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U.S. FOOD AND DRUG ADMINISTRATION

PUBLIC WORKSHOP:  
CLINICAL TRIAL DESIGN CONSIDERATIONS FOR  
MALARIA DRUG DEVELOPMENT

Thursday, June 30, 2016

White Oak, Maryland

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<p style="text-align: right;">Page 6</p> <p>1 Bryan Smith, M.D.                  2 Principal Medical Consultant                  3 Clinical Network Services, Washington, DC                  4                  5 Kalavati Suvarna, Ph.D.                  6 Microbiologist                  7 DAIP, OAP, CDER                  8 Food and Drug Administration                  9                  10 Peter Weina, M.D., Ph.D.                  11 Chief, Department of Research Programs                  12 Walter Reed National Military Medical Center                  13                  14 Tim Wells, Ph.D.                  15 Chief Scientific Officer                  16 Medicines for Malaria Venture, Geneva,                  17 Switzerland                  18                  19                  20                  21                  22</p>	<p style="text-align: right;">Page 8</p> <p>1 treatment of malaria. We all know that malaria                  2 remains a major global health problem, with an                  3 estimated number of malaria cases globally at 214                  4 million in 2015, with an estimated over 400,000                  5 deaths. So it continues to be a major issue is                  6 global public health. And we do have agents to                  7 treat patients with malaria, but unfortunately,                  8 know that resistance erodes away at our                  9 therapies. It's currently a problem and we can                  10 expect that will continue to happen in the                  11 future.                  12 So it's really important that we do have                  13 the development of new antimalarial drugs. That                  14 we have new treatments to be able to utilize for                  15 patients out there to be able to continue to                  16 treat patients with malaria and not lose the                  17 ground of success that we've achieved so far.                  18 We also know that developing drugs,                  19 really in any therapeutic area, isn't easy. And                  20 that's particularly true in the setting of                  21 developing new therapies for treatment of                  22 malaria. We also recognize, too, that, you know,</p>
<p style="text-align: right;">Page 7</p> <p>1 P R O C E E D I N G S                  2 MR. COX: Good morning. If we could have                  3 folks move towards their seats, we'll get going                  4 here in just a minute.                  5 Good morning, everybody. I just wanted                  6 to start out the day by saying thank you to all                  7 of you that have come to join us. I'm Ed Cox.                  8 I'm the Director of the Office of Antimicrobial                  9 Products, here within the Center for Drugs at                  10 FDA.                  11 We welcome everybody to today's workshop                  12 on Clinical Trial Design Considerations for any                  13 Malaria Drug Development. We're grateful to the                  14 many folks that have traveled from far and wide                  15 to come and join us. We recognize that there are                  16 tremendous rigors in travel and we thank all of                  17 those that have endured and managed to get here                  18 to do so in good shape and we thank you all for                  19 that.                  20 Today we look forward to discussing                  21 several important issues in clinical trial design                  22 for treatment -- for antimalarial drugs for</p>	<p style="text-align: right;">Page 9</p> <p>1 we, here at the FDA, regulate drugs in the United                  2 States, but we're also very mindful of the fact                  3 that what we do here in the U.S. and our                  4 recommendations with regards to trial design have                  5 global implications. So it's something that we                  6 think is very important to take into                  7 consideration as we're talking about trial                  8 designs and new drug development for malaria.                  9 So today's meeting we'll focus on really,                  10 two specific areas. We'll talk about clinical                  11 trial design issues first. And one of the issues                  12 that comes up fairly commonly is studying various                  13 different combinations of drugs. And there are a                  14 variety of ways to approach this. It depends a                  15 little bit on the drug, it depends a little bit                  16 on the disease. Whether you can use the drug                  17 alone, if you can use the drug alone. How long                  18 can you do that for?                  19 Bottom line is that anything that's done                  20 really needs to be acceptable from an ethical                  21 standpoint and also provide adequate patient                  22 protection. So I look at the issue of</p>

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<p>1 addressing, you know, how to study combinations                  2 of drugs. It's essentially a solvable problem                  3 and the solution just needs to be appropriate for                  4 the circumstance in the particular drug that                  5 you're studying. So we look forward to the                  6 discussions today. I think it will help inform                  7 on that particular aspect of any malarial drug                  8 development.</p> <p>9 In addition to talk some about trial                  10 design combination issues, we'll also talk some                  11 about methods of detection. As we work through                  12 this, I think we'll hear a lot of important                  13 information about the attributes of one test                  14 versus another test. I think that will be                  15 helpful in moving the discussion along about                  16 different types of tests that you might utilize                  17 to diagnose malaria to detect malaria in the                  18 setting of clinical studies.</p> <p>19 And I would encourage people -- this is a                  20 workshop, so it really is meant to be an open                  21 discussion. So please do. Feel free. If we get                  22 the opinions out on the table, if we get the</p>	<p>1 DR. SMITH: Brian Smith, I'm a principal                  2 medical consultant for clinical network services                  3 and the chief medical officer for 60 Degrees                  4 Pharmaceutical.</p> <p>5 DR. WEINA: Pete Weina. I'm the Director                  6 of Research Programs at the Walter Reed National                  7 Military Medical Center. I worked for almost 20                  8 years with the Walter Reed Army Institute of                  9 Research and Drug Development.</p> <p>10 DR. MURPHY: I'm Sean Murphy. I'm a                  11 clinical investigator at the Seattle Malaria                  12 Clinical Trial Center and I'm an Assistant                  13 Professor at the University of Washington.</p> <p>14 DR. LAUREN: Matt Lauren. I'm a clinical                  15 investigator at the University of Maryland School                  16 of Medicine, the Institute for Global Health.</p> <p>17 DR. FELGER: Ingrid Felger. I'm coming                  18 from the Swiss Public Health Institute in Basel.</p> <p>19 DR. ARGUIN: Paul Arguin, Chief of the                  20 Domestic Malaria Unit at the Centers for Disease                  21 Control and Prevention.</p> <p>22 DR. MOHRLE: I'm Jörg Möhrle from the</p>
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<p>1 science out on the table, I think that's really                  2 the best way to move things forward, so don't be                  3 shy, okay. I'm sure we'll have a rich                  4 discussion. And maybe what we'll do too, just so                  5 that everyone's aware of who's at the table, why                  6 don't we start and we'll just work this way down                  7 the table here. We'll start with Professor                  8 McCarthy and then we'll move over here to Dr.                  9 Felger, and then we'll go down this side.</p> <p>10 MR. MCCARTHY: So my name is James                  11 McCarthy. I'm a clinical investigator in                  12 Brisbane, Australia and I lead the blood stage                  13 human challenge system.</p> <p>14 DR. NAMBIAR: Good morning. Sumathi                  15 Nambiar, Director, Division of Anti-Infective                  16 Products.</p> <p>17 DR. KUBLIN: And I'm Jim Kublin, the                  18 Medical Director of the Seattle Malaria Clinical                  19 Trial Center.</p> <p>20 DR. SAUNDERS: David Saunders. I'm a                  21 clinical pharmacologist and internist with the                  22 U.S. Army.</p>	<p>1 Medicines for Malaria. I'm heading the                  2 translational medicine group there.</p> <p>3 DR. WELLS: Tim Wells, Medicines for                  4 Malaria Venture in Geneva.</p> <p>5 DR. O'SHAUGHNESSY: I'm Elizabeth                  6 O'Shaughnessy. I'm a medical officer in the                  7 Division of Anti-Infective Products at the FDA.</p> <p>8 DR. PROSCHAN: I'm Michael Proschan,                  9 mathematical statistician at the National                  10 Institute of Allergy and Infectious Diseases.</p> <p>11 MS. HIGGINS: Karen Higgins, I'm the                  12 statistical team leader supporting the Division                  13 of Anti-Infective Products.</p> <p>14 MR. COX: Great. Thank you all. And                  15 just so folks know, the meeting is being                  16 transcribed, so there'll be a transcript. So I                  17 just want to let folks know that. And also, too,                  18 we provide information on a potential conflicts                  19 of interest. There is information available at                  20 the front desk. We think that's helpful for                  21 folks and available should folks need it.                  22 So now let's move onto our first</p>

<p style="text-align: right;">Page 14</p> <p>1 presentation. Professor James McCarthy will be                  2 speaking first, stepping for Dr. Dondorp. We                  3 appreciate that very much. I'll just say a                  4 little bit. Not too much but a little bit.                  5 Professor McCarthy is a senior scientist                  6 at the Queensland Institute of Medical Research                  7 and Infectious Disease for the World Brisbane and                  8 Women's Hospital, which are both in Brisbane,                  9 Australia. And his clinical and research                  10 training were undertaken in Australia, the U.K.,                  11 at the University of Maryland and also at the                  12 Laboratory of Parasitic Diseases at the National                  13 Institutes of Health.                  14 And we were talking a little bit earlier.                  15 I was actually a fellow at the same time that he                  16 was a senior fellow within LPD at NIAID. So the                  17 world is a lot smaller than we think. The major                  18 focus of his research has been on the development                  19 application and clinical trial systems that                  20 entailed deliberate infection of human volunteers                  21 of malaria parasites, via intravenous injection                  22 of plasmodium effected red cells. So we're</p>	<p style="text-align: right;">Page 16</p> <p>1 that has this to the fore.                  2 And here is the slide of the four malaria                  3 parasites plus the zoonotic malaria parasite,                  4 plasmodium knowlesi. Just to make one point,                  5 we're going to be talking mostly today about                  6 plasmodium falciparum, which is the most lethal                  7 form of malaria. But many of the issues are                  8 equally apparent to the other three species, and                  9 in particular, plasmodium vivax, which I don't                  10 think we're going to get time to talk about                  11 today, but certainly there are some specific                  12 issues about relative activity of some drugs                  13 against P. vivax as opposed to P. falciparum.                  14 So here's the last stock of the life                  15 cycle of the malaria parasite. I really don't                  16 need to go into that this with this audience,                  17 just to make the point that we're going to                  18 talking mostly today about the blood stage, which                  19 is the stage that causes clinical illness in                  20 humans. But there is going to be quite a bit of                  21 discussion about the gametes I expect as well                  22 because this is the life cycle stage that is</p>
<p style="text-align: right;">Page 15</p> <p>1 grateful that Dr. McCarthy has joined us here                  2 today and we look forward to his talk.                  3 So James?                  4 DR. MCCARTHY: So thanks very much, Ed.                  5 It's a great pleasure to be here amongst friends                  6 and colleagues. I know many of the people in the                  7 audience through the work that we've been doing                  8 or from previous lives, as Ed has just mentioned.                  9 I'm stepping in for Arjen Dondorp, who many of                  10 you would also know, who leads a lot of the work                  11 going on in the Mahidol Oxford Research Group in                  12 Bangkok, Thailand. He was unable to make it due                  13 to some problems with travel that I don't want to                  14 go into.                  15 So he's kindly provided me these slides                  16 and I'm going to talk, really to set the scene                  17 about antimalarial therapy and why we need to be                  18 concerned and to develop new drugs and to deal                  19 with it as efficiently as possible. So here's a                  20 picture of Arjen, just so you recognize him. I'm                  21 really pointing out the center of the hot spot of                  22 mission resistance and he's led a lot of the work</p>	<p style="text-align: right;">Page 17</p> <p>1 transmitted to the mosquito and is the focus of                  2 increasing interest, both in terms of drug                  3 efficacy but also if it's to eliminate malaria.                  4 So artemisinin drugs are the key drugs                  5 that really saved the problems we were having                  6 with chloroquine resistance that all the                  7 antimalarials that were viable 20-odd years ago                  8 were filing in principal amongst those with                  9 chloroquine, which had been effective for 50-odd                  10 years. But the other aspect of the artemisinin                  11 was its key attribute in terms of -- we do see                  12 mortality.                  13 And these are the two pivotal clinical                  14 trials that were untaken, one in Asia in children                  15 which showed a 35 percent reduction in mortality                  16 when intravenous artesunate was used instead of                  17 quinine, which was then the drug of choice for                  18 severe malaria. And likewise, a larger study                  19 done in nine African countries where there was                  20 also a 23 percent reduction in mortality. So                  21 this is key issue that we need to think about                  22 when we're worrying about the need for new</p>

<p style="text-align: right;">Page 18</p> <p>1 antimalarials. If we lose these drugs, and there                  2 are data that we'll be showing in a moment, we                  3 are going to be faced with worldwide increasing                  4 immortality for malaria.</p> <p>5       And the reason why the artemisinin drugs                  6 are so effective is because they work across the                  7 whole parasite life cycle and not just at the                  8 letter. Part of the malaria parasite life cycle                  9 where most of the drugs that we have developed in                  10 the past only work from the trophozoite on                  11 through to sporozoite, whereas, the artemisinin                  12 also works in the early stages where the ring                  13 stages are present, and therefore, are more                  14 rapidly acting. This early stage of the malaria                  15 parasite life cycle, the artemisinin drugs seem                  16 to be losing their activity again, and therefore,                  17 are reducing their efficacy.</p> <p>18       The other aspect of the artemisinin drugs                  19 is the rate of which they kill parasites. So                  20 this is a slide that Nick White published and                  21 reviewed several years ago, showing the relative                  22 decrease in the number of parasites in a human</p>	<p style="text-align: right;">Page 20</p> <p>1 terms of being around for up to 24 hours. And                  2 then many of the other drugs that we use for both                  3 prophylaxis and treatment such as Piperaquine,                  4 Chloroquine and Mefloquine have a half-life                  5 measured in many weeks.</p> <p>6       So this means you can give a loading dose                  7 at the start of treatment and continue to have                  8 drive efficacy out for quite a long time when the                  9 drugs are effective.</p> <p>10       So the story of artemisinin resistance is                  11 really, first, properly documented in 2009 by a                  12 paper that Arjen and I were first author on in                  13 the New England Journal of Medicine. And it                  14 showed that we were seeing decreased rights of                  15 clearance of a malaria parasite in different                  16 sites in Asia. So this is site in Cambodia,                  17 where you can see the parasites are still                  18 disappearing from the blood, but there's a                  19 significant decrease in the right of clearance of                  20 the parasites. And this was the first clue that                  21 we were actually seeing a failure of the malaria                  22 parasite to kill those early life cycle stages of</p>
<p style="text-align: right;">Page 19</p> <p>1 host over weeks of treatment. And you can see                  2 when you give the artemisinin drugs, you can                  3 effectively eliminate all the malaria parasites                  4 by a week of treatment, whereas, with a more                  5 slowly acting drug such as Mefloquine,                  6 Piperaquine, and Malarone, there's a much slower                  7 decrement in the parasite clearance. And then a                  8 drug such as Doxycycline, which is widely used                  9 for prophylaxis, really means that you've got to                  10 give treatment for upwards of three weeks if                  11 you're going to achieve cure. So that's the                  12 other key attribute of the artemisinin drugs as                  13 their rapid activity.</p> <p>14       Now, as well as their different activity,                  15 these drugs have got very different                  16 pharmacokinetic profiles. So shown on this graph                  17 is plasma concentration, the drug vs. treatment                  18 time in weeks. And what you first see is that                  19 you can't see the artemisinin drugs because                  20 there, a plasma half-life is measuring now, so                  21 you don't really find the drug in the blood after                  22 24 hours. Quinine is a little bit longer in</p>	<p style="text-align: right;">Page 21</p> <p>1 the parasite.</p> <p>2       Since then, things have become worse. So                  3 in 2012 and 2013, here you've got a Kaplan Myer                  4 probability of cure estimate. So now you're                  5 seeing out at 70-odd percent cure rights in one                  6 particular location in Pursat compared to the                  7 other locations. So clearly, a very significant                  8 decline in the efficacy of antimalarials. And                  9 indeed, it's become even worse now. So you can                  10 see here, you won't be able to read the scale                  11 here, but you're seeing it in these locations in                  12 Cambodia. Basically, you're having the inability                  13 to cure the malaria with DHA Piperaquine, which                  14 is dihydroartemisinin, a derivative of                  15 artesunate. So you're getting a 42-day failure                  16 rates in the order of 80 or 90 percent.</p> <p>17       And we now know very well the mechanisms                  18 of this. This is the Kelch K13 propeller                  19 protein, whose function is not completely well                  20 understood, but there's a mutation at residue                  21 580, which confers significant resistance. This                  22 is now a molecular markup of artemisinin</p>

<p style="text-align: right;">Page 22</p> <p>1 resistance that is now well-described and can be                  2 used for epidemiologic purposes to map the spread                  3 of artemisinin resistance.                  4       And this is what it was in 2013, where we                  5 saw the focus of resistance really being along                  6 the border between Thailand and Cambodia and in                  7 certain parts of Cambodia. But more recently,                  8 it's moved into Myanmar as well, which will be                  9 shown in the next slide. But you can see in                  10 other parts of Asia, there was no evidence of                  11 resistance at all.                  12       Now, this is a genetic slide put up to                  13 map the origin of the artemisinin resistant                  14 mutation. And the point of this slide is really                  15 to show that mutation arose independently in                  16 Myanmar to Cambodia. So what this tells us is                  17 that the parasite is actually developed                  18 resistance at the same location in its genome,                  19 independently in two different places. So that                  20 really raises an issue, as the drug has become                  21 more widely used in Africa, that that mutation is                  22 likely to occur as more use of the drug takes</p>	<p style="text-align: right;">Page 24</p> <p>1 parasite. But in this case, in conjunction with                  2 Mefloquine, which is the partner drug used, where                  3 you have seen a major jump in the parasite                  4 clearance half-life, which is a major of how                  5 quickly the parasites are killed in 2010. And                  6 that's also associated with a decrease in the                  7 efficacy of artesunate-mefloquine also, occurring                  8 about that time.                  9       So not only is the artemisinin resistance                  10 developing, but it's also occurring with the                  11 partner drug which is, in this case, Mefloquine.                  12 And this is a slide prepared by Arjen, showing                  13 where we are with artemisinin resistance now. In                  14 Cambodia, the drug of choice in Cambodia, which                  15 is dihydroartemisinin Piperaquine, is by simply                  16 becoming ineffective. And new treatments are                  17 going to be required as well as with artesunate-                  18 mefloquine, which is the other widely-used                  19 combination in the greater Mekong subregion is                  20 now no longer effective in the Thai-Myanmar                  21 border.                  22       So this is the situation right now where</p>
<p style="text-align: right;">Page 23</p> <p>1 place. And the genetics of this is quite                  2 independent. And this was published some two                  3 years ago. So we now have clear data to suggest                  4 that we are going to lose artemisinin some time.                  5 And the question is when. And that will depend                  6 largely upon the pressure that is applied to the                  7 parasite by increasing use of the drug.                  8       Now, the situation in the greater Mekong                  9 subregions have become even more worrisome. This                  10 is a study published in the Lancet Infectious                  11 Diseases a year ago. And this is a map of                  12 Myanmar. And up in this far corner here is                  13 India. And you can see that the red spot is the                  14 mapping of the prevalence of this K13 propeller                  15 mutation. And you can see it's come right up to                  16 the border of India. So it's very likely that we                  17 have already got spread of this mutant parasite                  18 into India, which suggests that we are going to                  19 see the problem spread across Southern Asia in                  20 the near future.                  21       And this is just more data showing the                  22 increasing in prevalence of the drug resistant</p>	<p style="text-align: right;">Page 25</p> <p>1 our two most potent combination therapies have                  2 become effectively resistant to treatment. And                  3 this is also been mapped for mefloquine to be                  4 shown to be associated with the MDR drug                  5 transporting pump. So as you get increasing                  6 copies of the MDR, copy number from one down to                  7 more than two copies of the MDR, you can see your                  8 cure rate drops from 100 percent down to 60                  9 percent. So clearly, we've got good molecular                  10 data as to what's going on here. And the                  11 question is how long are we going to last?                  12       And the issue is not only will we see                  13 resistance, but we'll also probably see increased                  14 transmission because people who have decreased                  15 cure from the antimalarial drugs carry                  16 gametocytes. The sexual stage of the parasite                  17 ran for longer, so that means there's going to be                  18 a larger reservoir, more clinical cases, more                  19 drug used, more resistance. So this vicious                  20 cycle will continue. And this was certainly case                  21 when chloroquine resistance arose.                  22       So I don't need to again remind the</p>

