that  6 we'd have to consider in addressing and evaluating any  7 of these drugs. And I gather from this little bit of  8 discussion I've heard that there's been some back and  9 forth about whether fever neutropenia is a syndrome  10 versus is there, you know, is it something more than  11 that.  12       I think when we set out at the very  13 beginning of treating a patient, it is a syndrome to  14 start with. But within a pretty quick period of time,  15 thanks to the clinical and laboratory techniques that  16 we now have, within three days, two days often or  17 less, it's no longer a syndrome. It's a documented  18 infection or it's not.  19       And so, really, at that point, within  20 the first three days, we're going to start making  21 changes to any empiric regimen. So that would seem to  22 me to be the right point as one of our panelists has</p>	<p style="text-align: right;">Page 181</p> <p>1       DR. GIRGENTI: Thank you. I'm glad I  2 did because I'm glad I allowed the clinical  3 conversation to play out to Dr. Kim's question because  4 where my, I guess, question is very much in the same  5 territory but kind of taking this from the clinical  6 perspective to the pharmacodynamic perspective in this  7 population.  8       And, you know, to be clear, I'm a  9 clinician, I'm not a clinical pharmacologist. But,  10 you know, dialing back to the conversation that are  11 there other populations, for instance, HABP/VABP  12 versus UTI where patients with neutropenia could  13 provide more evidence that would support an indication  14 in febrile neutropenia.  15       You know, there's been some work,  16 Imipenem-cilastin comes to mind, and I think a few  17 others that have looked at the probability of target  18 attainment in patients with febrile neutropenia versus  19 other populations such as UTI and HABP/VABP, showing  20 that there is, you know.  21       And whether this is attributable to  22 augmented renal clearance or other factors, or whether</p>

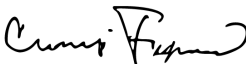
<p style="text-align: right;">Page 182</p> <p>1 it's something that we don't understand that's innate  2 to the condition, the syndrome, the symptom that  3 patients present with -- with febrile neutropenia. I  4 strongly suspect that part of the answer is to  5 Dr. Marr's comment that it's just too heterogeneous a  6 population to really identify.</p> <p>7         But, nonetheless, that the probability  8 of target attainment in patients with febrile  9 neutropenia may be substantially lower than similar  10 patients, similar body weight, similar characteristics  11 in HABP/VABP and UTI, and whether this creates itself  12 unique challenges in this population, or whether  13 there's something that could be learned from patients  14 with HABP/VABP, UTI, and other indications that are  15 likewise neutropenic.</p> <p>16         DR. IARIKOV: Thank you. Very  17 interesting.</p> <p>18         Dr. Sato?</p> <p>19         DR. SATO: Yes, thank you.</p> <p>20         So I'm Junko Sato, Associate Executive  21 Director, PMDA Japan. So I'd like to share what data  22 we would like to review as a regulator. So I'd like</p>	<p style="text-align: right;">Page 184</p> <p>1 clinical pharmacologist. But, you know, what I've  2 encountered are largely single-center studies, not,  3 you know, multi-center randomized trials, but that  4 have proposed that, again, the two that come to mind  5 are looking at Imipenem and Meropenem.</p> <p>6         That evaluating specifically in the  7 febrile neutropenia population that, and again,  8 attributing the differences to perhaps the volume of  9 distribution and difference in clearance that patients  10 may have a lower probability of target attainment for  11 similar bacterial pathogens with similar MICs than the  12 probability of target attainment in other pathologies.</p> <p>13         So, you know, from a sponsor  14 perspective, I would love to be able to extrapolate  15 and use nothing but modeling and simulation to  16 identify that we know how the drug is going to behave  17 in this population.</p> <p>18         My curiosity is to whether this would  19 complicate matters to know that we're, in fact,  20 dealing with a different population where the PK/PD  21 cannot be necessarily assumed to be identical as in  22 other hospital-acquired infections.</p>