<p style="text-align: right;">Page 26</p> <p>1 audience that was spread of chloroquine                  2 resistance that arose independently, both in                  3 South America and also in the same region of Asia                  4 and it's spread over a period of 10 years across                  5 Africa and caused probably an excess of millions                  6 of deaths in children in Africa when chloroquine                  7 was no longer effective. Likewise, we've seen                  8 the spread of resistant sulfadoxine-pyrimethamine,                  9 again, from Asia or across to other parts of the                  10 world.                  11       So this clear historic precedents when                  12 you see these resistance events occur that they                  13 are going to spread. And the question really is                  14 how quickly that's going to happen. So when                  15 Arjen and I were doing infectious diseases                  16 training, one of the paradigms we were taught by                  17 our mentors was you never add one drug to a                  18 filing regiment. So whether it be tuberculosis,                  19 HIV, or any of the other combination of                  20 infectious diseases that require multiple                  21 antibiotics, adding one drug to a filing                  22 regiment, really only buys you a little bit of</p>	<p style="text-align: right;">Page 28</p> <p>1 but then the adherence of your patient certainly                  2 diminishes. And there's the possibility, I                  3 suppose, of crop rotation, where you rotate                  4 different drugs around to try and decrease                  5 pressure on a particular drug, hoping that the                  6 survival advantage of the parasite with the wild                  7 type completes the mutant parasite.                  8       And then there are sequential uses as                  9 well or potentially, artesunate-pyrimethamine,                  10 which is otherwise known as Pyramax, which has                  11 recently been more widely licensed as the liver                  12 signal has diminished. So these are some of the                  13 strategies being contemplated in the greater                  14 Mekong region to try and reduce -- to try to                  15 really buy some time. And I think that's what my                  16 take on this is, what we're doing is buying time.                  17       So these are just some data on the                  18 combination therapies. The first is that there                  19 seems to be some mutual antagonism between                  20 piperazine and mefloquine when you use them                  21 together. That there is no enhanced cardiac                  22 signal as far as we can tell because both of</p>
<p style="text-align: right;">Page 27</p> <p>1 time and is not going to be a definitive                  2 solution. So the solution is being contemplated                  3 now in the greater Mekong region, basically doing                  4 exactly that. So we're adding mefloquine to                  5 dihydroartemisinin Piperazine or amodiaquine to                  6 artemether-lumefantrine. In the following                  7 slides, I'll show why this might have both                  8 pharmacokinetic and pharmacodynamic rationale,                  9 but the point being what we're doing is really                  10 only buying ourselves time.                  11       There are some new drugs around,                  12 artemolane, formerly known as OZ439 is a                  13 synthetic antimalarial which is being tried with                  14 the piperazine, but the data with this aren't                  15 particularly encouraging in the dose regimens                  16 that have been tried to date. But whether this                  17 will be an effective regiment when used for                  18 longer, we'll wait and see. And there are two                  19 clinical trial programs going on called Track 2,                  20 which you're looking at that. And then there's                  21 obviously the options of increasing the duration                  22 of treatment, which is certainly a possibility,</p>	<p style="text-align: right;">Page 29</p> <p>1 these drugs, you'll know, have some effect on the                  2 cardiac conduction but there doesn't appear to be                  3 any problem with that and that there is both some                  4 pharmacodynamic and pharmacokinetic reasons why                  5 these drugs can be used together. So that's the                  6 rationale for why the AK-piperazine can be used                  7 in combination with mefloquine. And potentially,                  8 it will rescue the situation in parts of Cambodia                  9 where the DHA-piperazine regiment is no longer                  10 effective.                  11       And likewise with artemether-                  12 lumefantrine, the proposal is that amodiaquine                  13 which is a log off of chloroquine, has both a                  14 pharmacodynamic and a pharmacokinetic reason for                  15 combination here and using these two drugs                  16 together. So this is otherwise known as Coartem                  17 or (inaudible). It is a very widely-used, in                  18 fact, the drug of choice in Australia and the                  19 U.S. for the treatment of malaria now is adding                  20 amodiaquine to this regiment actually probably                  21 will improve drug efficacy and reverse the                  22 situation where you're losing activity of the</p>



<p style="text-align: right;">Page 30</p> <p>1 artemisinin combination.                  2       So in conclusion, we're going a little                  3 more quickly than I had planned, the fast-acting                  4 drug, the artemisinin has a major survival                  5 advantage. And if we lose this artemisinin,                  6 we're going to lose that survival advantage. And                  7 in subsequent talks, they'll be a discussion                  8 about selecting a drug that does have a fast-                  9 killing property, which is obviously going to be                  10 critically important for saving the lives of                  11 people who severely have malaria. Certainly,                  12 this also means that you can select a partner                  13 drive with a long half-life, which really means                  14 you can identify a regiment of antimalarials that                  15 can be given in a very short course, which is                  16 clearly ideal when you're dealing in a situation                  17 in many countries that have malaria where having                  18 people come back to complete course of therapy                  19 can be a difficulty. And obviously, a drug                  20 combination, just in other areas of antimicrobial                  21 therapy, you increase the genetic barrier to                  22 resistance as you coformulate drugs with</p>	<p style="text-align: right;">Page 32</p> <p>1 effective artemisinin, you're going to lose your                  2 partner drugs. So you really need to anticipate                  3 that happening. And also, you're going to                  4 probably increase the transmission of malaria                  5 because there's going to be increase in                  6 gametocyte carriage.                  7       In terms of partner drug resistance, this                  8 is an increasing problem across Southeast Asia,                  9 and particularly in the greater Mekong subregion,                  10 where the partner drugs are basically running out                  11 of juice. And finally, this leaves us with the                  12 situation where there are now very few options                  13 left in this part of the world. And as I                  14 discussed, these triple combinations are now                  15 becoming necessary. In my view, at least, this                  16 is just buying us time. So therefore, we                  17 urgently need antimalarials and we need to think                  18 very carefully about the partner drug and the                  19 developmental pathways for licensure of the                  20 drugs.                  21       And just as a last slide, this is the                  22 global list of drugs that are available at the</p>
<p style="text-align: right;">Page 31</p> <p>1 complementary mechanisms of action. This is a                  2 concept that I don't think I need to explain to                  3 this audience, but it means that we really need                  4 to be thinking about this when we construct                  5 coformulations. A major theme of today's talk is                  6 that we have a significant increase in the                  7 complexity of drug development once we start to                  8 think about developing and licensing a                  9 combination antimalarial, given some of the                  10 difficulties that we'll discuss later in the day                  11 in terms of clinical trial design.                  12       So the other conclusions to make is                  13 artemisinin resistance is now with us. It's                  14 expanding across Southeast Asia. To date, there                  15 is no evidence that it's arrived in Africa, but                  16 because, as I said, the mutations have arisen                  17 independently, there's no reason to believe they                  18 weren't arisen in Africa either. It contributes                  19 the treatment failure and we're seeing clear                  20 cases of treatment failure in part of the greater                  21 Mekong region. It selects for the partner drug                  22 resistance. So once you lose your fast-killing</p>	<p style="text-align: right;">Page 33</p> <p>1 moment. So you've got drugs under research,                  2 which you're doing lead optimization,                  3 translational work, which will be discussed later                  4 in the morning. And then we only have one drug,                  5 which is a combination that is currently in                  6 clinical trial that doesn't include an                  7 artemisinin drug.                  8       So despite the fact that we got a large                  9 number of drugs all across this point, the only                  10 drug we currently have at the moment, having                  11 Phase II is the combination of OZ439 and                  12 ferroquine.                  13       So we really are in a very urgent                  14 situation because we need to somehow develop new                  15 combinations so that we have drugs in Phase II                  16 and Phase III so that we don't start having                  17 thousands of people having adverse outcomes                  18 because we don't have a drug to treat them with.                  19 So I think I might stop there. I'm not sure how                  20 we're doing for time. We got time for questions                  21 or we keep going?                  22       DR. NAMBIAR: Yeah. I think we have time</p>

<p style="text-align: right;">Page 34</p> <p>1 for a couple of clarifying questions. Any                  2 questions from the panel members? Any questions                  3 from the audience?                  4 We have one question.                  5 DR. BERMAN: Hello. An excellent talk,                  6 Professor McCarthy. I'm Dr. Berman from Fast-                  7 Track Drugs. Since you do have a little extra                  8 time, let me sort of think in broad terms for the                  9 last 20 or 30 years, we've had a prohibition                  10 about anything more than three-day dosing. And                  11 as you've well said, presented the origination of                  12 resistance in a certain part of the world and                  13 then spread to the rest of the world. So there                  14 are two questions that occurred to me as a                  15 listener.                  16 The first is this prohibition against                  17 anything more than three days really a strong                  18 barrier, just something that grew up with                  19 traditional chloroquine treatment and may be                  20 something that's not so much of a driver. It                  21 doesn't have to be so much of a driver these                  22 days.</p>	<p style="text-align: right;">Page 36</p> <p>1 we've seen in this part of the world and there                  2 has been speculation about particular                  3 epidemiologic factors located there, as well as                  4 drug use, counterfeit drug use. There's been a                  5 range of proposed explanations as to why the                  6 occurrence of these resistance mutations has                  7 taken place in that part of that world.                  8 It's also true to say that the mefloquine                  9 resistance mutations did revert once artemisinin                  10 in combinations came into use there. So there                  11 clearly is a fitness cost to the parasite                  12 carrying these extra MDR gene copy numbers and                  13 that is readily able to revert. So very quickly                  14 after artemisinin resistance arose, we saw                  15 reversion to these multiple copy number MDR copy                  16 number parasites in that part of the world.                  17 So I think it's an open question as to                  18 whether mefloquine will be widely resistance                  19 would be more widely seen if we used it, for                  20 example, in heart transmission settings in                  21 Africa. But also, as you're well aware, there                  22 are some significant toxicity issues that have</p>
<p style="text-align: right;">Page 35</p> <p>1 And the second question and this is just                  2 one of knowledge, is using the example of                  3 mefloquine. As mefloquine resistance jumped from                  4 the Mekong River locale to the rest of the world,                  5 the reason I'm saying that is very few of us                  6 travelers and people in the Western world really                  7 go to the Thai-Cambodian border or the Myanmar                  8 Cambodian border. And so the broad question of                  9 drug development is it to make products against                  10 what's there because it will spread or to make                  11 products against issues faced by 99.9 percent of                  12 the rest of the world which can use present drugs                  13 in spite of some of their difficulties, for                  14 example, mefloquine?                  15 DR. MCCARTHY: Maybe I'll tackle the                  16 second part first. To my knowledge, there may be                  17 people in the audience knowing who can answer                  18 this question better than I, but I don't believe                  19 that there's been widespread use of mefloquine                  20 in, for example, sub-Sahara in Africa. Certainly                  21 it's used in South America, but we have not seen                  22 the occurrence of mefloquine resistance like</p>	<p style="text-align: right;">Page 37</p> <p>1 really, I admit, although it may not be a problem                  2 with severe malaria there, obviously a                  3 significant opposition in the general public                  4 about the use of mefloquine, and certainly in                  5 Australia, we've had very recent examples with                  6 our military activists -- or ex-military activist                  7 blaming mefloquine for psychosomatic illnesses.                  8 The second part, I suppose, is a more                  9 philosophic one about duration of treatment.                  10 That the CIRCAP concept that was really                  11 promulgated with the malaria and control                  12 initiative that came about five years ago has                  13 come under question that we may need to consider                  14 longer courses of treatment, but we all know that                  15 in clinical practice that longer courses of                  16 treatment are not necessarily well adhered to.                  17 And if you have to have those long courses, it                  18 certainly increases the probability of failure.                  19 So ideally, one has a drug where you can                  20 have a prolonged period of time above the MIC                  21 with a drug that can be given in loading dose.                  22 So I think it is a philosophic question and I</p>

<p style="text-align: right;">Page 38</p> <p>1 don't pretend myself to have an answer to and I                  2 think this is something that could be debated,                  3 perhaps, later on.                  4 DR. NAMBIAR: Great. Thank you, Dr.                  5 McCarthy. So again, thank you for the excellent                  6 overview. And we'll looking for your clear                  7 message on the need for new antimalarial                  8 therapies and the need for combination therapies                  9 as well. So with, I think we'll move into the                  10 first session that Dr. McCarthy and I will co-                  11 chair. And the focus of this session is on                  12 clinical trial design considerations and use of                  13 multiple drugs in combination.                  14 So we have four speakers. And in the                  15 interest of time, what we'll do is we will get                  16 through the four talks and have time for                  17 questions and answers after the last speaker.                  18 The first speaker of this session is Dr.                  19 Elizabeth O'Shaughnessy. Dr. O'Shaughnessy is                  20 the medical officer in the division of anti-                  21 infective products in the Office of Antimicrobial                  22 Products at the FDA. We've been very fortunate</p>	<p style="text-align: right;">Page 40</p> <p>1 individual drugs to a combination regiment.                  2 With regard to regulations, for all new                  3 drug applications, we need substantial evidence                  4 of effectiveness that needs to be demonstrated                  5 through the inadequate and well-controlled                  6 clinical trials. If we look at the definition of                  7 substantial evidence, it means evidence                  8 consisting of adequate and well-controlled                  9 investigations, including clinical investigations                  10 performed by experts which demonstrate the drug                  11 or the combination of drugs that will have the                  12 effect it purports to have under the conditions                  13 of use prescribed in the label.                  14 And if anyone wants to look up the                  15 adequate and well-controlled trials, they're                  16 under CFR 314.126. So we also need data to                  17 demonstrate that each component of a fix-dose                  18 combination contributes a measurable advantage                  19 over the individual components. And this we                  20 refer to commonly as the combination rule. And                  21 this can be either increased efficacy, reduced                  22 emergence of resistance, better safety or, for</p>
<p style="text-align: right;">Page 39</p> <p>1 to have Dr. O'Shaughnessy as one of our                  2 reviewers. She has had experience in reviewing                  3 antimalarial products. She is trained in                  4 internal medicine and infectious diseases and has                  5 started her medical training in Ireland before                  6 moving to the United States.                  7 With that, welcome, Dr. O'Shaughnessy.                  8 Thank you.                  9 DR. O'SHAUGHNESSY: So my presentation                  10 today will be a high level description of the                  11 regulatory and scientific issues related to the                  12 development of antimalarial drug combinations.                  13 So I want to start with providing a regulatory                  14 framework or backdrop that pertains to the                  15 development of drugs in combinations for the                  16 discussions later this morning and then I'll                  17 comment on the challenge we encounter here with                  18 the development of antimalarial drugs in                  19 combination, and then go onto to talk about the                  20 FDA guidance document and the co-development of                  21 drugs, and then comment a little bit about study                  22 design options to assess the contribution of</p>	<p style="text-align: right;">Page 41</p> <p>1 example, a simplified regiment. And even for                  2 drugs that are not developed in a fixed                  3 combination are either not physically combined,                  4 we also require data to show that the individual                  5 components of the combination contribute                  6 something to the combination and that there's a                  7 measurable advantage.                  8 So the challenge here is how to                  9 demonstrate the contribution of individual                  10 antimalarial drugs to a combination regiment.                  11 And we can do this through preclinical studies                  12 and clinical studies and it's usually in a                  13 combination of both.                  14 For preclinical evaluations and                  15 antimalarial drug combinations may include in                  16 vitro activity of the combination versus the                  17 individual drugs against laboratory strains and                  18 clinical islets. And we can also look at the                  19 activity of the combination versus individual                  20 drugs in animal models. And we really look to                  21 the panel today to give us more information or                  22 help us to look at what in vitro studies and</p>

Page 42	<p>1 animal models would be suitable to study the</p> <p>2 contribution of individual drugs to an</p> <p>3 antimalarial drug combination.</p> <p>4 With regard to clinical studies, well,</p> <p>5 one approach to obtaining a rapid proof of</p> <p>6 concept for the activity of a malarial vaccine or</p> <p>7 an antimalarial drug in humans is the controlled</p> <p>8 human malarial infection study, which would be</p> <p>9 covered later this morning. And we would like to</p> <p>10 ask if a CHMI study in any way could help to</p> <p>11 assess the contribution of an individual</p> <p>12 component in an antimalarial drug combination as</p> <p>13 a whole. And also, we would like to ask your</p> <p>14 opinion on the feasibility of a factorial design</p> <p>15 study in adults in a semi-immune population, for</p> <p>16 example, with uncomplicated malaria. Obviously,</p> <p>17 there are ethical considerations. There is</p> <p>18 potential for some optimum efficacy, the safety</p> <p>19 of the patients and the development of</p> <p>20 resistance, if one includes a monotherapy arms.</p> <p>21 And obviously the patients require close</p> <p>22 monitoring and prompt rescue therapy and we would</p>	Page 44	<p>1 combinations and their contribution of the</p> <p>2 combination as a whole. One is where each drug</p> <p>3 alone has activity can be administered</p> <p>4 individually and they describe a factorial design</p> <p>5 situation where one compares the combination and</p> <p>6 in this, the combination is A and B and the SOC</p> <p>7 is the standard of care.</p> <p>8 So one can compare the two together</p> <p>9 versus A versus B versus the SOC, or one can</p> <p>10 consider adding the drugs to the standard of</p> <p>11 care. And we heard from Dr. McCarthy the issues</p> <p>12 with that. Before you compare the combination</p> <p>13 with the standard of care versus each of the</p> <p>14 components and then compare it to the standard of</p> <p>15 care plus placebo. And we just posed a question,</p> <p>16 could we consider administering drugs for a short</p> <p>17 duration of time, but long enough to establish</p> <p>18 proof of concept, where we look at the effect on</p> <p>19 malaria parasite reduction as an early time point</p> <p>20 after the start of treatment. And of course, all</p> <p>21 the ethical considerations that I described would</p> <p>22 apply to this kind of study.</p>
Page 43	<p>1 like your opinion on the feasibility of such a</p> <p>2 study.</p> <p>3 I'm now going to switch to the FDA</p> <p>4 Guidance document. So the FDA has a guidance</p> <p>5 document for the co-development of two or more</p> <p>6 unapproved drugs. So it applies to multiple</p> <p>7 therapeutic areas. It's not specifically related</p> <p>8 to infectious diseases and it's intended to</p> <p>9 provide guiding principles for the concurrent</p> <p>10 clinical development of two or more</p> <p>11 investigational drugs to be used in combination.</p> <p>12 The focus is on approved drugs, but we</p> <p>13 also refer to it for co-development of an</p> <p>14 approved or with an unapproved drug, for example.</p> <p>15 We had a malaria guidance that was published in</p> <p>16 2007. I say "had" because it's withdrawn from</p> <p>17 the FDA website right now and the plans are to</p> <p>18 update it and hopefully the discussion this</p> <p>19 morning will help us with this.</p> <p>20 In the co-development guidance, they</p> <p>21 provide different study scenarios for the</p> <p>22 evaluation of the components of individual</p>	Page 45	<p>1 So the goal, from our perspective, is to</p> <p>2 try and get a handle on the how the two drugs or</p> <p>3 the three drugs in a combination contribute to</p> <p>4 the combination as a whole before we get to Phase</p> <p>5 II trials because if the findings from in vitro</p> <p>6 and in vivo studies adequately demonstrate that,</p> <p>7 then the Phase III trials can compare the</p> <p>8 combination regiment up against the standard of</p> <p>9 care and that should be generally sufficient to</p> <p>10 establish effectiveness of the regiment.</p> <p>11 Before I finish, the combination rule can</p> <p>12 be very complicated. These are just some</p> <p>13 examples of how it's been applied in other areas.</p> <p>14 I'll do an example for malaria first then --</p> <p>15 actually, one from -- just look at Hepatitis C</p> <p>16 and tuberculosis. So as we heard, actually,</p> <p>17 Coartem was the most recently approved</p> <p>18 artemisinin combination. It was approved by the</p> <p>19 FDA in 2009 for the treatment of uncomplicated</p> <p>20 falciparum malaria. And the NDA for Coartem,</p> <p>21 among other studies contained two factorial</p> <p>22 design studies which evaluated artemether-</p>

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<p>1 lumefantrine alone and in combination.                  2       These studies are older studies. They                  3 were done in the early '90s in China, when issues                  4 related to monotherapy and antimalarial drug                  5 resistance were not as well established as they                  6 are now. And one of them was a double-blind                  7 comparative trial of Coartem versus artemether                  8 and versus lumefantrine alone. There were                  9 monotherapy arms in that study. And then a                  10 partially blinded comparative trial of Coartem                  11 versus lumefantrine tablets and capsules.                  12       So as I mentioned, these are older                  13 clinical data that the sponsor happened to have                  14 access to. And of course, it raises lots of                  15 ethical considerations now regarding the use of                  16 monotherapy; however, they did have access to                  17 this old data. And if there is old data out                  18 there that one can access, it certainly should be                  19 submitted to us.                  20       So with regard to Hepatitis C, that                  21 guidance talks about an alternative to a                  22 factorial design study where sponsors can show</p>	<p>1 background regiment.                  2       I think that's my final example. Yes, it                  3 is. So the assessment of the contribution of                  4 individual drugs to an antimalarial drug                  5 combination is challenging. And we look forward                  6 today to hearing from the panel what in vitro                  7 studies, animal studies and clinical studies                  8 could help look at this issue. And before I                  9 finish, I would certainly encourage sponsors to                  10 communicate early with division when they're                  11 considering co-development of antimalarial drugs                  12 so that we can address the kinds of questions                  13 that I've discussed earlier, early in                  14 development.                  15       Thank you for your attention.                  16       (Applause.)                  17       DR. MCCARTHY: Thank you for that                  18 presentation. Our next speaker is Jim Kublin,                  19 who is director the HIV Vaccine Network based                  20 Fred Hutchinson in Seattle. He's also the                  21 medical director of the Seattle Malaria Clinical                  22 Trial Center, faculty member of the Department of</p>
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<p>1 the contribution toward efficacy of a multiple                  2 direct-acting antiviral combination using in                  3 vitro and clinical data. And the guidance goes                  4 on to describe that subcultural data showing that                  5 the antiviral combination slower prevent the                  6 emergence of resistance compared to single drugs.                  7 Our early Phase II data, where the addition of a                  8 drug to a combination improve sustained viral                  9 response reduces emergence of resistance. So the                  10 point being here that one can use a combination                  11 of in vitro and clinical data to make the case.                  12       My last example is tuberculosis. And of                  13 course, we have the early bactericidal activity                  14 studies which are used to evaluate individual                  15 drugs and combinations of drugs with -- using a                  16 microbiological outcome in patients at early time                  17 points from 7 to 14 days. And the MDR-TB, if a                  18 superiority study can be done, one could look at                  19 adding the investigational drug with an optimized                  20 background regiment versus a placebo with an                  21 optimized background regiment. Of course, a lot                  22 depends on the efficacy of the optimized</p>	<p>1 Global Health at the University of Washington.                  2 Jim trained extensively in clinical research in                  3 HIV and malaria across South America, Asia, and                  4 Africa, including clinical trials of therapies                  5 and vaccine.                  6       Jim completed his B.S. and M.D. at                  7 Georgetown University and then his MPH residency                  8 of preventative medicine at Johns Hopkins.                  9       DR. KUBLIN: Thank you, Jim. And thank                  10 you for the organizers. As disclosure across the                  11 HIV TB and malaria fields, we're funded by GSK                  12 Novartis and Santa Fe.                  13       I'll hopefully help set the stage for the                  14 application of CHMI to the therapeutic potential                  15 of antimalarial compounds. And we're focusing                  16 today primarily on the target product profiles                  17 for therapeutic purposes, but of course, we have                  18 extensive experience in applying the CHMI model                  19 for preventive drugs and vaccines.                  20       We'll discuss briefly the methods of                  21 infection in the CHMI model of diagnosis, of                  22 product administration. Of course, highly</p>

<p style="text-align: right;">Page 50</p> <p>1 dependent on the potential for the antimalarial                  2 drug and opportunities here and for discovery.                  3 So of course, the target product profile is first                  4 and foremost in the thoughts of individuals who                  5 are trying to develop antimalarial therapies for                  6 the purposes of preventive and therapeutic                  7 purposes.                  8 For the purpose of today's discussion and                  9 focus on therapeutic outcomes, this is highly                  10 dependent, of course, on the plasmodium species;                  11 the focus and the control of severe disease.                  12 Control of further transmission, as was                  13 highlighted by James in his introductory talk and                  14 of course, in light of today's discussion,                  15 combination with other drugs. And personal                  16 interest is how diverse and complex oftentimes                  17 the endemic subjects biome is with the occurrence                  18 of concurrent infections.                  19 As James highlighted, the malaria cycle                  20 is one that it first transfixed me in the early                  21 '80s with regard to my interest in the basic                  22 biology of the parasite, and particularly, the</p>	<p style="text-align: right;">Page 52</p> <p>1 controlled fashion, and very much adhering to                  2 GMP. And now we're testing it, applying it for                  3 the evaluation of drugs and vaccines and have                  4 essentially three methods in which we can expose                  5 individuals to malaria, resulting in 100 percent                  6 infection rates among those in control arms.                  7 That's the sporozoite-induced malaria infection                  8 via direct venous inoculation, currently Sanaria                  9 is providing the crowd preserved sporozoites and                  10 of course, via the Gold Standard natural root of                  11 the infected anopheles bites. But also, thanks                  12 to James and his team, the induced blood stage                  13 malaria infection gaining great progress for the                  14 evaluation of acute therapeutic antimalarial                  15 drugs.                  16 The methods of sporozoite-induced malaria                  17 infection, as I mentioned, include both the                  18 infected mosquito bite and via direct venous                  19 inoculation. We have an ongoing study in Seattle                  20 in which we have the opportunity to compare these                  21 two methods of exposure and infection to malaria                  22 in a clinical trial. And to my knowledge, is the</p>
<p style="text-align: right;">Page 51</p> <p>1 gametocyte oogenesis and fertilization in the                  2 mid-gut of the mosquito.                  3 As a matter of interest, it's interesting                  4 to look back historically, and what breakthroughs                  5 occurred to make progress in moving forward into                  6 the development of the controlled human malaria                  7 infection models; the first being Ronald Ross's                  8 segment of work over 100 years ago. And then                  9 followed up by the second Nobel awarded for                  10 malaria in the application of the therapeutic                  11 value of malaria inoculation and the treatment of                  12 dementia paralytica at the time, eventually                  13 attributed, of course, to treponema and syphilis                  14 infection, making significant headway in the                  15 application of malaria infection for the                  16 treatment of neurosyphilis.                  17 And this was most recently applied as                  18 late as the 1960s in which you see here an                  19 individual was intentionally infected with                  20 plasmodium in the great city of Boston in the                  21 1960s. But of course, since then, we've applied                  22 the CHMI model extensively and in a very</p>	<p style="text-align: right;">Page 53</p> <p>1 only clinical trial that has the opportunity to                  2 compare these in identical cohorts. There are a                  3 variety of pros and cons to each methodology.                  4 The infected mosquito bite model is particularly,                  5 you know, I think the best for understanding any                  6 immunomodulatory effects, starting directly from                  7 the inoculation from the proboscis of the                  8 mosquito. And we know there are tremendous                  9 amount of dermal interactions between the                  10 parasite and people right up front.                  11 There are some cons to this, as is                  12 highlighted by some of the subsequent slides in                  13 describing what is necessary for the rearing of                  14 these infected mosquitos. And similarly, there                  15 are pros and cons to the direct venous                  16 inoculation method. There are certainly some                  17 advantages by easier implementation, a lower cost                  18 by not having to maintain the insectary at the                  19 clinical research site and location. It appears                  20 to have a more consistent infectious dose and I                  21 think Sanaria is working on optimizing the crowd                  22 preservation process to improve the viability of</p>

<p style="text-align: right;">Page 54</p> <p>1 those parasites. But it does, of course, bypass                  2 the skin immune system by directly inoculating                  3 through the vein and the sporozoites transfer                  4 directly to the liver without the intradermal                  5 exposure.                  6       So the mosquito infection, of course, in                  7 Seattle we have the facility at the Center for                  8 Infectious Disease Research, in which we can rear                  9 the infected mosquitos. We pass these infected                  10 mosquitos eventually through a pass-through to                  11 the where the exposure does occur. They're                  12 returned to the facility for assessment of the                  13 bloodmeal dissection and assessment for                  14 sporozoites and grading of those sporozoites.                  15 And all of this is documented and we repeat this                  16 process until five infected bites with a greater                  17 than equal to two plus rating is achieved. And                  18 these are just images highlighting the process                  19 and the approximately seven weeks that it                  20 requires from the (inaudible 53:33) sites in                  21 culture to the ready and infected anopheles.                  22       The mosquito challenged kinetics is</p>	<p style="text-align: right;">Page 56</p> <p>1 at the crowd-preserved sporozoite challenge                  2 kinetics, on the lower left is data that we've                  3 just collected last month, reflecting a very                  4 similar kinetics to what we've seen in the                  5 mosquito. And Sean has compiled a comparison of                  6 the various crowd preserved methods of                  7 application, whether intradermal or intramuscular                  8 or the direct through the vein, and appear to be                  9 consistent with the thick blood smear and nucleic                  10 acid test. They're compared on the right.                  11       And then there's been, fortunately, very                  12 good success by James and colleagues in the                  13 inoculation of blood stage malaria, evaluating                  14 the parasitemia of the falciparum red blood cell                  15 banks that they've established and just recently                  16 published on, looking at 78 percent parasitemia                  17 in those cell banks. There's confirmation of                  18 identity, evaluation of the viability. Of                  19 course, adventitious agent testing, identity                  20 testing and an extensive quality review                  21 highlighting that now with these red blood cell                  22 banks of infected RBCs, there's a tremendous</p>
<p style="text-align: right;">Page 55</p> <p>1 something that we've been focusing on well                  2 because this is something that we want to compare                  3 the crowd preserved sporozoite application. And                  4 so far, without a direct comparison, they appear                  5 to be quite similar. This is data from an                  6 infection treatment vaccination study that we                  7 conducted and presented at Trial Med a couple of                  8 years ago, demonstrating in the red and green,                  9 some very consistent kinetics with regard to the                  10 emergence of the asexual erythrocytic stage. And                  11 in the black, highlighting individuals who did                  12 demonstrate partial immunity and protection to                  13 the asexual stage.                  14       And then more recently we have                  15 experienced in Seattle with the malaria                  16 challenge, via the direct venous inoculation.                  17 This requires transfer of the prior preserved                  18 sporozoites to the clinical site and liquid                  19 nitrogen and dilution in PBS with the direct                  20 venous inoculation via tuberculin syringe, which                  21 is very quick and quite easy.                  22       So in investigating and looking further</p>	<p style="text-align: right;">Page 57</p> <p>1 opportunity to apply the inoculation of blood                  2 stage malaria model in future work.                  3       Similarly, the growth kinetics has been                  4 published, appears to reflect that of the                  5 merozoites as they exit the liver and is very                  6 typical of the asexual replication in the                  7 periphery.                  8       Moving on, methods of malaria diagnosis                  9 is also something that we'll be discussing and                  10 has various pros and cons with regards to its                  11 application. Of course, the standard in the                  12 field is the thick blood smear, rapid diagnostic                  13 test are also more frequently used now. In                  14 Seattle, we're using the quantitative RTPCR, and                  15 we're hear more about that from Sean.                  16       So in our hands, the diagnosis versus                  17 clinical symptoms is something that we've had                  18 experience since our first demonstration project                  19 that we conducted in close collaboration with our                  20 good colleagues at Walter Reed to help establish                  21 the Seattle Malaria Clinical Trial Center.                  22       We looked at the days of incubation</p>

<p style="text-align: right;">Page 58</p> <p>1 period and the onset of symptoms. And here in                  2 the lower right, you can see that the blood                  3 smears were frequently positive after the initial                  4 presentation of symptoms with the application of                  5 nucleic acid testing, and in particular, that of                  6 the QRT PCR in our hands, were able to identify                  7 and diagnose most people prior to the                  8 presentation of symptoms.</p> <p>9 So product administration and the methods                  10 vis-à-vis CHMI is also something that is under                  11 much consideration when looking forward to                  12 designing a clinical trial in the CHMI model.                  13 For the preventative and prophylaxis studies, I                  14 presented previously extensively on how we                  15 establish those different models. We've called                  16 them a time shift of single administration.                  17 That's being at fixed dose prior to CHMI and                  18 provides a tremendous amount of precision with                  19 regard to the PK and PD.</p> <p>20 There's a dose de-escalation at a fixed                  21 time point prior to CHMI, and the, of course,                  22 we're looking at designing multiple dose,</p>	<p style="text-align: right;">Page 60</p> <p>1 first in man studies and which one looks at that                  2 early PK data, what the metabolites are and what                  3 the combinations may be, of course, will heavily                  4 influence how one takes this initial PK data and                  5 translates that into the clinical trial design.</p> <p>6 And then what model of challenge, whether                  7 we use the sporozoite inoculation method or the                  8 inoculation of infected red blood cells is again,                  9 highly dependent on the factors I've discussed.</p> <p>10 This is an example of CHMI via the sporozoite                  11 inoculation method diagnosed with nucleic acid                  12 testing, which one does potentially provide a                  13 multiple therapeutic purposes, whether it's three                  14 days or longer is something that I think we have                  15 to consider.</p> <p>16 In the case of thick blood smear, that                  17 will be shifted to the right and the application                  18 of drugs and the PK resulting from that, of                  19 course, will be a primary focus and target for                  20 the endpoints of the clinical trial. So we do a                  21 lot of work in HIV vaccines, and of course, the                  22 Holy Grail are the major focus of much of our</p>
<p style="text-align: right;">Page 59</p> <p>1 multiple CHMI exposures which may be more                  2 representative of the field.</p> <p>3 For therapeutic studies, and particularly                  4 those in drug combinations, there's quite a bit                  5 more potential for these factorial designs.                  6 Questions around dose de-escalation, or                  7 escalation in the context of multiple combination                  8 is also something that can be integrated in such                  9 a factorial design. What the diagnostic                  10 threshold and the endpoint will be. The timing                  11 of the rescue therapy may be contingent upon the                  12 diagnostic test, intermittent presumptive therapy                  13 and how to translate IPT that may be the end                  14 target product profile reversed back to the CHMI                  15 model is something that we've also discussed.                  16 And again, this issue of co-infections and how                  17 that may impact anti-microbial chemotherapy and                  18 even drug resistance is an issue that's come up                  19 repeatedly and even more frequently.</p> <p>20 So the method of product administration,                  21 of course, and the dose and the timing of that is                  22 highly dependent on the preclinical work and the</p>	<p style="text-align: right;">Page 61</p> <p>1 research is to identify correlate of protection                  2 for further vaccine development. Pierre Gilbert                  3 is our statistician in that, and I know many of                  4 you have worked with us in this effort in trying                  5 identify correlate of protection in that area is                  6 a tremendous focus of our efforts.</p> <p>7 We do have opportunities for discovery in                  8 the controlled human malaria infection model that                  9 I think is quite unique in the conduct of HIV                  10 preventative vaccine studies, we must go into the                  11 field and enroll thousands of individuals. And I                  12 think the CHMI model within our field here in                  13 malaria is a really tremendous opportunity to try                  14 to stay ahead of this wave of drug resistance                  15 that we've seen over the past 30, 40 years.</p> <p>16 So with that, I'd acknowledge, of course,                  17 all of our study participants, as usual, but a                  18 tremendous team in Seattle based at Fred Hutch                  19 Center for Infectious Disease Research at the                  20 University of Washington and our funders and                  21 colleagues. Thank you.</p> <p>22 (Applause.)</p>



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<p>1 DR. MCCARTHY: Thanks very much, Jim. I</p> <p>2 think we're running well with time, so we might</p> <p>3 see if there are any questions for Jim before we</p> <p>4 move on.</p> <p>5 (No response.)</p> <p>6 DR. KUBLIN: Most interesting talks to</p> <p>7 come, I think.</p> <p>8 DR. MCCARTHY: Thank you. Thank you very</p> <p>9 much.</p> <p>10 DR. NAMBIAR: Thank you, Dr. Kublin. The</p> <p>11 next speaker is Professor McCarthy, who needs no</p> <p>12 introduction to this group. So with that, we</p> <p>13 look forward to your talk on Induced Blood Stage</p> <p>14 Malaria: A Tool to Facilitate Development of</p> <p>15 Anti-Malarials.</p> <p>16 DR. MCCARTHY: Thanks very much again.</p> <p>17 And thanks to Jim for introducing the topic. I</p> <p>18 first wanted to make a comment about</p> <p>19 nomenclature. We tend to use the CHMI acronym to</p> <p>20 describe what we do. We believe that it</p> <p>21 certainly can cause confusion locally in</p> <p>22 Australia because our IRB wants to know where the</p>	<p>1 the talk, we've been doing this now for several</p> <p>2 years and have had major developments in terms of</p> <p>3 how we do it.</p> <p>4 I wanted to also discuss in some detail</p> <p>5 the study endpoints because they are obviously</p> <p>6 why we're doing the study, how we describe those.</p> <p>7 I want to also talk a little bit about</p> <p>8 generalizability. It's certainly a question in</p> <p>9 the field that we're using this time laboratory</p> <p>10 strain of plasmodium falciparum that would derive</p> <p>11 from an airport worker in the Netherlands in the</p> <p>12 1970s and how is that in any way relevant to</p> <p>13 describing what will happen to patients with</p> <p>14 clinical malaria in endemic regions.</p> <p>15 I wanted to also talk about safety</p> <p>16 issues. Safety is obviously extremely important</p> <p>17 in conducting any sort of clinical trial, but</p> <p>18 when you're giving a potentially lethal parasite</p> <p>19 infection to healthy human volunteers, there's</p> <p>20 obviously very major issues in terms of study</p> <p>21 safety. We would also like to talk about ethics,</p> <p>22 but we really don't have time for that today.</p>
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<p>1 control group is. And we've got good data that</p> <p>2 we could share if there was more time to show</p> <p>3 that our system is very reproducible and</p> <p>4 therefore, we don't need control groups. And in</p> <p>5 fact, we are think it is ethically inappropriate</p> <p>6 to use a control group, not giving an</p> <p>7 antimalarial or given a different antimalarial.</p> <p>8 It increases complexity in the clinical trial</p> <p>9 design; so therefore, we've adopted to remove the</p> <p>10 word -- the letter "C" from our studies. And</p> <p>11 therefore, referring it to induced blood stage</p> <p>12 malaria. But I think I'm fighting a losing</p> <p>13 battle in terms of the literature and the</p> <p>14 nomenclature.</p> <p>15 So with those comments, I'll move onto,</p> <p>16 just quickly, my disclosures. We've worked with</p> <p>17 both Novartis and Sanofi in some of the clinical</p> <p>18 trials that we've undertaken. So what I wanted</p> <p>19 to do in this talk is really to outline how our</p> <p>20 clinical trial system works. Really, not taking</p> <p>21 a historic approach but actually describing what</p> <p>22 we actually do today. Because as you'll see from</p>	<p>1 And then if time permits, we can discuss a little</p> <p>2 bit about the future options of where we think</p> <p>3 this field may go.</p> <p>4 So this is the outline of what we do. So</p> <p>5 what we've got here is our intravenous injection</p> <p>6 of effectively, 2,000 infected red cells on Day</p> <p>7 0. So these are prepared by thawing out a prior</p> <p>8 preserved vile of malaria parasites that we have</p> <p>9 held since the 1990s. And then we have</p> <p>10 volunteers in outpatients. So they come in every</p> <p>11 day from Day 4. The phone calls take place in</p> <p>12 the first few days, and from Day 4, they would</p> <p>13 come in twice daily for a PCR test.</p> <p>14 We have now accumulated data of over 170</p> <p>15 volunteers, and I'll show you some of that data</p> <p>16 in a moment, to show that we reach a situation</p> <p>17 where we can get really very use PK/PD data by</p> <p>18 administering an antimalarial drug on Day 7. We</p> <p>19 admit the volunteers to our clinical trials unit</p> <p>20 at Q-Pharm for a period of three days, where we</p> <p>21 do PK sampling, as well as intensive PCR for</p> <p>22 getting the pharmacodynamic endpoint.</p>