<p style="text-align: right;">Page 183</p> <p>1 to touch the possibility to utilize real-world data.  2 There are many confounding factors such as the change  3 of neutrophil count.</p> <p>4         So we would like to evaluate data that  5 excludes these influence for the purpose we are  6 considering the possibility of using real-world data  7 because therapeutic data is generated every day in a  8 clinical site.</p> <p>9         If we accumulate and analyze such data,  10 we can obtain real-world evidence. We think such data  11 is so helpful to review for FN product.</p> <p>12         Thank you.</p> <p>13         DR. IARIKOV: Thank you so much.</p> <p>14         I have a follow-up question for  15 Dr. Girgenti. You mentioned that PK/PD data might be  16 different for, again, for unknown reason for now in  17 febrile neutropenic patients. Here we come  18 across -- does it kind of antibacterial class specific  19 or it's hard to say at this disjuncture, and any  20 explanation for these differences?</p> <p>21         DR. GIRGENTI: From my perspective,  22 again, not being the expert, I'm a clinician, not a</p>	<p style="text-align: right;">Page 185</p> <p>1         DR. IARIKOV: Thank you.</p> <p>2         Dr. Marr, I see you.</p> <p>3         DR. MARR: So you can absolutely assume  4 that it's not identical to other hospitalized  5 populations, but it's not the fever neutropenia that's  6 driving it. It's the absolutely everything else. I  7 mean the gamut of fever neutropenia patients runs from  8 18-year-olds with aplastic anemia to 75-year-olds with  9 relapsed leukemia.</p> <p>10         And there's a very, very different, and  11 you know, a bag of variables there that's going to be  12 driving your target attainment and your PK/PD that is  13 not about fever and neutropenia itself. It's, again,  14 a reflection of a very different heterogeneous  15 population.</p> <p>16         DR. TAPLITZ: Yeah. That's just one  17 aspect of it.</p> <p>18         DR. MARR: Yeah.</p> <p>19         DR. IARIKOV: All right. Any comments  20 on question four? Any additional comments that people  21 might have on any questions that have been discussed  22 or not discussed or that matter? All right. I'm not</p>

<p style="text-align: right;">Page 186</p> <p>1 going to assume that we've exhausted the subject, but  2 at least at this juncture, it seems that --  3 DR. TAPLITZ: Actually, I do want to  4 bring up one thing. Kieren made the comment about  5 machine learning, AI. And I just think that maybe  6 that's something that we should be talking about.  7 I mean as we head into this burgeoning  8 field and this new era, kind of what role, you know,  9 machine learning can play and help with in assisting  10 with risk stratification since we've talked about how  11 difficult risk stratification is.  12 DR. IARIKOV: Any takers on artificial  13 intelligence-related questions?  14 DR. TAPLITZ: I mean, I guess, perhaps  15 the fact that nobody is answering it says something.  16 I mean shouldn't we be at least thinking about it?  17 We're thinking about it in so many other ways. I'm  18 not saying that there's going to be, you know, any  19 improvements or solutions, but probably it should be  20 at least considered in risk stratification.  21 DR. IARIKOV: Dr. Lyman?  22 DR. LYMAN: Yeah, just a short answer.</p>	<p style="text-align: right;">Page 188</p> <p>1 more -- it's not so much the idea of necessarily using  2 them as studying them while you're studying, you know,  3 the questions that you have. Because I think we're,  4 many of us, I think, are very impressed with just how  5 many different models there are out there and how can  6 one choose.  7 And again, if someone is going to do a  8 large, randomized, controlled clinical trial, then you  9 can get so much information about that kind of  10 modeling in the setting of doing that trial. It just  11 seems like it's something worth considering.  12 DR. LYMAN: As an adjunct, I  13 think --  14 DR. TAPLITZ: As an adjunct.  15 DR. LYMAN: -- tradition. Yes.  16 Absolutely.  17 DR. TAPLITZ: Exactly. Yes, as an  18 adjunct.  19 DR. IARIKOV: Dr. Marr, let me remind  20 you that -- everyone that actually we are  21 unfortunately nearing the end time of our panel  22 discussion.</p>
<p style="text-align: right;">Page 187</p> <p>1 Obviously, there is an enormous excitement, I agree  2 completely. We should be thinking about it, but it  3 comes with a great deal of caution. There've been  4 extensive studies, a lot of them outside of the cancer  5 setting, showing the challenges of the interpretation,  6 the methodology, the validity of models generated by  7 machine learning techniques.  8 So, you know, this is clearly in our  9 future, but I think we need to proceed cautiously and  10 always being very vigilant as we should be with any  11 technique we use for modeling, but very cautious about  12 the limitations. And that the need for them to abide  13 by the tripod statement or from machine learning,  14 other standardized techniques, or standardized  15 criteria and make sure all this is done.  16 Otherwise, we get into a quagmire  17 because these models are black boxes, at least to most  18 of us and certainly to clinicians. And we want to  19 make sure if we begin to use them, which is the  20 ultimate goal, that they are accurate, reliable,  21 valid, and we don't do more harm than good.  22 DR. TAPLITZ: Yeah. And I think it's</p>	<p style="text-align: right;">Page 189</p> <p>1 Dr. Marr, please.  2 DR. MARR: This won't be long. I just  3 want to say, I agree with all of that. But, you know,  4 I think I'm thankful that we've got a technology that  5 we are putting the guidelines around to say that we  6 need to validate and support it with data.  7 Because to date, having us sitting  8 around a table which is the genesis of most of the  9 guidelines and models that have come up there is not  10 validated and it's not data-driven.  11 And so either way, we take it with all  12 of those bruises and warts, and in all of these  13 analytic platforms, at least we're inching towards  14 more validated data-driven modeling. And I think that  15 that's a really good movement in this field.  16 DR. IARIKOV: Thank you so much.  17 And, again, unfortunately, we are  18 nearing the end of our moderated panel discussion and  19 I'll try to summarize today's discussion. Let me  20 start by thanking presenters and panelists for their  21 outstanding presentations and discussion. We've  22 covered a lot of material in a short time. And,</p>



<p style="text-align: right;">Page 190</p> <p>1 again, in the next ten minutes or so, I'll try to  2 summarize some key points.  3         So during the first session following  4 Dr. Kim's overview of the workshop objectives,  5 Dr. Taplitz walked us through the 60 year evolution of  6 approaches to prophylaxis and therapeutic therapy of  7 febrile neutropenia, highlighting a rise of resistant  8 infections, increasing complexity of febrile  9 neutropenia patients in terms of their infectious  10 risks, and suggesting that new treatment paradigm and  11 effective options for febrile neutropenia are needed.  12         Dr. Zimmer then reviewed current  13 febrile treatment options for various infectious risk  14 categories and presented the causes of bacteremia and  15 the part of the initial antibiotic use in high-risk  16 febrile neutropenia patients in the United States  17 showing that Cefepime remains the most commonly used  18 antibiotic.  19         Then Dr. Hanson discussed diagnostic  20 testing in febrile neutropenia indicating that while  21 blood culture remains an essential component of the  22 febrile neutropenia workup, culture-independent</p>	<p style="text-align: right;">Page 192</p> <p>1         And the two key questions in his  2 presentations were what does the current febrile  3 neutropenia population look like, and what does the  4 microbiology of febrile neutropenia look like?  5 Dr. Girgenti pointed out that the heterogeneity, this  6 is the word of the day, of febrile neutropenia  7 patients, indicating that about 50 percent of patients  8 will be diagnosed with fever of unknown origin.  9         And he questions whether there's an  10 opportunity to use advanced testing to refine  11 enrollment criteria in febrile neutropenia trials to  12 increase the proportion of patients with  13 microbiologically proven infection.  14         He also reviewed primary endpoints and  15 other trial design considerations and provided  16 outlines of a hypothetical efficacy study and clinical  17 development program for a drug for febrile  18 neutropenia.  19         And he concluded his presentations by  20 posing questions about the possibility of a more  21 streamlined clinical approach in febrile neutropenia,  22 and we touched on these questions during our moderated</p>
<p style="text-align: right;">Page 191</p> <p>1 methods including agnostic approaches may complement  2 the diagnostic workup.  3         And rapid organism and  4 antimicrobial-resistant markers stratification from  5 positive blood cultures have become standard of care  6 to inform the adjustment of antimicrobial therapy.  7 And Dr. Hanson also indicated that colonization status  8 may inform risk for invasive infection and optimize  9 its prophylaxis and febrile neutropenia.  10         And then Dr. Sheoran presented an  11 antibiotic managements of neutropenic patients with  12 acute radiation syndrome stressing high rates of fatal  13 infection in this patient population as compared to  14 neutropenic cancer patients, which in the setting of  15 increasing rates of drug resistant infections calls  16 for more treatment options.  17         Dr. Girgenti concluded session one by  18 providing industry perspective on clinical development  19 of antibiotic for empiric therapy febrile neutropenia.  20 He pointed out that current recommendations for  21 empiric treatment of febrile neutropenia are largely  22 based on decades-old research.</p>	<p style="text-align: right;">Page 193</p> <p>1 panel discussion.  2         Session two started with Dr. Pease's  3 presentation on regulatory considerations to expedite  4 drug development for empiric antibacterial therapy in  5 febrile neutropenia where he summarized applicable  6 regulatory standards, pathways, and programs, pointing  7 out that for febrile neutropenia no new antibacterial  8 drugs have been approved in more than 25 years, and no  9 oral antibiotics have ever been approved.  10         Then Dr. Kapoor discussed regulatory  11 perspective on clinical trial design considerations  12 for empiric antibacterial therapy in febrile  13 neutropenia patients. She also noted challenges  14 related to the inclusion of subjects whose fever  15 remains unexplained in febrile neutropenia trials.  16         Dr. Kapoor noted that in a superiority  17 trials, this will likely make demonstration of  18 superiority more difficult. Whereas for a  19 non-inferiority trial, it could make the justification  20 of a non-inferiority margin challenging. Dr. Kapoor  21 also discussed advantages and limitations of candidate  22 efficacy and points for febrile neutropenic trials.</p>