<p style="text-align: right;">Page 66</p> <p>1 We give a single dose of drug. We don't                  2 give more than one dose because we believe, and                  3 I'll show data in a moment, that we get adequate                  4 data from a single dose, and to date, have not                  5 been required to undertake the trial. We've                  6 given repeated doses. We obviously follow the                  7 volunteers after they leave the unit. And I'll                  8 show you data on rescue treatment that we give                  9 volunteers when and if they have a recrudescence.                  10 We continue out to 28 days, and in fact,                  11 in some of our studies, we've gone out to up to                  12 35 days. So we clearly have the opportunity to                  13 follow through recrudescence which is a really                  14 important endpoint. And then Sean will discuss                  15 later in the session some issues that have come                  16 up with regards to gametocytes, and I'll show you                  17 a little bit of data about this. And then more                  18 recently, we've become interested in looking at                  19 transmission as an endpoint when we're looking at                  20 transmission blocking activity of the                  21 antimalarial drug.                  22 And a number of subjects that have been</p>	<p style="text-align: right;">Page 68</p> <p>1 the patient the investigational drug and we                  2 typically see quite a rapid fall in the parasite                  3 levels in the blood by PCR and able to                  4 intensively sample by PCR the level of parasites                  5 in the blood over this time period.                  6 You'll also notice, interestingly, and                  7 you'll see this in further data later on that                  8 there's this typical lag phase that we see with                  9 many of the antimalarial drugs which goes back to                  10 the early talk where we discuss the fact that                  11 many of the drugs only work against certain life                  12 cycle stages of the parasite.                  13 We also see typically what is called the                  14 tail phase, when the parasite killing tends to                  15 tail off. And that's often due to the fact that                  16 that we're seeing clearance for the drug and                  17 therefore, decreased rate of parasite killing.                  18 So what we then do is undertake statistical                  19 analysis of the log linear phase of parasite                  20 clearance. So this is basically where we use a                  21 statistical technique to actually eliminate the                  22 lag phase and the tail phase and then using a</p>
<p style="text-align: right;">Page 67</p> <p>1 through this particular system now amounts to 178                  2 people. So we've got data on quite a large                  3 population of subjects that really allows us now                  4 to get some really quite useful statistical                  5 analysis that we have yet to publish, but we are                  6 very confident that this information will be                  7 extremely useful when it comes to having                  8 regulatory interactions about what we're doing.                  9 So here's a hypothetical -- it's not                  10 actually a hypothetical, but a redrawn clinical                  11 study in one single patient. So this is                  12 parasites per mL on a log scale and days on the X                  13 axis. And this is the typical growth in                  14 parasitemia that we see. This is incredibly                  15 reproducible. In a log scale, we first see                  16 parasites detected by PCR on Day 4. We see the                  17 typical sign of exponential growth phase of our                  18 malaria parasites. And we typically treat                  19 volunteers when they reach the threshold of                  20 parasitemia that you will detect with a blood                  21 smear of the order between 10 to 50 parasites per                  22 hour, which is 10,000 to 50,000 per mL. We give</p>	<p style="text-align: right;">Page 69</p> <p>1 modeling approach to actually measure the slope                  2 of this curve. And this is one of the key                  3 pharmacodynamic endpoints that we identified in                  4 our clinical trials. And the more recently                  5 accepted version of this is the parasite                  6 clearance half-life. So this is a measure of how                  7 quick your drug kills the parasite.                  8 As well, we very frequently see                  9 recrudescence. And this is actually data from a                  10 single patient which has been redrawn. So we can                  11 see the parasites have come back and we've been                  12 able to watch them come back. What we see if we                  13 get rid of those particular things and then                  14 superimpose upon this the drug concentration,                  15 this time graphed on a log scale as well, so you                  16 see a rapid increase in drug concentration when                  17 the volunteers administered the drug. And then                  18 with log transformed there, you see a linear                  19 decline in drug concentration if you're dealing                  20 with a drug with first order kinetics.                  21 Now, if you focus on this time point here                  22 with the volunteers, you've reach the asymptote</p>

<p style="text-align: right;">Page 70</p> <p>1 of the parasite clearance curve. Here, you see                  2 the situation where parasite replication is                  3 equivalent to parasite killing. You're in an                  4 equilibrium situation. So if you draw a vertical                  5 line from this period of equilibrium up to where                  6 you reach your parasite or your drug                  7 concentration at that particular time point and                  8 then drop that line across to your drug                  9 concentration, this is actually a very good                  10 approximation of what the MIC of your drug is in                  11 your volunteer.</p> <p>12 So what you've done in a small group of,                  13 and typically, I didn't say before, we typically                  14 do this is cohorts of eight volunteers. We                  15 effectively identified the MIC of the drug as                  16 well, as I've previously showed, the parasite                  17 clearance half-life.</p> <p>18 So, you know, a very small study of eight                  19 volunteers we've collected two very key                  20 parameters and able to inform further development                  21 of the drug. This is data from a study that we                  22 published last year. Again, the parasite</p>	<p style="text-align: right;">Page 72</p> <p>1 challenge system so we can then develop a really                  2 good understanding of what the pharmacodynamic                  3 PK/PD relationship is between your drug and the                  4 parasite growth and clearance.</p> <p>5 So many people ask me and I raised the                  6 question before, well how does the parasite                  7 clearance I see in my very subclinical malaria                  8 relate to what is seen in patients with clinical                  9 malaria?</p> <p>10 So going back to the old literature, in                  11 fact, much of the old literature describes                  12 parasite clearance of blood smear and there is                  13 very little kinetic data available in the old                  14 literature about how quickly parasites had                  15 cleared by serial blood smears. But there are,                  16 as was mentioned in Elizabeth's talks, some very                  17 useful historic data -- and this is data from the                  18 study of mefloquine that was done in the 1980's                  19 where two studies were undertaken, one in Africa                  20 in children and adults with falciparum malaria,                  21 and one in Thailand in adult toy soldiers with                  22 chloroquine-resistant falciparum malaria. Both</p>
<p style="text-align: right;">Page 71</p> <p>1 clearance is drawn out over a different timeframe                  2 with the lag phase and the tail phase. And you                  3 can see here some lovely reproducible log linear                  4 parasite clearance kinetics so that we can                  5 statistically model and then to perform an                  6 optimal regression line with a 95 percent                  7 interval. And you can see this data is very                  8 tight and we're able to really get, I think, very                  9 accurate estimates of this key pharmacodynamic                  10 property of the antimalarial drug.</p> <p>11 So you can then go on and do modeling.                  12 And I'm not a modeler at all, but even someone                  13 like me can understand that the rate of parasite                  14 clearance, over time, it's dependent upon growth;                  15 parasite growth versus clearance. And the drug                  16 effect can then be modeled in here. And using                  17 differential equations with the data that we                  18 accrue in these situations, instead of modeling                  19 packages, we can really get quite useful data on                  20 this particular precise mathematical modeling.                  21 Jörg, who will follow me, will discuss the                  22 utility of getting these key data from the human</p>	<p style="text-align: right;">Page 73</p> <p>1 studies were published. So we extracted the data                  2 from these two studies and compared data from one                  3 of our clinical studies where one of our early                  4 clinical studies where we tested mefloquine as a                  5 single dose at 5 milligrams per kilogram, 10                  6 milligrams per kilogram or 15 milligrams per                  7 kilogram. And just quickly, what we saw with                  8 five was that the drug failed and we had to                  9 rescue all the volunteers. With 10 and 15, we                  10 saw complete clearance of the parasitemia and you                  11 can see here quite nicely demonstrated the lag                  12 phase that you see with mefloquine in our human                  13 challenge system.</p> <p>14 You also see that there is a five log                  15 difference here between the level of parasitemia                  16 in our human volunteers and the level of                  17 parasitemia in these clinical trial undertaking                  18 in Africa and in Thailand. But what you can also                  19 see is if you draw a linear regression of the                  20 parasite clearance in these human patients with                  21 quite severe malaria, if you draw the line of the                  22 parasite clearance as determined by a blood smear</p>

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<p>1 and compare that to the parasite clearance curve                  2 as determined by QPCR in our system, those two                  3 lines, the slope of those two lines are                  4 indistinguishable.                  5       So this is one of our pieces of argument                  6 that makes us believe that what we really are                  7 seeing in the data that we're getting from our                  8 human challenge studies in this quite artificial                  9 system are actually clinically relevant and                  10 predictive of what's going to happen in the field                  11 with our experimental antimalarial drug. And                  12 that's not to say there may be exceptions with                  13 drugs that have specific effects. For example,                  14 one of the earlier ozonide compounds was clearly                  15 -- it had different properties, it's                  16 pharmacokinetic properties in patients with                  17 malaria. So this is something that needs to be                  18 closely observed. But certainly, at least this                  19 data is encouraging to say what's the data that                  20 we get in these very low level infections do have                  21 translational value in terms of what one would                  22 see in a real clinical trial in human subjects</p>	<p>1 cells. We've actually done and continue to do a                  2 red cell antibody assays in volunteers, both at                  3 the start of the study and at the end of the                  4 study. And to date, in the 178 volunteers we've                  5 studied, we've seen nobody develop a red cell                  6 antibody.                  7       So this also is consistent with the                  8 experience, in terms of generation of RHD                  9 antiserum for use in pregnant women. That's                  10 actually quite difficult to generate antibodies                  11 against minor red cell antigens, even when you                  12 give people 20 mls of mismatched blood for minor                  13 red cell antigens.                  14       So then the other obvious safety question                  15 comes up, in terms of the malaria. What is the -                  16 - do we have malaria induced adverse events and                  17 severe adverse events? And I can happily say to                  18 this audience that we've seen no malaria-induced                  19 severe adverse events prior to drug                  20 administration in any of our volunteers. So                  21 people will get a small amount of fever. And                  22 I'll show you some data on that in a moment. But</p>
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<p>1 with clinical malaria.                  2       So safety issues. So when it comes up,                  3 everybody asks me about this. So it's good to be                  4 able to speak about this briefly in this                  5 audience. There are obviously safety issues in                  6 terms of what's in this inoculant of malaria                  7 parasites. Are there any advantageous                  8 contaminants? For example, bacteria, viruses and                  9 prions. And I'm happy to report that the donor                  10 or the red cells are 20 years on from donating                  11 the unit of blood that is used to inoculate all                  12 my human volunteers still works in the                  13 pharmaceutical industry. So I think that speaks                  14 to his sanity that 20 years later he can still                  15 work in pharmacy. So I'm fairly certain that he                  16 doesn't have a prion disease at the moment.                  17       There's also the issue of red cell                  18 alloimmunization we're giving these human                  19 volunteers, potentially, they had all this blood                  20 transfusion of the order of the couple marked                  21 liters of blood. And the question comes up do we                  22 actually institute an alloreactivity to donor red</p>	<p>1 before treatment, we have seen no evidence of any                  2 safety issue arise. After treatment, we've seen                  3 some interesting side effects including a kidney                  4 stone that arose -- a left-sided kidney stone                  5 which made me worry that the volunteer had                  6 ruptured their spleen, but luckily, it was a                  7 renal colic and not a ruptured spleen.                  8       We've seen a volunteer who went out to                  9 celebrate the end of the clinical trial in the                  10 usual way that college students celebrate the end                  11 of their exam and they had a fall from a height                  12 and broke arms, and legs, and ribs and ended up                  13 in their intensive care unit. So that had to be                  14 reported to their regulator, but we believe that                  15 it was not in any way related to the malaria.                  16       (Laughter.)                  17       DR. MCCARTHY: And then there's the issue                  18 of one with transmission that we have clear                  19 observation of our volunteers becoming PCR                  20 positive for gametocytes. And I'll show you this                  21 is a moment from one of our studies. We need to                  22 think about this as an issue, in terms of we're</p>

<p style="text-align: right;">Page 78</p> <p>1 doing this in a setting where we may discharge                  2 someone from our clinic. And if there they are                  3 in a malaria infected environment, we need to                  4 worry about this. We are fortunate in Brisbane,                  5 although it's a subtropical area, we don't have                  6 malaria vectors in Brisbane.</p> <p>7       So the safety of the inoculum. This                  8 blood has been given to 205 subjects at our site,                  9 27 subject before I become involved. And as I                  10 said, 178 since then and 30 cohorts in 15                  11 studies. So we've really accumulated quite a                  12 large safety database locally with this, as well                  13 as inoculum has been given to 55 subjects                  14 elsewhere in the world for vaccine studies                  15 conducted in Nijmegen in the Netherlands and                  16 Oxford in the UK.</p> <p>17       As well as mentioned by Jim, we've                  18 actually improved the situation to develop                  19 resources in an ongoing -- in ways of developing                  20 other resources for doing a blood stage                  21 challenge. So we've successfully did a "wild                  22 type" P. falciparum. This was a patient who came</p>	<p style="text-align: right;">Page 80</p> <p>1 at plasmodium vivax, blood stage infection, both                  2 for our drug and vaccine development. And we now                  3 have data on 26 volunteers, using two different                  4 banks with plasmodium vivax.</p> <p>5       So the other question that obviously                  6 comes up is can we identify recrudescence and                  7 safely rescue these volunteers? So on this slide                  8 that I've previously shown you before are drawn                  9 across the line of where one would find people                  10 being blood smear positive. And you can see here                  11 that we have got one, two, three, four, five,                  12 six, seven serial observations of PCR before the                  13 blood smears become positive. And we've been                  14 able to prospectively observe the recrudescence                  15 of infection way before we become blood smear                  16 positive and way before volunteers become                  17 symptomatic.</p> <p>18       So we believe we've got several days of                  19 safety margin here present. And these are real                  20 data from a single volunteer. And in fact, in                  21 preparation for this talk, I went back and                  22 counted how many people we've had to rescue and</p>
<p style="text-align: right;">Page 79</p> <p>1 back to our hospital with falciparum malaria, was                  2 shown to be infected with a single genotype.                  3 We've harvested his blood. We've tested it,                  4 validated it and released it. And I did a pilot                  5 study in two volunteers with a wild type strain.                  6 This is more-so to look at the vaccine efficacy,                  7 but it demonstrates the feasibility of looking at                  8 parasites with different genotypes and                  9 potentially different drug resistant patterns.</p> <p>10       We've also remanufactured, under GMP,                  11 blood stage P. falciparum banks. I've got a 37                  12 bank that we've tested in two individuals. The                  13 Goal Coast has manufactured an NA54 strain from                  14 the same strain that Steve Hoffman uses at                  15 Sanaria. As well, he also has a 7G8 bank that                  16 was recently produced. And some of these papers                  17 are in press or published.</p> <p>18       As well, we've recently had great success                  19 in doing plasmodium vivax challenge studies using                  20 two banks, again, collected from patients back                  21 from endemic areas of plasmodium vivax. And this                  22 is greatly extended out to capacity. You'll look</p>	<p style="text-align: right;">Page 81</p> <p>1 the numbers are four. So I think that we can say                  2 with strong confidence in our system that we are                  3 able to protect our volunteers from having our                  4 recrudescence infection by ensuring, obviously,                  5 they come back to be tested, but also that we can                  6 identify people having a recrudescence infection                  7 way before they're going to become symptomatic                  8 and still being able to identify this key idea                  9 point, which really enables us to do                  10 pharmacodynamic modeling.</p> <p>11       So we still are struggling with the                  12 issues, what is a safe treatment threshold. My                  13 modelers love to see lots of data points down                  14 here. So that means if we can get our                  15 parasitemia up to here, we get more data points,                  16 but at some stage or another, we are going to                  17 make people symptomatic. And we are not entirely                  18 sure this safety threshold is and we're obviously                  19 being very cautious about that. It depends as                  20 well on what your known drug potency is. So if                  21 you're working with a drug such as an ozonide                  22 antimalarial, well, you know you're going to get</p>

<p style="text-align: right;">Page 82</p> <p>1 rapid clearance. You can probably with a little                  2 more safety margin. But if you're working with                  3 one of those more slowly acting antimalarial                  4 drugs where you want to be able to observe                  5 treatment effects over a longer period of time,                  6 you probably don't have the luxury of allowing                  7 your parasitemia get to a point where you may be                  8 seeing a clinical safety endpoint. So we still                  9 haven't answered this question clearly.                  10 We've also developed a clinical score                  11 system. So we are really trying to standardize                  12 our way of recording what the symptoms our                  13 volunteers experience because this will be a way                  14 of comparing clinical outcomes and getting a good                  15 safety database that we can then accumulate that                  16 will ensure that what we're doing is really easy                  17 to record and therefore, gives everybody                  18 confidence, both our ethical committee, ourselves                  19 as investigators, and the regulator that what we                  20 do has got a reproducible system of collecting                  21 outpatient safety, in this case, volunteer safety                  22 data.</p>	<p style="text-align: right;">Page 84</p> <p>1 there's reappearance of parasite genomes in the                  2 blood of these people, but at much lower levels                  3 than what one would see if there was an                  4 exponential increase in parasitemia. And                  5 consistent with that, you see this appearance of                  6 a molecular marker of a gene that's produced by                  7 female P. falciparum gametocytes called Pfs25.                  8 So we see the appearance of this gene in                  9 the blood some seven to ten days after we treat                  10 them. And this particular transcript because                  11 you're using RT-PCR appears in the blood and                  12 persists for the duration of the treatment and it                  13 only disappears when you give the volunteers a                  14 dose of primaquine, which is known to kill female                  15 gametocytes.                  16 So you see basically clearance of                  17 gametocytes and disappearance of the genomes from                  18 the blood, using your standard Q-PCR assay. What                  19 as well is present is that there's a molecular                  20 marker of asexual parasites. So this is an mRNA                  21 produced by asexual parasites, but not by                  22 gametocytes. And what you see on this X axis</p>
<p style="text-align: right;">Page 83</p> <p>1 So getting towards the end of this, I                  2 just wanted to highlight data from a just                  3 recently published paper where we're using the                  4 drug piperazine. So piperazine was developed                  5 by the Chinese back more than 20 years ago and                  6 there was very little pharmacodynamic safety data                  7 available for how effective this drug is.                  8 So we were asked by medicines for malaria                  9 really to go back to piperazine and do single-                  10 dose piperazine to assess its activity. And as                  11 you can see here, these are two single volunteers                  12 in our study. And you can see in black shown                  13 here is the parasitemia growth in the volunteers.                  14 And in fact, in very dramatic and rapid clearance                  15 of parasites after a single dose of 960                  16 milligrams of piperazine.                  17 What we then were able to do is follow                  18 these volunteers out, and this was because we had                  19 accumulated data on this. And in black, you see                  20 a reappearance of parasite genomes in the blood                  21 of the volunteer. And what you'll see here, and                  22 Sean will go into this is more detail is that</p>	<p style="text-align: right;">Page 85</p> <p>1 here are these red dots here. So you're seeing                  2 no replication of asexual parasites.                  3 So if you then drop to this person down                  4 at the bottom, what you see in this person here                  5 is having a recrudescence because you can see                  6 there's a period of constancy in there, actual                  7 number of parasites in the blood, as well as a                  8 constant number of Pfs25 genomes in their blood.                  9 But what you're seeing here is this red line                  10 going up and that is an early appearance of                  11 asexual parasites in the blood that and it dates                  12 by three or four days, the appearance of the                  13 increase of genomes here. So this really gets to                  14 the point that we believe that we can confidently                  15 predict recrudescence infection by using a                  16 messenger RNA marker that is produced by asexual                  17 parasites.                  18 So getting towards the end, we've also                  19 been working very closely with meds and some                  20 malaria. So this is a typical drug development                  21 pathway, where one would be doing a Phase I study                  22 to look at safety in pharmacokinetics of your</p>

<p style="text-align: right;">Page 86</p> <p>1 drug. You would then move into a Phase II study;                  2 for example, doing -- study sizes of increasing                  3 complexity endemic areas with patients -- with                  4 all patients initially but then escalating to get                  5 efficacy for antimalarial drug.                  6 Working with MMV, we've been able to                  7 develop an integrated program now where we can                  8 nest within the Phase I study, a human challenge                  9 study. So within one year, we're able to get                  10 safety and pharmacokinetic data doing a dose                  11 escalation study, but once we hit our target                  12 point for doing human challenge, we move straight                  13 into human challenge. So within 12 months, we                  14 can do a package of data that really is very                  15 informative for drug development. And Jörg will                  16 be following me, talking a little bit about this.                  17 So we believe using this system, we can                  18 get really good early safety in PK data;                  19 obviously from the standard Phase I assay. But                  20 really, we can identify the dose for efficacy at                  21 a very early stage. So within the 12-month                  22 period, we've got data to guide a design of a</p>	<p style="text-align: right;">Page 88</p> <p>1 that are going nowhere but are still listed on                  2 the website. Some studies that are in human                  3 volunteers and then studies that are actually now                  4 in more advanced development.                  5 So what we do, we count the numbers here.                  6 So we've got eight drugs in preclinical                  7 development. We've got two drugs which we know                  8 are in the Phase I study already and we've got                  9 six drugs that are in patient exploratory. So                  10 then if you do the numbers, you've got 16 Phase I                  11 studies where you get Phase I and safety in PK.                  12 Now I think we've got ample global capacity to do                  13 16 Phase I studies with these drugs. The problem                  14 comes is that you then need to do 16 proof of                  15 concept antimalarial drug activity. So you've                  16 got to go somewhere, do a clinical trial with                  17 people with malaria and figure out which of these                  18 drugs is worth moving on with.                  19 In the global situation with malaria,                  20 where we need to do these studies doing these 16                  21 proof of concept studies will become a logistic                  22 challenge. And then if you're thinking about, as</p>
<p style="text-align: right;">Page 87</p> <p>1 later phase clinical trials. This has been                  2 working very closely with our local ethics                  3 committee. We've been able to generate quite a                  4 flexible adaptive design so that we build into                  5 our clinical trial protocol a range of options                  6 that we can go down, depending on the outcome of                  7 the first cohorts. We can also kill drugs early.                  8 The drug is not working in the system, we don't                  9 waste time taking in a later development stage.                  10 And I think you'll see an example of that.                  11 And then we can obviously go back where                  12 we see a problem in terms of pharmacokinetic                  13 properties that suggest that we're not going to                  14 reach our input. We go back and reformulate                  15 before going into the human challenge.                  16 So I just wanted to finish. Again,                  17 return you to the meds of malaria development                  18 pathway and look at the -- I think we have a good                  19 fortune, there is quite a large number of drugs                  20 in research in terms of lead optimization. There                  21 are drugs that are listed here that are without                  22 the permission of MMV that list some of the drugs</p>	<p style="text-align: right;">Page 89</p> <p>1 the topic was started today, we need to then do a                  2 combination study. So if you go back to your                  3 high school mathematics and do the factorial                  4 analysis, this requires 120 possible combination                  5 studies to evaluated with these 16 drugs. This                  6 is clearly not an option that we've got available                  7 to us. And with the early discussion that we had                  8 about drug resistance, obviously we're not going                  9 to do 120 factorial designs, but we need to                  10 figure out if we need to do 20 of them. We                  11 really don't have global capacity to do this,                  12 probably within the bounds of my professional                  13 career, given this pace which some of these drug                  14 studies are done.                  15 So I really think we've got to think                  16 creatively about how we're going to actually move                  17 the promising candidates from this particular                  18 pile here into this particular pile here. And                  19 given the conversations we had early on about how                  20 we need to combine these drugs together, how we                  21 need new targets and we need drugs with different                  22 targets to work together, we really do face some</p>

<p style="text-align: right;">Page 90</p> <p>1 challenges that require, I think some creativity,                  2 both from a clinical trial design perspective,                  3 but also working very closely with our regulators                  4 so that we can actually reach a point where we                  5 can actually do something about the fact that                  6 we're really in (inaudible) therapy, and                  7 certainly in the Mekong region now because of                  8 artemisinin resistance becoming more and more of                  9 a problem.                  10 So just in conclusion, in blood stage                  11 malaria provides a rapid, safe, and efficient                  12 means of having pivotal early efficacy data. It                  13 can be integrated and combined Phase I                  14 pharmacokinetic safety study, a standard Phase I                  15 study. And then it provides actionable data for                  16 modeling activities to predict clinical dosing                  17 for light stage studies.                  18 So I just really would like at the end of                  19 this to thank all my collaborators, particularly                  20 my colleagues at Medicines at Malaria who has                  21 supported me along the journey that we've been                  22 over in these last several years, as well as</p>	<p style="text-align: right;">Page 92</p> <p>1 that equation are just constants, right? They do                  2 not or they do?                  3 DR. MCCARTHY: I'm not sure. We can go                  4 back to it. I'm not a modeler, so you probably                  5 going to have to help me along the way here.                  6 There we go. So P is the parasite concentration.                  7 We know that. The parasite growth rate is at                  8 constant. We know that because we've done this                  9 in 178 people. Drug-specific parasite reduction                  10 ratio, we should be able to calculate that from                  11 the parasite clearance half-life, but you can                  12 solve this equation, obviously, different ways.                  13 And then there's a drug concentration effect,                  14 obviously, and then the IC-50. And then                  15 there's also a fudge factor, which is the                  16 optional non-linearity parameter defining the                  17 steepness of the concentration effect.                  18 This is not my work. This has been a                  19 standard equation that's been used in the past.                  20 And obviously, it could be optimized and there                  21 are people who are very skilled at doing this                  22 sort of work. I couldn't possibly understand the</p>
<p style="text-align: right;">Page 91</p> <p>1 funders from the Australian government and the                  2 Bill and Melinda Gates Foundation. And the                  3 wonderful team of people whom I collaborate with                  4 because these studies really are a very large                  5 team activity and in order to be able to carry                  6 this off successfully and ensure volunteer safety                  7 and good data integrity requires a really large                  8 team effort.                  9 So with that, I think I might stop.                  10 (Applause.)                  11 DR. NAMBIAR: So are there any clarifying                  12 questions for Professor McCarthy. Yes? You                  13 might want to introduce yourself for the                  14 transcription. Thank you.                  15 DR. PROSCHAN: Pardon? I didn't hear.                  16 DR. NAMBIAR: I said it would help if the                  17 speaker introduce themselves so that the                  18 transcriber can capture your name. Thank you.                  19 DR. PROSCHAN: Okay. Mike Proschan. You                  20 gave a differential equation for parasitemia over                  21 time. In that equation, obviously P is a                  22 function of time, but all those other parts of</p>	<p style="text-align: right;">Page 93</p> <p>1 language that they talk, but certainly, it's my                  2 job, I think, to generate data that enable                  3 modeling activities so that we can really arrive                  4 at a more precise understanding of the                  5 concentration effect relationship between the                  6 drug of choice and the parasite. And                  7 particularly when you start to look at model                  8 drugs. I think you all will be talking about how                  9 we can use this with a combination therapy.                  10 Obviously, the complexity increases, but we                  11 believe that you can use these sorts of                  12 approaches to actually model combination                  13 approaches and that's the standard approach that                  14 is in other clinical pharmacology applications.                  15 PUBLIC COMMENTER: Thank you. It was                  16 really very well done. I had one specific                  17 technical question. When you're looking at the                  18 rate at which parasite counts fall and you're                  19 looking at the slope, did you see any consistent                  20 differences in the slope when the drug like                  21 artemisinin was being used as opposed to say                  22 drugs like piperazine or mefloquine or Coartem?</p>



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<p>1 DR. MCCARTHY: So in the interest of</p> <p>2 time, I didn't put up a slide, but obviously, one</p> <p>3 of the luxuries I have is being able to put up a</p> <p>4 slide with every single drug I've tried and you</p> <p>5 see very dramatic differences between them all</p> <p>6 and you get a very quick read-out. About a week</p> <p>7 after I begin the study, I can graph out, in a</p> <p>8 preliminary way, how the drugs are doing, feed</p> <p>9 that back to the sponsor and say well, look, this</p> <p>10 is how your drug is doing. And obviously, it</p> <p>11 takes a little longer to get that data all</p> <p>12 formalized, but certainly there are very</p> <p>13 significant differences.</p> <p>14 With the artemisinin, it's an interesting</p> <p>15 story. It was the first drug we ever used and we</p> <p>16 weren't as good at doing it as what we did then.</p> <p>17 So next year, one of our plans is to go back and</p> <p>18 look at artesunate with a Kelch mutant parasite</p> <p>19 to see what the effect is there. So we do have</p> <p>20 lots of opportunities now because we've got a lot</p> <p>21 more expertise, in terms of design of the studies</p> <p>22 sampling frames, getting our Q-PCR working as</p>	<p>1 because they get sick of coming back every day</p> <p>2 for blood tests, but we certainly see quite</p> <p>3 frequently light recrudescences. I mean, in the</p> <p>4 malaria community, they go out to six weeks. We</p> <p>5 don't have the luxury of being able to do that,</p> <p>6 but our volunteers are not immune, so light</p> <p>7 recrudescences in an immune population, you've</p> <p>8 got to deal with the fact that there's probably</p> <p>9 an effect of the immune system in parasite</p> <p>10 counts.</p> <p>11 You make a good point that maybe three</p> <p>12 weeks after treatment may not be sufficiently</p> <p>13 long to absolutely identify everybody who's going</p> <p>14 to recrudescence. We do, however, at the end of</p> <p>15 treatment, send everybody home, having been given</p> <p>16 a therapeutic course of Coartem. So nobody</p> <p>17 leaves our study without being cured of potential</p> <p>18 (inaudible) malaria.</p> <p>19 DR. NAMBIAR: Maybe we can go to the</p> <p>20 next.</p> <p>21 DR. MCCARTHY: Yes. Maybe we'll move on</p> <p>22 now. Our next speaker is Jörg Möhrle from</p>
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<p>1 best we can so we can really improve data quality</p> <p>2 as we get better at doing this.</p> <p>3 DR. NAMBIAR: Dakshina.</p> <p>4 DR. CHILUKURI: Dakshina Chilukuri, FDA.</p> <p>5 You've shown one slide which showed the</p> <p>6 recrudescence source of the safety profile for</p> <p>7 the one patient and you said that there were 70</p> <p>8 or 80 other patients that you rescued.</p> <p>9 DR. MCCARTHY: Yes.</p> <p>10 DR. CHILUKURI: Did you see the profile</p> <p>11 for any other patients, a similar profile itself?</p> <p>12 DR. MCCARTHY: Sometimes we see PCR being</p> <p>13 completely negative. So we interpret that as</p> <p>14 being the parasite count as below the limit of</p> <p>15 quantitation of PCR. So there may be only 10</p> <p>16 viable parasites in the body. They may be</p> <p>17 sequestered somewhere and therefore, potentially</p> <p>18 protected from a drug. In fact, in some of our</p> <p>19 studies, we see recrudescence upwards of two</p> <p>20 weeks after the parasites have disappeared from</p> <p>21 the blood. So we certainly don't give up on</p> <p>22 them. We increase our intervals between PCR</p>	<p>1 Medicines of Malaria. He's the head of</p> <p>2 translational medicine, MMV. A career in</p> <p>3 development and pharmaceutical and biotech,</p> <p>4 followed by joining MMV in 2005. Since 2010,</p> <p>5 he's head of the translation medicine team and</p> <p>6 brings the new drugs from the laboratory to proof</p> <p>7 of concept in patients.</p> <p>8 Jörg obtained his PhD from Basel</p> <p>9 University for work on protein kinases Plasmodia,</p> <p>10 and in 2006 he attained his MBA from Lorange</p> <p>11 Institute in Zürich and SUNY New York.</p> <p>12 DR. MÖHRLE: Thank you for the</p> <p>13 introduction and especially for outlining the</p> <p>14 blood stage challenge studies so then I don't</p> <p>15 have to explain so much.</p> <p>16 So I'd like to talk you through what our</p> <p>17 challenges are in moving from the challenge, that</p> <p>18 is from the early phase human studies into</p> <p>19 combination studies. I would like to illustrate</p> <p>20 and take you along a story of MMV's project OZ439</p> <p>21 and DSM265. These are two projects -- OZ went in</p> <p>22 demand the first time in 2009, DSM in 2011/2012.</p>

<p style="text-align: right;">Page 98</p> <p>1 So it's really -- I want to show you how we                  2 learned ongoing and I want to also show how the                  3 ongoing learnings from the different studies                  4 helps us to really get to better study design,                  5 better dose selection for the latest trials. I'd                  6 like to show through that journey how we can also                  7 show in early phase trials the contribution of                  8 each compound in the effect on malaria and                  9 briefly some words on the impact this could have                  10 using this early stage controlled human malaria                  11 infection trials, combined with Phase II A                  12 trials, what is the impact on developing new                  13 drugs and bringing new drugs to the market.                  14 What our challenges are, I think we heard                  15 this morning, we need combination treatment to                  16 ensure that patients are cured and no resistance                  17 is developing. One of the questions is how do we                  18 get to the right dose of each individual                  19 component later in the fixed dose?                  20 We don't have historic data. We're                  21 talking about NCEs. We don't have historic data                  22 like with lumefantrine or with piperazine where</p>	<p style="text-align: right;">Page 100</p> <p>1 because we will develop -- or we might already                  2 develop resistance at that stage in clinical                  3 development. I will also say change alluded to                  4 what I call the MIC study; so studies where you                  5 give a single dose, not a curative dose. You                  6 observe parasitemia and PK over a period to see                  7 when do we reach the nadir of parasites and when                  8 do we see regrowth of parasites? These are                  9 doable in the field. MMV has done a study of                  10 part of this, but they are very, very difficult                  11 to conduct in the field. So we need to find                  12 other ways to do this MIC studies in a better                  13 controlled -- where we have better access and                  14 where the volunteers or patients have better                  15 access to the healthcare facilities.                  16 The question is yes, a lot of people ask                  17 me, "Why are you doing this, Jörg?" This is                  18 interesting experimental medicine but how can you                  19 use that later to really transfer the information                  20 into the clinical studies. So that is one of our                  21 challenges. And then yes, one question is we                  22 have here studies, the challenge studies where we</p>
<p style="text-align: right;">Page 99</p> <p>1 they were used in monotherapy. There are                  2 operational and ethical obstacles to conduct full                  3 factorial design studies in the relevant patient                  4 populations. Remember the maturity of malaria                  5 patients are children. If you want to run full                  6 factorial design studies in the pediatric                  7 populations, the maturity of these children in                  8 the trials will be either on doses that are too                  9 low or too high. Not optimized. So we have to                  10 find a way to go into the target population for                  11 malaria with limited small number of doses that                  12 are likely to succeed and likely not to overdose.                  13 Operationally, I think James made a very,                  14 very good point. The number of new trials in the                  15 pipeline and the number cohorts in the full                  16 factorial study make this study huge. If we have                  17 several full factorial Phase II B studies with                  18 different drug combinations, I'm not sure whether                  19 they are enough clinical trial sites in the world                  20 that could handle that burden.                  21 Again, large monotherapy studies in                  22 clinically infected patients are not advisable</p>	<p style="text-align: right;">Page 101</p> <p>1 have parasites per milliliter and in the field,                  2 we have parasites per microliter. So it's about                  3 1,000-fold higher parasitemia. Can we                  4 extrapolate the information on MIC, on kill rates                  5 or parasite reduction half-life from the                  6 challenge studies into the real live situation?                  7 So these are some of the challenges we                  8 are facing and I hope I can at least give answers                  9 to a few of them. Again, change is already                  10 shown. Most of that explains the graph of how                  11 the challenge studies are done. We are                  12 collaborating now with QMIR and (inaudible) in                  13 six years. These are four publications that have                  14 been published recently in the last two months.                  15 So now, finally, we're getting to publishing the                  16 work we are doing. These are available now and                  17 they are open access, so everyone can access the                  18 papers.                  19 So the K study, or the story I want to                  20 take you along on two molecules in MMV's                  21 pipeline, one is OZ439, a fully synthetic                  22 ozonide, where we conducted the PoC study in the</p>

<p style="text-align: right;">Page 102</p> <p>1 field. And the challenge study in this sequence,                  2 so it's the other way around. We went first into                  3 the field before we had the challenge study                  4 available. And then DSM265, a DHODH -- DHODH                  5 inhibitor, specific to falciparum malaria where                  6 we did the Phase I and the challenge study within                  7 one protocol. And we actually used both the                  8 information we generated in the previous study,                  9 but also the availability of these molecules to a                  10 combination challenge study last year at QMIR.                  11 So OZ439 Proof of Concept Study, this was                  12 -- it's a new chemical entity. We did not know                  13 how it works against parasites. We went into                  14 patients because at the time when we did that                  15 study in October of 2010, the challenge model was                  16 not that developed yet.                  17 Based on the discussion we had with the                  18 investigators, with the ethical committee, the                  19 study design was that the patients received, when                  20 they presented to the hospital with clinical                  21 malaria after confirmation that their criteria                  22 were met, they received a drug. They were</p>	<p style="text-align: right;">Page 104</p> <p>1 turn? Where is the midlevel concentration where                  2 parasite regrowth starts again?                  3 With the 36-hour design, we only could                  4 measure to the black line. So the next study we                  5 conducted was a challenge study where we                  6 investigated single doses of 100, 200 and 500                  7 milligrams of OZ439. And at that time, we only                  8 could observe until study dates 16. So again,                  9 that was the early phase of the challenge. We                  10 could really see here are the individual graphs                  11 and here is the 100, 200, and 500 milligrams. At                  12 200 milligrams, you can really see parasite PK                  13 line and regrowth. And if you look at the                  14 individual graph here, you can also see that we                  15 can estimate the nadir of the parasite growth and                  16 overlay that in green with the PK information and                  17 ozonide exposure.                  18 It's also interesting that this study was                  19 conducted between September 12 and February 2013.                  20 So within half a year, we had three doses with                  21 the full information of parasite reduction rate                  22 and MIC and parasite clearance half-life. We</p>
<p style="text-align: right;">Page 103</p> <p>1 observed for 36 hours. And after 36 hours, the                  2 patients received standard of care quarantine.                  3 So the observation period, what does the                  4 drug OZ439 do to parasites lasted 36 hours.                  5 Afterwards it's mixture of quarantine and OZ439.                  6 So the output of this design of the study was                  7 that we had information is yes, the drug kills                  8 falciparum malaria. We could estimate the                  9 parasite reduction rate, the parasite clearance                  10 half-life, parasite clearance time and fever                  11 clearance time.                  12 The study was conducted between October                  13 2010 and May 2012. We had four, since we did not                  14 have any prior information of how much drug we                  15 need, what is the potency in humans. We actually                  16 had an open sequential cohort design and we                  17 recruited four cohorts of 10 volunteers or                  18 subjects each.                  19 This slide, you have already seen from                  20 James. So what we are interested in is the                  21 parasite reduction clearance half-life -- sorry,                  22 I'm away from the microphone. Where is the curve</p>	<p style="text-align: right;">Page 105</p> <p>1 have done in the meantime also done an MIC study                  2 in the field where patients presented, got a                  3 single dose of OZ439 and were observed over 28                  4 days because the patients had to come back every                  5 day to the clinic in the field base. That study                  6 took one and a half years to recruit. Here we                  7 had half a year.                  8 So the data, I have here the PRR, the                  9 parasite half-life of the MIC data between the                  10 field study and the challenge study is                  11 comparable. So there is no difference between                  12 the PRR and the MIC of no significant difference                  13 between whether it's in patients or in                  14 volunteers. Taking the learnings of the OZ                  15 program, we then went with a new compound,                  16 DSM265. And as James has already explained, it                  17 was one protocol single-dose in healthy                  18 volunteers and nested within that protocol when                  19 we reached a dose where we thought it has an                  20 antimalarial effect. We had a cohort of                  21 challenge volunteers.                  22 The volunteers received 150 milligrams of</p>