<p style="text-align: right;">Page 194</p> <p>1 Her presentation was followed by  2 Dr. Rubin who discussed statistical consideration in  3 clinical trials in febrile neutropenia starting with  4 general consideration for superiority and  5 non-inferiority trials and then described the  6 limitations of the applicability of some historical  7 trial information to inform the design of contemporary  8 trials.  9 Dr. Rubin also described statistical  10 trade-offs related to the selection of an analysis  11 population and provided estimates of sample sizes for  12 superiority and non-inferiority trials in febrile  13 neutropenia.  14 Dr. Botgros provided the EU perspective  15 for the febrile neutropenia indication. He noted that  16 for antibacterial drugs this indication is not  17 supported any longer in the EU and is to be replaced  18 with the statement reading that the drug may be used  19 in the management of neutropenic patients with fever  20 that is suspected to be due to bacterial infection.  21 Dr. Botgros also noted that further  22 discussion of clinical trial design to support such an</p>	<p style="text-align: right;">Page 196</p> <p>1 this drug would be also important.  2 Then it was noted that other approach  3 would be to develop targeted -- kind of to reconsider  4 the paradigm or broad-spectrum empiric approach and  5 maybe to develop a more targeted approach to treatment  6 of febrile neutropenia.  7 And it was noted that certain drawbacks  8 related to broad-spectrum coverage in all patients for  9 potentially prolonged period of time and de-escalation  10 strategies were discussed. And it was also repeatedly  11 noted that our current understanding of febrile  12 neutropenia needs to be revisited.  13 That it might not be and it's not  14 apparently well-defined syndrome or maybe if it's not  15 a syndrome altogether, it might be considered as a  16 symptom of an underlying disease or condition not  17 necessarily of infectious etiology.  18 And it's -- right. And it's dovetailed  19 to question number two regarding trial design  20 consideration, primary endpoint, and trial population,  21 and it was a repeated theme over the discussion. The  22 need to better define study population in trials in</p>
<p style="text-align: right;">Page 195</p> <p>1 indication has not taken place but would be highly  2 recommended if the drug developer decided to pursue  3 it.  4 Dr. Ichimaru concluded session two by  5 reviewing the approval of antimicrobial drugs for  6 febrile neutropenia in Japan. He noted that several  7 drugs have been approved with this indication in Japan  8 and indicated that foreign data can be utilized to  9 obtain approval.  10 And during the remaining time, I'll try  11 to summarize the panel discussion points, but, again,  12 forgive me if I'm going to be a little bit -- I'm  13 going to follow my notes.  14 So for question one regarding the  15 greatest unmet needs for empiric treatment of febrile  16 neutropenia, it was noted that one approach might be  17 to develop a drug with a broad-spectrum coverage,  18 including multidrug-resistant pathogens such as  19 gram-negative pathogens and gram-positive pathogens.  20 And also a novel oral drug or a  21 long-acting parental drug might meet an unmet need in  22 the outpatient setting and improve safety profiles for</p>	<p style="text-align: right;">Page 197</p> <p>1 febrile neutropenia and implement potential enrichment  2 strategies.  3 And this was covered by Dr. Hanson who  4 listed several factors that might be considered,  5 including cost factors, clinical signs for -- such as  6 fever, clinical findings, biomarkers, predictor for  7 bacterial infection.  8 And she also mentioned that  9 this -- more novel biomarkers such as cytokine profile  10 and immune response profile that might potentially  11 inform and better define population in trials for  12 febrile neutropenia. Also, the microbiome and any  13 colonization status of course.  14 It was also commented that another  15 approach would be to make these trials more pragmatic  16 and thinking not only about inclusion criteria but  17 maybe make exclusion criteria less excessive, again,  18 to make this trial more generalizable to the clinical  19 setting.  20 The question of de-escalation was  21 discussed repeatedly. And, again, it seems that if  22 trial in this space might be feasible, enrichment</p>