<p style="text-align: right;">Page 106</p> <p>1 DSM265. Four out of the seven volunteers                  2 experienced a recrudescence. The estimated PRR                  3 was two and the MPC estimated to be between 900                  4 and 1,400 nanograms.                  5       Based on that information, a new                  6 estimation for the human efficacious dose was                  7 made to be around 320 milligrams. We tested and                  8 used that information to set up a proof of                  9 concept study in patients. First of all, because                  10 we had already these prior information, we were                  11 allowed by the ethical committee to extend the                  12 observation period from 36 hours in the previous                  13 protocol with OZ439 to now a full 28 days. So                  14 the patients received the drug that were in the                  15 hospital until they cleared parasites and could                  16 then go home and return on a regular basis for a                  17 follow-up.                  18       So we have now data of over 28 days for                  19 the patients. What is also interesting is that                  20 we had selected a stocking dose of 400                  21 milligrams. And in the first cohort, 12 out of                  22 13 patients were a treatment success. We dropped</p>	<p style="text-align: right;">Page 108</p> <p>1 have a 40 percent treatment success or six                  2 failures. And with 200 milligrams OZ, 50                  3 milligrams of DSM265, the 28-day success rate was                  4 predicted to be less than 5 percent. We didn't                  5 really trust ourselves yet, therefore, we said                  6 let's go with the higher dose before we don't see                  7 anything of addition.                  8       So we started with 200 milligrams and 100                  9 milligrams. And four out of eight volunteers had                  10 the recrudescence before the end of the follow up                  11 period. So close to the 40 percent. And on the                  12 bottom, you can see the estimation MIC. The                  13 apparent MIC of OZ in the presence of DSM and                  14 apparent MIC of DSM in the presence of OZ439.                  15 And I have a summary table later.                  16       With the 250 milligrams of DSM, I think                  17 we only had unfortunately, five volunteers                  18 because of a recruitment issue, but we really can                  19 see the patient -- the parasite reduction and                  20 then the regrowth in the majority of these                  21 volunteers which had a very, very good handle on                  22 estimating and calculating the MIC -- that parent</p>
<p style="text-align: right;">Page 107</p> <p>1 the dose to 250 milligrams, and there we had                  2 seven out of 10 volunteers or patients that were                  3 a treatment success.                  4       If we compare the OZ proof of concept                  5 protocol, having the challenge information with                  6 better data because we can follow up for 28 days,                  7 we have PRR parasite clearance half-life                  8 estimation of MIC, but we also, instead of having                  9 to treat four cohorts to get some information, in                  10 this case, we got with two cohorts, a very good                  11 estimation on the dose and efficacy.                  12       And now we use the information of both                  13 OZ439 and DSM265 to do a combination during this                  14 trial. We wanted to see what is the effect of                  15 the individual doses and we selected,                  16 deliberately low doses of both compounds.                  17 Remember DSM265, we had 150 milligrams for                  18 treatment for recrudescence out of seven. With                  19 OZ439, we had eight recrudescence out of the                  20 eight cohort.                  21       We did some modeling work. And the                  22 prediction was 1,000 milligram DSM265, we will</p>	<p style="text-align: right;">Page 109</p> <p>1 MIC for both drugs OZ439 and DSM265. And this is                  2 the summary table. So if you look at the single                  3 dose OZ439, single-dose DSM265, OZ in combination                  4 with a 100 milligrams DSM, OZ 200 with the                  5 combination of 50 milligram DSM, we can see there                  6 is an additive effective which is significant on                  7 the PRR for OZ439 from 2.2 to 2.8; from 2.2 to                  8 2.7. And we also see that the MIC of OZ439, the                  9 apparent MIC in the presence of DSM, 100 dose                  10 goes down to .3 and in the presence of 50                  11 milligrams goes down to 1.2 nanograms per                  12 milliliter. Similar apparent MIC of DSM265 is                  13 reduced in the presence of DSM265. So I think                  14 it's very clear that we can, in that model, by                  15 using two non-curative doses demonstrate that                  16 both drugs have an effect on the parasite and                  17 that effect is additive.                  18       So the contribution, I feel we can                  19 demonstrate it very nicely. You've seen our                  20 model for the parasite growth and kill rate. We                  21 can also calculate a factor for the contribution                  22 of both drugs in that model now. So it's</p>

<p style="text-align: right;">Page 110</p> <p>1 possible to quantify the effect and have a model                  2 for both drugs together.                  3       So now, this is not the end of the story.                  4 We are using the updated model and the updated                  5 information based on the combination challenge                  6 study to prepare a study in the field. This                  7 planning is ongoing. One change, obviously from                  8 the challenge study into the field study is                  9 nontherapeutic doses are not acceptable. We                  10 cannot, in that field -- in that area, we want to                  11 do the study, we cannot have patients coming back                  12 every day and induce treatment failures.                  13       So we're looking to select two cohorts,                  14 both cohorts with an aim to have an efficacious,                  15 curative dose. And a two-dose combination that                  16 predict treatment success based on the PK/PD                  17 modeling of the three controlled malaria                  18 infection studies that I just described.                  19       And this is what we propose for the MMV                  20 drug development of combination drugs. We were                  21 looking at animal data and I haven't talked about                  22 that. Animal data of scid mice infected with</p>	<p style="text-align: right;">Page 112</p> <p>1 because a) the studies in the field will be                  2 smaller. And we don't have to do additional                  3 studies in the field like what I described as the                  4 OZ439 MIC study that took one and-a-half hours to                  5 recruit patients. And I think these exams also                  6 shows that we can demonstrate the contribution of                  7 each compound on parasite reduction rate,                  8 apparent MIC and the probability of success                  9 through the challenge studies. So that early, we                  10 can already show the contribution of the                  11 individual compounds, even in combination.                  12       And with that, I would like to thank you                  13 for inviting me and to thank our patients, the                  14 volunteers, their caregivers, our departments,                  15 especially the clinical side and especially the                  16 sides in Brisbane and in Seattle for the                  17 volunteer studies. Our mentors, our advisors and                  18 our colleagues and our funding partners, without                  19 them wouldn't be possible.                  20       (Applause.)                  21       DR. NAMBIAR: Thank you, Dr. Möhrle.                  22 Thank you to all the speakers in the first</p>
<p style="text-align: right;">Page 111</p> <p>1 monotherapy and combination, used that data,                  2 analyze, model it to prepare the human challenge                  3 study. Used the human challenge data to prepare                  4 a field study monotherapy but also field studies                  5 in combination. But at the end, using all these                  6 data from monotherapy human challenge doses,                  7 combination human challenge studies, monotherapy                  8 and combination Phase II A studies to be able to                  9 move into Phase II B already with a combination                  10 and with a limited dose so that we can avoid full                  11 factorial design studies at this stage.                  12       So I hope I could explain that controlled                  13 human malarial infection studies, plus modeling                  14 and simulation were successful in generating                  15 already in Phase I, pharmacodynamic information                  16 by including challenge studies into the classical                  17 Phase I programs. That we can reduce the size of                  18 the first in-patient studies, OZ439, four                  19 cohorts, DSM265. Two cohorts, we can generate                  20 more and better data because we will have more                  21 studies, better studies, lower follow-up in the                  22 field. We can reduce the overall timelines</p>	<p style="text-align: right;">Page 113</p> <p>1 session this morning. So we'll take a 20-minute                  2 break and we'll be back at 10:50. We'll have a                  3 few minutes to ask clarifying questions of our                  4 four presenters this morning before we go into                  5 the panel discussion.                  6       Thank you.                  7       (Brief recess.)                  8       DR. NAMBIAR: All right. So in the                  9 interest of time, we're going to get started. We                  10 see that you are all having a very interesting                  11 and robust discussion, but it would be great if                  12 people could take their seats so we can get the                  13 first panel discussion going because we have only                  14 about an hour to discuss many important topics.                  15       Before we start the panel discussion, we                  16 wanted to check if there might be any clarifying                  17 questions for any of the speakers this morning.                  18 Does anyone on the panel have a question for the                  19 speakers?                  20       DR. MURPHY: I have a question for Dr.                  21 McCarthy. I noticed in the recrudescence curve                  22 that you showed, I realize it was just from one</p>

<p style="text-align: right;">Page 114</p> <p>1 patient, but in the initial phase pretreatment,                  2 there is the very characteristic secondary saw                  3 tooth rise of parasitemia. When people                  4 recrudescence, there was not that rise, there was a                  5 slower slope. So I'm wondering whether in                  6 addition to the point at which you declare that                  7 they are recrudescing, whether there's                  8 information to be gained in a secondary rise in                  9 parasitemia.                  10 So for instance, if you saw an immediate                  11 secondary saw tooth slope, you'd say there's no                  12 adequate drug on board. The parasite is exactly                  13 back to its wild type state. And if there is a                  14 gradual slope with no saw tooth, you'll see                  15 persistent drug effect. Does that tell you                  16 anything about the drug?                  17 DR. MCCARTHY: I think there are two                  18 questions there really. The first is that we                  19 don't always sample it at the same frequency. So                  20 when we are doing the early stage of assessment,                  21 we're sampling twice daily. So we've got a                  22 really good chance to actually identify that saw</p>	<p style="text-align: right;">Page 116</p> <p>1 the course of the blood stage inoculations?                  2 DR. MCCARTHY: Deep sequencing is                  3 certainly something that's becoming increasingly                  4 sensitive in terms of being able to do single                  5 cell sequencing. And I think that's certainly                  6 the way things are going. At the moment, we                  7 haven't sought to do that, but one of the things                  8 that we are very careful in doing is preserving                  9 all nucleic acid material for purposes, for                  10 example, working with Sean and other, we're                  11 looking at market discovery to try and understand                  12 parasite biology, particularly focused on                  13 gametocytogenesis. So we'll look at                  14 transcriptional activity, for example, of                  15 different signaling pathways that may be important                  16 in terms of gametocytogenesis.                  17 So I think all those things are going to                  18 be possible, it's just a matter of how many hours                  19 there are in the day and can I interest a                  20 molecular biologist to do that sort of work.                  21 DR. NAMBIAR: Are there any questions                  22 from the audience for the speakers this morning?</p>
<p style="text-align: right;">Page 115</p> <p>1 tooth rise and fall of parasitemia as                  2 sequestration takes place. But when we're doing                  3 assessment for recrudescence, we're not doing                  4 nearly as rich sampling. So I think that might                  5 be a sampling out effect. You do also raise the                  6 question of whether we can identify in vivo                  7 induction resistance. In the DSM265 study, we                  8 had clear evidence from preclinical data that it                  9 was possible to induce the resistance. And one                  10 of the potential mechanisms of resistance was a                  11 mutation in the target enzyme. So we were able                  12 to actually retrieve sufficient parasite DNA to                  13 sequence across the target at which resistance                  14 had been induced in vitro and demonstrate that                  15 the parasite genotype hadn't changed from the                  16 early stage of the parasitemia until later on.                  17 DR. NAMBIAR: Any other questions from                  18 the panel for the speakers this morning?                  19 DR. KUBLIN: James, I also had a                  20 question. Have you considered nucleic acid                  21 testing for either the discovery drug or the                  22 rescue -- the study drug or the rescue drug in</p>	<p style="text-align: right;">Page 117</p> <p>1 PUBLIC COMMENTER: I just wanted to ask a                  2 question of how predictable is the MIC that you                  3 are determining in the scid mice for the data                  4 that you have seen in your challenge model or for                  5 the data you see in the clinic. I don't know                  6 whether --                  7 DR. WELLS: So just to rephrase the                  8 question. In preclinical, obviously we do cell                  9 biology studies and then was the routine testing                  10 vehicle. These days we use a scid mouse, so it                  11 has human red blood cells and P. falciparum, and                  12 we do it in two test centers. One is actually                  13 done GSK is a service to everybody in the                  14 community. So we see from the mouse model then                  15 we get parasite reduction rates and we also get                  16 an MIC. So the first thing is that the absolute                  17 parasite growth rate, so we're talking about                  18 growth and death before. The absolute parasite                  19 growth and death rates are different in the mouse                  20 from human, even though it's the same parasite                  21 and the same host cell.                  22 But the correlation between the parasite</p>

<p style="text-align: right;">Page 118</p> <p>1 reduction rates in generally quite good but not                  2 perfect. In terms of the MICs, the MICs actually                  3 transfer really well. I mean, James showed a                  4 paper that he's just published which has                  5 mefloquine in patients and volunteers, but we                  6 actually forced the mefloquine data in the scid                  7 mouse so you can actually see the correlation                  8 across.                  9 I guess the question then becomes later                  10 on we do see some nuances. So for example, you'd                  11 expect that all of the formula quinolones will be                  12 equally active in patients and in volunteers and                  13 they're not. So I think it's fair to say it's                  14 good to use the scid mouse model as a way of                  15 triaging, but finally to get the data in real                  16 people is much, much more accurate for producing                  17 the clinical outcome.                  18 PUBLIC COMMENTER: So I would like to                  19 perhaps plant the seed and ask a question to the                  20 colleagues from the FDA. You know, the flip side                  21 of antimalarial treatment is antimalarials that                  22 prevent infection. And I was wondering whether</p>	<p style="text-align: right;">Page 120</p> <p>1 can take it. So I'm glad you're here. I'm glad                  2 you're asking the question, but let's talk some                  3 more about the models and see where we get today.                  4 DR. MCCARTHY: I'd just like to make a                  5 comment as well. I think if you're able to                  6 define the MIC in vivo, then hypothetically, that                  7 should be the concentration you're going to need                  8 to maintain your blood stage prophylactic agent                  9 at in order to prevent blood stage infection.                  10 That's not to say if you're looking at causal                  11 prophylaxis in the liver, there is blood stage                  12 activity if we're able to define an MIC in vivo                  13 then that will be very informative.                  14 And certainly, the data we have shown                  15 with primaquine, in terms of clearance of Psf25                  16 as an endpoint of clearance of gametocytes, I                  17 think there is an ongoing interest in using the                  18 CHMI system that we have developed where we can                  19 actually deliberately make people gametocytemic.                  20 As a potential exploratory approach to validate                  21 preclinical data on the activity of antimalarial                  22 drugs against my own female gametocyte, which is</p>
<p style="text-align: right;">Page 119</p> <p>1 in fact the CHMI model, which has been used                  2 extensively, first in the vaccine and now being                  3 adopted very nicely in drug, whether there                  4 couldn't be a regulatory strategy of approval of                  5 antimalarials that prevent infection. It may not                  6 be the purview of this meeting today, but it                  7 ought to be at least considered. And also for                  8 antimalarials that interrupt transmission. I                  9 think those are two large efforts in the                  10 worldwide malaria community. And one could                  11 envision using CHMI as a regulatory strategy as                  12 the FDA has recently adopted approval of vaccines                  13 for (inaudible) based on CHMI alone.                  14 So I'd like to hear maybe any                  15 perspectives, if that would be appropriate.                  16 DR. COX: Yeah, so I think the question                  17 may go beyond what I can answer right now. But I                  18 think part of the panel here today is to have a                  19 discussion about these models and their potential                  20 utility. I do think that the models provide a                  21 lot of important information about how a drug is                  22 working. And the question is really how far you</p>	<p style="text-align: right;">Page 121</p> <p>1 certainly an important piece of the puzzle in                  2 terms of informing priorities for drug                  3 development.                  4 MR. CLAY: Thank you. My name is Bob                  5 Clay. I'm a consultant to MMV. I also have                  6 worked in the pocket with critical path NTB. And                  7 I wanted to raise an issue and hope that this is                  8 discussed. What we see in malaria with the                  9 challenge that you've seen today and Dr.                  10 O'Shaughnessy's presentation highlighting viral                  11 diseases and TB, my observation is that we have                  12 an opportunity here to do something we really                  13 can't do with an EBA model.                  14 So I think it would be useful for you, at                  15 least from my point of view, to compare and                  16 contrast across some of the different diseases                  17 and how reliable you think this information may                  18 be. I just wanted to highlight that. Thank you.                  19 DR. NAMBIAR: So thank you for that                  20 comment. I think that takes us right into the                  21 panel discussion. So we do have five questions                  22 and we have about an hour to discuss them. Some</p>

<p style="text-align: right;">Page 122</p> <p>1 of these questions, at least one of them has five                  2 sub-bullets. So we need to keep time in mind.                  3 I think we have seen some promising data                  4 on how CHMI studies can be used for drug                  5 development. There are certainly some unanswered                  6 questions that we need to work our way through,                  7 but certainly encouraging information at hand so                  8 far.                  9 So with that, I would be interested in                  10 hearing the panel's thoughts on the first                  11 questions which pertains to the CHMI studies and                  12 how one can use that to assess the effect of                  13 individual drugs. I think that the specific                  14 areas that we really look forward to getting your                  15 input on how one can use CHMI studies to predict                  16 the efficacy of a new drug to assess the effect                  17 of the drug on later endpoints, because typically                  18 these endpoints in CHMI studies are sooner than                  19 what we would use in clinical trials.                  20 Generalizability of the findings, which did come                  21 up in the presentation by Professor McCarthy                  22 given that certain specific strains are used in</p>	<p style="text-align: right;">Page 124</p> <p>1 light public, particularly focused on the -- and                  2 I know there has been publication both over this                  3 side of the Pacific Ocean as well as in Australia                  4 about how much we're bribing our volunteers. So                  5 there's some really clear ethical and practical                  6 issues about extending study durations beyond a                  7 month that limit our ability.                  8 I think the other thing in our favor is                  9 that we're dealing with non-immune. So light                  10 recrudescences in immune populations probably                  11 occur partly because we've got an immune effect                  12 on retarding parasite growth. In a non-immune                  13 population, I would propose that you're going to                  14 see recrudescences earlier.                  15 DR. WEINA: Well, since nobody else will                  16 say anything, I'll jump in. I usually say really                  17 dumb things, so we'll get the ball rolling. The                  18 idea of CHMI studies and moving toward regulatory                  19 approval, the questions you have are actually                  20 quite interesting and I'd like to kind of turn it                  21 around and say why are we sure that the                  22 traditional trial methodology that we're using is</p>
<p style="text-align: right;">Page 123</p> <p>1 CHMI studies and certainly differences between                  2 that and what you would see in a field trial and                  3 how one might use the result of the CHMI study,                  4 again, it did come up in Jörg's presentation to                  5 design a future clinical study.                  6 So I think these are the topics we would                  7 like to cover under the umbrella of the first                  8 question and welcome thoughts from members of the                  9 panel. And certainly, we'll take comments from                  10 the audience as well. Yes, Karen.                  11 MS. HIGGINS: Regarding the assessment of                  12 drug effect on later endpoints, I noticed from                  13 the talks earlier today that in fact you do                  14 follow people out to 28 days, and in fact, maybe                  15 a CHMI study could be used to assess the later                  16 endpoint. Is that true?                  17 DR. MCCARTHY: Yeah. It's certainly                  18 possible to go out. We find that our volunteers                  19 start to lose enthisiam to come back and have a                  20 blood test every day after about three weeks. We                  21 have been successful in increasing the interval                  22 between assessments, but you need to realize, the</p>	<p style="text-align: right;">Page 125</p> <p>1 any better or actually even gives us good                  2 information. If you look at infectious disease                  3 clinical trials versus, say, something for a new                  4 cardiac drug or a new lifestyle drug, the size is                  5 huge, as far as the difference. When we go out                  6 and do a Phase II in an endemic population or a                  7 Phase III in an endemic population, the amount of                  8 information we gather is very hit or miss. We                  9 gather so little amount of data that is out                  10 there. We really, you know, just addressing some                  11 of the issues like, you know, how many strains                  12 are going to be necessary? I mean, where did we                  13 say well, two Phase II's are good? Or two non-                  14 human animals populations are good enough? Where                  15 was the analysis that was done that actually came                  16 up with that?                  17 But when we look at what information                  18 we're able to gather from such a small group of                  19 individuals, very carefully studies, looking at                  20 the PK and the effect on parasite clearance and                  21 everything else all put together in one tight                  22 little package, the information we gather from</p>



<p style="text-align: right;">Page 126</p> <p>1 even eight people is better than we get out of                  2 300 in a typical Phase II.                  3 So the idea is, at least in my mind is                  4 that even ethical with this information to                  5 continue to use Phase II trials and Phase III                  6 trials as the basis of approval when we're                  7 getting so much better information and so much                  8 more controlled data out of the CHMI. And it                  9 just comes, as I said, I think it kind of comes                  10 down to the ethics of the issue of the ethical                  11 argument of the other. But the issue of cost and                  12 time associated with the development, the idea                  13 that we can do better dosing optimization and                  14 everything else, and early kill design for                  15 getting rid of drugs that are going to be a                  16 problem for us with very small populations rather                  17 than exposing huge endemic populations to a                  18 clinical trial that's probably flawed.                  19 So my argument and the question that I                  20 think people should take on and think about is                  21 that even ethical with this background                  22 information for us to continue do in our</p>	<p style="text-align: right;">Page 128</p> <p>1 there's noise. There is reinfection and other                  2 things that make it a difficult thing to sort of                  3 sort through. And maybe when you say "flawed,"                  4 that's what you're referring to.                  5 DR. WEINA: The whole argument that we                  6 get into as far as the difference between                  7 effectiveness and efficacy of a drug. You're                  8 absolutely right; how it's going to be used in                  9 the real world. But it's just like kids are                  10 remarkably resistant. They are ruined by their                  11 patients. Our patients are remarkably resistant                  12 to not using a drug the way that we've asked them                  13 to use it, no matter what you put on the label                  14 because half the time the label is not read.                  15 DR. COX: So I do think there is a                  16 certain degree of messiness and noise and                  17 otherwise that make the trial less efficient. I                  18 don't know that I would say it was flawed, per                  19 se. It's got some traditional Phase III trial                  20 will have some issues that can make it difficult                  21 to interpret in some circumstances. It can make                  22 the trial less efficient. And I think, what</p>
<p style="text-align: right;">Page 127</p> <p>1 traditional trials and shouldn't we be using the                  2 technology that we have and the massive amount of                  3 information that we're getting to modify how we                  4 approach regulatory approval.                  5 DR. COX: Thanks, Pete. I figured that                  6 was the place to start. In your comment, you                  7 raised a lot of issues. Let me see if I can sort                  8 of sort through at least a few of them. So the                  9 Phase III trial really is designed to try and                  10 study the drug in the way in which it would be                  11 used in the population it would be used. So                  12 there's going to be heterogeneity in the patient                  13 population. There's going to be different                  14 strains and you're going to gather information                  15 that really should help you to understand how the                  16 drug would be used in the real world.                  17 So there may be something specific that                  18 you're talking about when you say the trial is                  19 flawed. And I'm not exactly sure what you're                  20 referring to. I mean, I understand that you may                  21 be saying that it may not be the most efficient                  22 way to gather information; there's heterogeneity,</p>	<p style="text-align: right;">Page 129</p> <p>1 you're getting at is really -- I mean, the                  2 science and what you all have brought the science                  3 to really is fairly impressive. You know, the                  4 tools that you all have developed to be able to                  5 look at drugs, you know, their effect on parasite                  6 count is really quite remarkable, quite helpful.                  7 And to be honest with you, there are two                  8 things; I mean, that information that you are                  9 able to get from the various different tools and                  10 methods that have been developed in these                  11 experimental infection models can really even                  12 make the Phase III trial more ethical because                  13 you're less likely to venture into a Phase III                  14 trial with a drug or a drug combination that's                  15 not going to pan out or a dose that's going to be                  16 less likely to be effective. So I actually think                  17 that the tools can help to make the Phase III                  18 trials better.                  19 And I think one more aspect of what it is                  20 that you're bringing up here is how far can we                  21 take these models? How much can we get out of                  22 the models? I think that really is sort of what</p>

<p style="text-align: right;">Page 130</p> <p>1 we're here talking about today to try and figure                  2 that out. I mean, is it that we can use the                  3 models to get the combinations correct, get the                  4 dosing correct so that we go into a Phase III                  5 trial and that we're in the best circumstance to                  6 be able to come out with a successful outcome?                  7 Or I think the point you're raising is does the                  8 science allow us to even utilize that data for                  9 even more and is it so good that we can                  10 understand more? We're actually hoping to see                  11 what folks think about that? What do folks                  12 think? It's a laboratory strain. It's a                  13 controlled setting. It sounds like maybe in                  14 James's model it's mostly non-immune patients.                  15 Perhaps, in some of the data that Jörg was                  16 presenting, it was immune patients. So just sort                  17 of sorting through the science, I'll stop there.                  18 Good point.                  19 DR. O'SHAUGHNESSY: I just wanted to add,                  20 though, from the Phase III trial perspective, we                  21 do need the safety of the drug in the population                  22 in which we're going to study. So we definitely</p>	<p style="text-align: right;">Page 132</p> <p>1 you know, based upon whether you're treating,                  2 whether you're prophylaxing, and all these                  3 factors do figure in. So usually, safety                  4 databases, you know, probably on the lowest end                  5 is something in the order of a probably like 300                  6 patients or thereabout. That is sort of on the                  7 lowest end. You're going to see safety databases                  8 more in the several hundreds and getting them to                  9 1,000 or a couple of thousands for antimicrobial                  10 drugs, depending upon the seriousness of the                  11 condition, the availability of alternatives and                  12 such.                  13 I mean, it does seem that as we're                  14 approaching drug development, we ought to be                  15 thinking about, you know, we do need some safety                  16 data and trying to strike that balance point how                  17 much we need to understand the risk, how much we                  18 need to bound the risk of the drug, balancing                  19 that against the seriousness of the condition                  20 that it's being used for.                  21 DR. PROSCHAN: Can I go ahead? It's                  22 always a scary prospect to try and use short-term</p>
<p style="text-align: right;">Page 131</p> <p>1 should limit the CHMI as far as we can, but I                  2 think in regards to safety, we need the numbers                  3 in the patients who have the disease for safety.                  4 DR. WEINA: I mean, you bring up a great                  5 point on safety and that's always paramount in                  6 our mind and yet, we still, you know, when we                  7 talk about an infectious disease agent, we're                  8 willing to accept numbers of 300, or 400, or 500                  9 versus thousands and thousands or tens of                  10 thousands in an anti-hypertensive.                  11 So where do you actually draw that line?                  12 And where you draw that line for safety is never                  13 going to be enough until you've tested every                  14 single person, right.                  15 DR. COX: So just in general, I mean,                  16 safety databases, usually we're looking at the                  17 benefit that a particular compound brings the                  18 seriousness of the disease, the degrees of unmet                  19 need. And, you know, if you look across a                  20 variety of different drug development programs,                  21 or I should say at the point that the drug is                  22 approved, you'll find that that number does vary,</p>	<p style="text-align: right;">Page 133</p> <p>1 endpoints to predict the longer term endpoints.                  2 I do think the earlier comment, though, if you                  3 could extend these CHMI studies to get the longer                  4 term outcome, you would feel a lot better, I                  5 think about using information from the CHMI and                  6 saying maybe there's not as much of a need for                  7 Phase II or III. But I don't know, I always                  8 worry about anytime you try and make a conclusion                  9 based on shorter term endpoints and think that                  10 that that's going to have an effect on the later                  11 endpoint.                  12 DR. MCCARTHY: I think the other issue is                  13 the PK profile of your drug. So if all your                  14 drugs are gone after five days and you have seen                  15 no recrudescence two weeks later, I mean, I think                  16 there's no logic in continuing to follow the                  17 volunteer further beyond that. If you're                  18 dealing, however, with drugs -- and some of the                  19 drugs we work with MMV on have -- well, depending                  20 on how you look at it, really encouraging with                  21 long half-lives or long half-lives that may                  22 select for resistance in other people's mind,</p>

<p style="text-align: right;">Page 134</p> <p>1 then you've got, obviously, to address that issue                  2 in your clinical trial. You can obviously                  3 address that as well by giving sub-therapeutic                  4 doses or being clever in terms of how you design                  5 your study. So I think there are ways of getting                  6 at it. But I do agree, if recrudescence is your                  7 endpoint, then you're going to need to carefully                  8 study the design to be sure that your study                  9 design will be efficient, in terms of detection                  10 of recrudescence. And I think a non-immune                  11 population is a perfect population to study for                  12 recrudescence.                  13 DR. MÖHRLE: I think there's not a big                  14 difference between the long-term endpoints in                  15 Phase III malarial trials and the studies we are                  16 conducting. As I said there was 16 days because                  17 it was at the beginning when we were doing these                  18 studies, but now we routinely go out to 21, 28                  19 days in the challenge trials. We are at the 28-                  20 day time point, which was the primary endpoint,                  21 at least until now with FDA at the malarial                  22 trials. So I don't see that there is a big</p>	<p style="text-align: right;">Page 136</p> <p>1 parasite burden and so forth, which is very                  2 carefully controlled in challenge models is never                  3 controlled in the field. So we've seen that, for                  4 example, artesunate efficacy may be influenced by                  5 baseline parasitemia. So these are things that                  6 you would sort of miss if you were just to rely                  7 on a challenge model.                  8 DR. WELLS: One of the things that came                  9 out from the talks is the fact that the challenge                  10 models actually reduce the complexity of the                  11 problem. So if you look at the Phase II trial                  12 designs, you know, we normally talk about the                  13 factorial designs of a nice sort of 5x5 or 4x4,                  14 but in fact, if you throw on top, as you said,                  15 the geographic distribution, the difference                  16 between Africans and Asians, and then the fact                  17 that we're aiming to get drugs out for pediatrics                  18 simultaneously, or ahead of when we get the adult                  19 drugs out. So we've got the dose de-escalation.                  20 When you look at those charts of what you're                  21 trying to do in the Phase II B combo study, it's                  22 actually a full dimensional problem.</p>
<p style="text-align: right;">Page 135</p> <p>1 discrepancy between this trial design for                  2 challenge trials and the trial design for patient                  3 trials.                  4 DR. COX: Would anyone like to comment on                  5 parasite burden or count? I mean, it seems like                  6 we're catching folks fairly early in the                  7 experimental models of infection. Any thoughts                  8 on that?                  9 DR. SAUNDERS: Yeah. I looked at a                  10 couple of things. I mean, I think one of the                  11 things that you give up, if you were to rely only                  12 on challenge data would be the variation in                  13 parasites and geographic variation in parasites.                  14 In a couple of example, artemether-lumefantrine                  15 and artesunate do not work all that well in                  16 Cambodia and some other places in Southeast Asia.                  17 And we don't understand exactly why that's the                  18 case completely. There may be some evidence of                  19 cross-resistance, but had you relied only on                  20 challenge data and non-immunes, that would not                  21 have been revealed.                  22 And I think your point about initial</p>	<p style="text-align: right;">Page 137</p> <p>1 So just being able to look at some of the                  2 problems and say we have a fair degree of                  3 confidence that the midpoint here is going to be                  4 this dose of Drug A and this dose of Drug B is                  5 really, really important for reducing the                  6 complexity. Historically, if you didn't do that,                  7 I mean, the historical thing to do is to do the                  8 whole Phase II program and then do it in children                  9 and then do it in the other population.                  10 So in knowing what the starting points                  11 are and having some idea, you know, within a                  12 factor of three or whatever, then it really does                  13 make the information you get out of the Phase II                  14 B studies much more useful. And I was interested                  15 when Pete was pushing forward, initially, it                  16 sounded like you were trying to get rid of Phase                  17 III. Obviously, it would be nice if we could get                  18 rid of the Phase II B combos as well. At the                  19 moment, then the question you pointed out is can                  20 you use this to get rid of these Phase II A                  21 monotherapy studies where you're in a single                  22 population in a single country, is it really that</p>

<p style="text-align: right;">Page 138</p> <p>1 much use? And I think there we've managed to                  2 show that we can predict the historical data and                  3 you've got one case now, maybe two cases where                  4 we're forward-predicting what would happen. And                  5 the question is how much more data do you need to                  6 get confident?                  7 DR. MURHPY: So I have a comment about                  8 the number of strains. It's not that the CHMI                  9 model has just one strain. There are at least                  10 three strains that are being used in vaccine                  11 studies, including one that's chloroquine                  12 resistant. And James is working on some others.                  13 We typically infect with strains that are either                  14 pan resistant chloroquine resistant. And one of                  15 the things we tell subjects is we have a whole                  16 range of drugs to treat you, should you                  17 recrudescence or not tolerate the therapy.                  18 But should we be developing CHMI strains                  19 that are selectively resistant for some of the                  20 drugs that we're encountering resistance to and                  21 that we're trying to work around with these                  22 combination therapies?</p>	<p style="text-align: right;">Page 140</p> <p>1 DR. COX: And to the issue of do you want                  2 to construct various resistance strains and study                  3 them in a CHMI model, I mean, I think you have to                  4 sort of back up a little bit and think about the                  5 question that you're trying to ask. I mean, if                  6 in fact the mechanism of action of the drug is                  7 completely unrelated to the existing mechanism                  8 resistance, it's knocking out other drugs, then                  9 it may not be the most informative experiment to                  10 do. In all settings, the experiment would need                  11 to be one that didn't pose excessive or                  12 unacceptable levels of risk to the patient.                  13 So I think the question is, at least as I                  14 think about it, if there's a resistance mechanism                  15 you're concerned about, you've got a new drug                  16 that operates via different mechanism, you know,                  17 to the extent that you can study that outside of                  18 humans, whether that be in another preclinical                  19 model, animal models, that may be helpful. But                  20 if the real question is does the drug have an                  21 effect on parasite count and it's mechanism of                  22 action is different or unaffected, then you may</p>
<p style="text-align: right;">Page 139</p> <p>1 DR. MÖHRLE: I think we should. I think                  2 the capacities we now have to do high quality GMP                  3 production of parasite banks. And the capacities                  4 we have now to do targeted gene disruption really                  5 provide us opportunities if we do the                  6 manufacturing and validation and release of                  7 parasites correctly. We have the opportunity to                  8 make designer parasites for use in CHMI studies.                  9 And while it may cause some people to become very                  10 concerned, I think it really will provide us with                  11 an opportunity to greatly accelerate studies and                  12 also to be -- given our slides, I think we need                  13 to be mindful of what the context here is that if                  14 we can sit around and think about what the                  15 world's most perfect malaria drug development                  16 strategy would be versus the possibility that we                  17 will see very large numbers of deaths in children                  18 because we have a parasite strain that's                  19 resistant to viable drugs. I think we need to                  20 put this into perspective and think about how we                  21 can be creative with the modern molecular tools                  22 we now have.</p>	<p style="text-align: right;">Page 141</p> <p>1 be able to essentially use other strains that                  2 aren't necessarily resistant to particular drugs                  3 to be able to address that question.                  4 If you are in the setting where the                  5 particular resistance mechanism is one that may                  6 knock out various different drugs and have                  7 broader effects, then there may be real questions                  8 to be answered there. And we certainly want to                  9 proceed in doing that in a safe manner, whatever                  10 that was, you know, particularly starting in                  11 preclinical models and then deciding whether it's                  12 something that needs to be addressed in humans.                  13 So that's just my thoughts on that.                  14 DR. WEINA: When I see that question, the                  15 thing that pops into my head is thinking about                  16 the indication and the labeling and how it's                  17 actually going to be used. So when you talk                  18 about what strain is used in there, the things                  19 that run through my head is okay, so most of the                  20 time we're targeting either falciparum or vivax,                  21 but we don't actually put on the label well, we                  22 don't know crap about obali (ph), so don't use it</p>

<p style="text-align: right;">Page 142</p> <p>1 obali. That's just not what we put on the label.                  2 And the reality is that even if we come across                  3 one of the zoonotic ones like, you know, the                  4 Brazilian crawled into our population, you know,                  5 you have that. You're going to go ahead and                  6 you're going to use whatever drug you have on                  7 hand. And if it works, great. And you're going                  8 to continue to use it. And if it doesn't work,                  9 then that's a data point that you can put out                  10 there and you can say okay, well, we've got to                  11 try a different one. This is how we're going to                  12 learn, but we're certainly not going to do                  13 clinical trials and say okay, well, now we have                  14 to test against malaria to say that this is an                  15 antimalarial drug.                  16 So the question kind of becomes, as you                  17 brought up the issue of what is that strain going                  18 to be able to tell us about how that parasite is                  19 responding to what we're doing to its                  20 environment. So the number of strains that are                  21 there, whether it's one strain, the perfectly                  22 designed strain or if it's five strains that all</p>	<p style="text-align: right;">Page 144</p> <p>1 generalizability and how much, if it is from a                  2 CHMI study. If you're looking at one or two                  3 strains, is that generalizable to P. falciparum                  4 across the board? Are there exceptions and what                  5 do we know about that? I mean, it seems like                  6 that's really the heart of your question and the                  7 heart of the scientific issue at play.                  8 DR. LAURENS: Thanks. Just to borrow                  9 from the malaria vaccine development community,                  10 we can see that RTSS is a case in point where the                  11 CHMI model did predict field efficacy of the RTSS                  12 vaccine and the CHMI model is still the basis of                  13 dose optimization choice. So I think that we can                  14 see the success of this vaccine product and                  15 borrow from it and be assured that there is high                  16 likelihood that CHMI would predict field efficacy                  17 for drugs as well.                  18 So just to comment also on the use of                  19 field-adapted strains for a CHMI model, it would                  20 be great to get strains that are culture adapted                  21 that we could use in CHMI studies. Certainly,                  22 taking safety into consideration, we wouldn't,</p>
<p style="text-align: right;">Page 143</p> <p>1 have different characteristics. It kind of                  2 becomes, in some ways, more of a regulatory                  3 burden question than a true scientific one.                  4 DR. COX: When I think about the                  5 regulatory approach, I mean, to the extent that                  6 the science is there, that allows us to do things                  7 that are scientifically valid. The regulations                  8 really shouldn't be pushing us to do things that                  9 we don't think are scientifically valid or                  10 important.                  11 So what we may be in is a situation where                  12 the science is evolving and there may be sort of                  13 differences of opinion on the gray areas and all                  14 that, but I think we really are trying to figure                  15 out exactly what can we get out of these various                  16 different models. What can they tell us? It                  17 certainly, I mean, there's no question that it                  18 will help inform Phase III and prevent situations                  19 where you embark upon a program that probably was                  20 not a good choice or something like that.                  21 There may be more to be learned too about                  22 the number of strains you're looking at and</p>	<p style="text-align: right;">Page 145</p> <p>1 for example, want to develop an artesunate-                  2 resistant strain and use that in CHMI without                  3 having drugs that would work against it. But the                  4 use of field-adapted strains should be priority                  5 as well.                  6 DR. WELLS: I think that's a really                  7 important point. If you look at the discussion                  8 about how we face artemisinin resistance and                  9 could you develop drugs that were working against                  10 artemisinin resistance, not just by killing all                  11 parasites, then one of the thing you come up                  12 against is you don't actually have very much to                  13 go on, in terms of developing because it's not a                  14 classic IC-50 shift, it's a shift in the speed of                  15 kill. So any in vitro assay, you know, we have                  16 in vitro assays, but you were worrying about how                  17 they fit.                  18 And then going back to the animal model                  19 question, you said well, people put strains into                  20 mice and you have no idea that they link back to                  21 the clinical reality because in the clinical                  22 studies and the Phase II studies we do, yes, we</p>