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<p>1 strategies would be the key for potential feasibility                  2 of the trials.                  3 Am I good on time? Sorry. I'm just                  4 looking at my timing. So I have two minutes.                  5 Endpoints, again, mortality does not                  6 seem to be an appropriate endpoint at this time. A                  7 competent endpoint that includes clinical                  8 and -- response would be -- seems to be more a way to                  9 go.                  10 In regards to timing, early evaluation                  11 seems to be a better place to start maybe within the                  12 first 72 hours. By that time, we should have an                  13 understanding whether we still deal with what we're                  14 dealing with. If it's a fever of unknown origin or                  15 it's a microbiologically defined infection.                  16 And as regards to question four, other                  17 data for febrile neutropenic patients are needed. It                  18 seems that this not necessarily -- that this                  19 population might not be that special for the lack of a                  20 better word, that data on kind of generally use of an                  21 antibacterial drug might be sufficient to inform the                  22 use of a drug in this population.</p>	<p>1 deliberation. So thank you very much for your                  2 participation.                  3 THE REPORTER: Off the record? Hi,                  4 this is the reporter. Are we off the record?                  5 DR. KIM: Yes.                  6 THE REPORTER: Okay. We are off the                  7 record at 1:02 p.m.                  8 (Whereupon, the meeting concluded at                  9 1:02 p.m.)                  10                  11                  12                  13                  14                  15                  16                  17                  18                  19                  20                  21                  22</p>
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<p>1 On the other hand, there was discussion                  2 that PK/PD for multiple reason, it's very confounded,                  3 but we don't maybe fully understand why, but PK/PD                  4 might be different in febrile neutropenic patients.                  5 We touched on artificial intelligence                  6 use over the last few minutes, but I'm not going to                  7 venture on commenting on that. And, again, it was                  8 pointed out that data to inform these models are                  9 critical to have these models meaningful.                  10 And in conclusion, I would like to                  11 thank again speakers and panelists for taking the time                  12 to share their insights and expertise on challenges                  13 with developing drug for empiric therapy in febrile                  14 neutropenia and for making this workshop so                  15 informative and rewarding. Thank you so much.                  16 Any last-minute comment from anyone                  17 from FDA or from outside panelists?                  18 DR. KIM: Hi, this is Peter Kim. I                  19 would also like to thank everyone who put in the time                  20 and the effort in preparation for this workshop. This                  21 has been quite valuable to us. We'll certainly                  22 consider the discussion from this workshop in future</p>	<p>1 CERTIFICATE                  2 I, CHANYRI FIGUEROA MONSANTO, the officer                  3 before whom the foregoing proceedings were taken, do                  4 hereby certify that any witness(es) in the foregoing                  5 proceedings, prior to testifying, were duly sworn;                  6 that the proceedings were recorded by me and                  7 thereafter reduced to typewriting by a qualified                  8 transcriptionist; that said digital audio recording of                  9 said proceedings are a true and accurate record to the                  10 best of my knowledge, skills, and ability; that I am                  11 neither counsel for, related to, nor employed by any                  12 of the parties to the action in which this was taken;                  13 and, further, that I am not a relative or employee of                  14 any counsel or attorney employed by the parties                  15 hereto, nor financially or otherwise interested in the                  16 outcome of this action.                  17                    18 CHANYRI FIGUEROA MONSANTO                  19 Notary Public in and for the                  20 State of New York                  21                  22</p>

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