<p style="text-align: right;">Page 146</p> <p>1 have Kelch mutations in very, very small numbers.                  2 So in this Phase II study, you have 19 Kelch to                  3 the 10 genotypes in there. So it's not                  4 brilliant to be relying on the Phase II B study.                  5 So I think given the seriousness of the                  6 artemisinin resistance phenotype and given the                  7 fact that it's actually this weird kinetic                  8 things, it's not an IC-50 shift, then having                  9 something -- if James comes back with a model                  10 where he's got artemisinin change in slope in the                  11 CHMI, then you can go back into the mice and you                  12 say we see this in the scid mice and work                  13 backwards, is much more healthy than what we do                  14 at the moment, which is building up from cell                  15 biology to animals to people. But I think that                  16 could be really powerful because we can come up                  17 with new generations of drugs which solve the                  18 artemisinin resistance problem by completely                  19 different mechanisms. But if you had something                  20 that would just add to ACTs and bring them back                  21 to life then that would be worth having.                  22 DR. NAMBIAR: Are there any questions</p>	<p style="text-align: right;">Page 148</p> <p>1 concentration of one dose and increase the dose                  2 or increase the concentration or decrease the                  3 concentration that we can show that we've got a                  4 greater effect or less effect. That shows that                  5 each of those two drugs is contributing to the                  6 overall effect.                  7 So what I'm trying to get at is, is there                  8 a difference between what we're going to use to                  9 show the contribution and what we're going to use                  10 to select the dose for Phase III?                  11 MS. HIGGINS: I can comment briefly.                  12 Certainly. If you have a combination of two                  13 drugs and you hold one of them constant and show                  14 the dose response of the other one, I would say                  15 that is certainly a valid way to show the added                  16 contribution of the drug.                  17 PUBLIC COMMENTER: (Off mic).                  18 THE REPORTER: You cannot make a comment                  19 unless you're at the microphone.                  20 MS. HIGGINS: So you said hold the                  21 concentration. It would depend on the design,                  22 how we could interpret it.</p>
<p style="text-align: right;">Page 147</p> <p>1 from the audience regarding this particular                  2 question before we move onto the next? In the                  3 interest of time, we'll keep it short. We've got                  4 four more question to tackle. Thank you.                  5 PUBLIC COMMENTER: I just wanted to ask                  6 about a slightly different perspective here. If                  7 we consider that perhaps, it's difficult to cover                  8 all the potential parasite strains, et cetera.                  9 Would we consider, would we think about taking                  10 the highest well-tolerated combination dose as                  11 our Phase III dose. So I'm wondering if there's                  12 a difference between finding the Phase III dose                  13 and showing the contribution. So is the Phase                  14 III dose the highest well-tolerated dose                  15 combination? That dose will always cure more                  16 patients, have longer prophphalis, have greater,                  17 longer protection against resistance. And then                  18 it's a question of how best can we show the                  19 contribution? And that, effectively, could be                  20 any of these approaches, including also Phase II,                  21 where we can show a concentration effect                  22 relationship. So we know that if we fix the</p>	<p style="text-align: right;">Page 149</p> <p>1 PUBLIC COMMENTER: So if you characterize                  2 your exposure response relationship, then you can                  3 look at the effect of changing the concentration                  4 of each of your drugs and you show the                  5 contribution. So not necessarily dose because                  6 the thing is, when we're in Phase II and Phase                  7 III, we always variability. We don't necessarily                  8 need to vary the dose.                  9 But anyway, it was a fundamental question                  10 about what is the dose for Phase III and how do                  11 you feel the contribution -- and they may not be                  12 the same sets of information.                  13 DR. COX: So just one quick comment.                  14 You're raising a good point. If I understand                  15 your question, you're saying that the dose at                  16 which you might be able to show and effect when                  17 adding A plus B in combination may be different                  18 than the dose, the sort of maximal effect for A                  19 alone.                  20 Yeah, it does seem important to                  21 understand if the response profile for each of                  22 the drugs and take that into consideration as</p>

<p style="text-align: right;">Page 150</p> <p>1 you're trying to decide what doses to go forward.                  2 I get your argument. Your argument is that B may                  3 only show additional benefit beyond A alone at a                  4 dose where A and B and not on the flat point of                  5 the curve. So you're arguing that if you had                  6 both of these drugs on the flat part of the curve                  7 above, maybe you'd be better off and you'd get                  8 more benefit. But if you were to try and study                  9 that in a model at that flat part of the curve, B                  10 may not add much to A. I get your point. It a                  11 good question.                  12 MR. MCCARTHY: I mean, the other side of                  13 that is the resistance selection issue that I                  14 think we see in just about any other area of any                  15 infected HIV, Hep C, TB, we want to have drugs                  16 that have different mechanisms of action at                  17 therapeutic levels in order to counter a                  18 selection for resistance. There has been some                  19 elegant modeling done for malaria about frequency                  20 of mutation that will be driven at a specific                  21 concentration. And also, I think it raises the                  22 issue of the duration of dwell time and how below</p>	<p style="text-align: right;">Page 152</p> <p>1 doing a controlled human infection study with two                  2 drugs, varying the doses. If we move on to the                  3 Question 2 on the monitor, we might just ask if                  4 there are any points to be made from the floor or                  5 from the panel as to whether there are any issues                  6 that we need to revisit in terms of that. And                  7 then in terms of the in vitro studies that Tim                  8 spoke about, the relevance, the scid mouse model                  9 in forming drug development. There may be people                  10 who want to revisit either of these two questions                  11 and we should give them the opportunity to do so.                  12 So I'll open the floor up to that right now.                  13 DR. WEINA: So I don't think it would be                  14 impossible to do large feasibility studies in a                  15 semi-immune population. It would be very                  16 difficult. You have, first of all, a very large                  17 trial. So you would have to enroll a large                  18 number of subjects. You have approval from IRBs                  19 to use monotherapy. That may or may not be                  20 doable, depending on which country you're in.                  21 And then you're going to have the issue of                  22 follow-up, which I think is maybe less of an</p>
<p style="text-align: right;">Page 151</p> <p>1 the MIC you are with some of the more longer-                  2 acting drugs and whether that will be a selection                  3 mechanism for resistance. And that's not the                  4 topic or today, but it's an existential question                  5 that we face thinking about combination therapy                  6 for antimalarials.                  7 DR. COX: Implicit in your question, too,                  8 is that the drugs were both well tolerated. So                  9 you're at a point where you're able to get to the                  10 flat part of the curve and not have adverse                  11 effects that would limit your dosing otherwise.                  12 Very good point.                  13 DR. MCCARTHY: Moving on. I think the                  14 second question was about the factorial design                  15 issue. I think that both Jörg and I have made a                  16 strong case that factorial design, at least at                  17 the Phase II level is going to be particularly                  18 problematic. That we don't have capacity to do                  19 such factorial designs to the sky that we would                  20 like and also that we could obviate doing that by                  21 carefully designing our early phase human                  22 challenge studies and then as well, potentially</p>	<p style="text-align: right;">Page 153</p> <p>1 issue in a controlled setting.                  2 So clearly, it would be advantageous, I                  3 think, to all concerned, to consider evidence                  4 from a controlled study in assessing the                  5 combination rule first, compared to trying to do                  6 that in a field study. I think that would be                  7 very challenging.                  8 I just have one quick comment on the idea                  9 of the factorial design and just again, stepping                  10 back from what we're looking at and that is one                  11 of the big paradigm shifts that we did was that                  12 we sat there and we looked at HIV and we looked                  13 at TB and we said, you know, we're not dumb                  14 enough to use a single drug against these                  15 organism, and yet we're arrogant enough to think                  16 that a single drug is going to take care of                  17 malaria and the big paradigm shift was oh, gee,                  18 let's not do that. Let's use two drugs. Let's                  19 combine the drugs.                  20 Maybe one of the other things we can do                  21 is kind of step back and learn again from HIV and                  22 from TB, and rather than trying to push</p>

<p style="text-align: right;">Page 154</p> <p>1 everything in a marketed fix dose combination or                  2 marketed, you know, these things are always put                  3 together, maybe we ought to just have a suite of                  4 drugs that a clinician can choose from, just like                  5 we do for TB, just like we do for HIV. And using                  6 different combinations in different places                  7 because where we get into trouble, I think, is                  8 the fact that we went ahead and mefloquine failed                  9 in Southeast Asia, so we added artemisinin to it.                  10 And sure, hey, it reversed mefloquine for                  11 resistance for a while but now it's failing.                  12 Now both of the drugs are going to fail                  13 instead of single one, where if we had a suite of                  14 drugs to choose from, the clinician could choose                  15 from a bunch of different combinations. And                  16 yeah, maybe some of the combinations you have to                  17 stay away from, just like you do for HIV, but                  18 could be part of the packaging. It simplifies                  19 the development of it, first of all, in a lot of                  20 ways. Second of all, it helps kind of prevent                  21 these little pockets of basically monotherapy of                  22 two different drugs. So it's just a thought of</p>	<p style="text-align: right;">Page 156</p> <p>1 so easily taken care of, we can just hand                  2 somebody a drug and say take this for the next                  3 three days and forget about it. Maybe bring them                  4 back and make sure that they're taking the drug                  5 right in front of us, like we do with TB.                  6 DR. MURPHY: So to me, this is my major                  7 reflection on really, the whole summation of the                  8 morning's questions is that it presupposes that                  9 the only way to move forward is to fulfill the                  10 combination rule. And certainly, one can imagine                  11 scenarios where that would make a lot of sense,                  12 but I'm wondering, are we ad-mixing the                  13 scientific issues and/or the practice of medicine                  14 and public health issues and the regulatory. And                  15 if we put it, really within the context of what                  16 do we have here within the United States to use,                  17 everything we talked about in the introductory                  18 slide, we have only agents and Coartem.                  19 So within the confines of what would a                  20 sponsor do? Who would bring it to be able to                  21 fulfill those fixed combination rules become,                  22 even from the business side, very problematic.</p>
<p style="text-align: right;">Page 155</p> <p>1 getting around this idea of having factorial                  2 design studies and having all these ways of just                  3 marketing a single combination of drugs.                  4 DR. MCCARTHY: I think if Nick Watt was                  5 here, he would point out that the loose                  6 combinations of artemisinin and the partner drug                  7 are really problematic in a clinic setting where                  8 you don't have good patient adherence. That                  9 someone feels a lot better after taking a couple                  10 of tablets of artesunate and doesn't want to                  11 follow-through with mefloquine. There are some                  12 real problems, I think with formulation and                  13 adherence if you have a situation where you give                  14 people the option of taking the drug that makes                  15 them feel better but doesn't cure them. So I                  16 think that's a real issue.                  17 DR. WEINA: Same problem we've got with                  18 TB worldwide. And we fixed that by directly                  19 observed therapy or at least made a dent in it                  20 with directly observed therapy. So again, maybe                  21 another lesson of rather than being arrogant and                  22 thinking that we can just hand somebody malaria</p>	<p style="text-align: right;">Page 157</p> <p>1 And to take Dr. Aukinshouse's point, if one then                  2 imagines what in the armamentarium of                  3 antimalarial use -- what other types of ways                  4 would clinicians want to use these drugs? Then                  5 suddenly, just the combination rule may not be                  6 exactly what you want to do if there was a drug                  7 that was available for intermittent presumptive                  8 treatment.                  9 So these tools, to me, seem like they                  10 open up the ability to quarry triple drug                  11 regiments, maybe quadruple drug regiments. You                  12 were talking about it's inadvisable to add just                  13 one more drug to a failing regiment. So it may                  14 be two. But to think about doing that in a                  15 regulatory context where those have to be defined                  16 and then tested in that is overwhelming.                  17 Honestly, I don't think you can get there from                  18 here box, certainly not from a practical sponsor                  19 standpoint.                  20 So I would just put out there that let's                  21 make sure we haven't set the criteria up front                  22 that have artificially backed us into a corner</p>



<p style="text-align: right;">Page 158</p> <p>1 that we needn't necessarily have to be. That                  2 there may be some single agents and in ways that                  3 could get a regulatory approval and then be                  4 useful of multi-drug regiments. If a sponsor                  5 says I have no intention of putting it out and                  6 marketing it in these other kind of other ways.                  7 I guess one thing to just follow on is                  8 let's face it, by forcing it into co-                  9 formulations, if one of those is an already                  10 approved drug, which can imagine all kinds of                  11 scenarios. Artesunate still works. It's just                  12 isn't working as well as it did, the shift in the                  13 curve, right. But it'd not like we lost our drug                  14 for severe and complicated malaria.                  15 So one can imagine all kinds of partner                  16 drugs we want, but the second that comes, you've                  17 lost any of the incentive for the PRVs. You've                  18 complicated that, but that may be the only way                  19 that this makes any business sense for a sponsor                  20 to pick that up and agree to take it forward. So                  21 again, let's be careful to not back ourselves                  22 into a corner that we can't get out of.</p>	<p style="text-align: right;">Page 160</p> <p>1 fields, what oftentimes happens is you see                  2 proliferation of a new entities. That happens                  3 for a variety of reasons. Sometimes a company                  4 has just one drug, so in the developmental phase                  5 it may be difficult to actually start to combine                  6 but at other times it's not such of a problem.                  7 So it can evolve either way. You can                  8 either have singles or you can move to fixed dose                  9 combinations. And you can see there's pros and                  10 cons to both ways of doing this. Then the other                  11 thing is the combination rule. So when we were                  12 talking about this, you know, we said don't feel                  13 like you're a victim of the combination. The                  14 combination rule is really to try and figure out                  15 that the components that you have and the drug                  16 regiment are active.                  17 And I think the importance of treating                  18 malaria with effective drugs, you know, you want                  19 to go in with Drug A being effective, Drug B                  20 being effective and adding something. That's                  21 really the heart of this. That's what we're                  22 trying to understand. We want to make sure that</p>
<p style="text-align: right;">Page 159</p> <p>1 DR. WELLS: I just -- sorry. Go ahead.                  2 DR. COX: Maybe I should just make a                  3 couple of comments. With regards to fixed dose                  4 combinations or singles, James brought up the                  5 issue of resistance. There are reasons to do                  6 fixed dose combination. Sometimes they're more                  7 convenient for patients. You don't end up with,                  8 you know, the idea there is to avoid therapy and                  9 gender resistance. I think Pete's bringing up                  10 the point of well, if the patient is already                  11 resistant to one of the drugs anyways, then                  12 you're essentially going back in with functional                  13 monotherapy.                  14 So there is a setting when it's nice to                  15 be able to have the singles and have enough                  16 information to be able to determine what an                  17 appropriate treatment regiment is for the patient                  18 so that you're not giving them drugs to which                  19 they are already resistant.                  20 So there's pros and cons to both sides of                  21 whether you're going to do fixed dose                  22 combinations or singles. If you look -- in many</p>	<p style="text-align: right;">Page 161</p> <p>1 the components of the regiment are actually doing                  2 something, and there are a variety of ways to do                  3 it. And you can see that, if you look at HIV,                  4 we've been successful there in trying to figure                  5 out various different combinations drugs. The                  6 same, I think, more with Hepatitis C more lately                  7 with different combination of drugs being                  8 studied. So there are ways to do it. There are                  9 particular challenges in doing it in the field of                  10 malaria drug development. I think the real                  11 question is, is sort of gathering the scientific                  12 information and what can we learn from these                  13 various different experimental models of                  14 infection that will help us to understand how                  15 each of the components are contributing to the                  16 overall effect and is the science good enough it                  17 essentially establishes that and that's what I                  18 think we're sorting through.                  19 DR. WELLS: I think there is a difference                  20 between HIV, TB, and malaria, the principal one                  21 being that you don't actually have many malaria                  22 patients in the country. So you get into this</p>

<p style="text-align: right;">Page 162</p> <p>1 position where -- I mean, we talk about this all                  2 the time. It would be much easier if we could                  3 just register things as a single agent with the                  4 FDA and then put them in combination afterwards.                  5 The next step after an FDA, and Ed talked about                  6 that, approval, is it goes to WHO for going on                  7 the treatment guidelines where it has to be a                  8 combination. If you then say well, let's do the                  9 clinical trials and we do them in say, Uganda,                  10 the Ugandans want to know that WHO has approved                  11 it before they will register it.                  12 So the idea of actually being able to do                  13 the clinical trial much easier just because the                  14 drug is approved by the FDA as a single, it just                  15 doesn't work that way. But I think it is                  16 important we make the drugs available as singles                  17 for testing in the right environment. And I'm                  18 not sure it has to be registered by the FDA for                  19 that, it's still part of the clinical trial. But                  20 we mustn't lock the combinations too early.                  21 Somebody was asking me that earlier, saying one                  22 of the things about malaria, which is important</p>	<p style="text-align: right;">Page 164</p> <p>1 then for example lumefantrine will work fine. It                  2 will give you a 90 percent cure if it give it for                  3 three days. Artemisinin will work fine if you                  4 give it as a single dose for seven days. But                  5 each time, what you're having to do it is you're                  6 having to extend the duration of therapy. So                  7 it's very difficult to set criteria of what a                  8 single dose, of what a single drug would have to                  9 do.                  10 In a sense, the 95 percent ACPR, the WHO                  11 sets is an arbitrary one anyway. It's just sort                  12 of saying well, we can get there with ACT, so                  13 that's our new threshold. So I think if we went                  14 the single dose route, excuse me, a single drug                  15 route, we'd have to do quite a lot of work in                  16 thinking about what we were trying to achieve                  17 with a single drug anyway that has not been                  18 thought about.                  19 DR. NAMBIAR: I'm sure there are some                  20 comments in the audience as well.                  21 PUBLIC COMMENTER: The first comment is,                  22 mefloquine has saved a lot of lives in Southeast</p>
<p style="text-align: right;">Page 163</p> <p>1 is that if the right combination is bringing two                  2 drug companies together, we can do that. And                  3 that's very different from some of the                  4 therapeutic areas.                  5 DR. COX: So if I understood correctly,                  6 you're making a fairly strong push for                  7 combinations being the route to go here rather                  8 than singles?                  9 DR. WELLS: I think it would be -- yeah,                  10 exactly. For doing the development, ultimately,                  11 our goal is not to register the drug with the                  12 FDA. Ultimately, the goal is to treat the first                  13 million or 10 million children. And once you                  14 start to map out that clinical path, then if the                  15 combination can't be defined, then the WHO isn't                  16 going to approve it. So far we haven't seen that                  17 much advantage of having -- apart from things                  18 like the priority review voucher, it's not that                  19 much advantage to being able to register as a                  20 single drug.                  21 The other issue that comes up if you make                  22 a list of all the clinical data on monotherapies,</p>	<p style="text-align: right;">Page 165</p> <p>1 Asia, even though it was not an ideal                  2 combination. And for a small company active in                  3 this space, the PRV is the only financial                  4 incentive. So if monotherapy development through                  5 to the initial registration is taken off the                  6 table, then it eliminates a lot of private sector                  7 resources that could be brought to the bear on                  8 the problem as well.                  9 Just reflecting on an earlier comment,                  10 ultimately, the genetic barrier to resistance is                  11 to combine the maximum tolerated dose of multiple                  12 agents. And so shouldn't that be the focus is                  13 getting regulatory approval for the safety of a                  14 drug that can them be used in practice of                  15 medicine? Thanks.                  16 DR. COX: Before you leave, could you                  17 just clarify, you said monotherapy? Did you mean                  18 development of the drug not as a fixed dose                  19 combination or do you mean --                  20 PUBLIC COMMENTER: Correct.                  21 DR. COX: Okay. So you don't mean                  22 necessarily monotherapy. You might actually</p>

<p style="text-align: right;">Page 166</p> <p>1 develop it in combination with another drug, but                  2 you would have it as a single agent in a separate                  3 table or something like that. Just to clarify.                  4 PUBLIC COMMENTER: So even MMV, which is                  5 an organization that is well resourced don't have                  6 enough money to take every drug in their                  7 portfolio through using a standardized fixed dose                  8 combination approach.                  9 So there are other organizations in the                  10 community that want to move forward with new                  11 approaches as well and they operate in a                  12 different environment where you have to be able                  13 to justify the financial return on investment.                  14 So the only thing that is attractive to investors                  15 is the PRV, which dictates a regulatory strategy,                  16 additionally around monotherapy.                  17 So if that's your goal, then the                  18 challenge is to identify the maximum safe dose                  19 and take that forward to initial regulatory                  20 approval and then leave the issue of combinations                  21 to clinicians as a practice of medicine issue,                  22 combining it with other things that have also</p>	<p style="text-align: right;">Page 168</p> <p>1 right dosing regimen. Even if you say let's keep                  2 the maximum tolerated dose, but you still have to                  3 combine the seven-day artesunate with the three                  4 days piperazine or the seven days artesunate                  5 with the three days mefloquine.                  6 So I don't see how, for the ultimate                  7 goal, which is new antimalarial drugs for people                  8 who have limited access to resources or                  9 clinicians. We can accelerate it by developing                  10 single compounds until registration because then                  11 the cost to get a combination treatment and the                  12 evidence for a combination and dose and regimen                  13 has then to start again after the single                  14 compounds have been registered.                  15 DR. WEINA: I think I'm kind of missing                  16 something here because we're arguing about three                  17 days versus days. I mean, for TB, we're talking                  18 about four drugs for two months and two drugs for                  19 four months. So we're talking about six months                  20 of therapy. I mean, it's not working great.                  21 It's working, at least in some areas. That was                  22 just more of a random thought that came up.</p>
<p style="text-align: right;">Page 167</p> <p>1 come through. And that just highlights what                  2 Colonel Weina was going with that point.                  3 DR. NAMBIAR: Thank you. Dr. Möhrle you                  4 had a comment?                  5 DR. MÖHRLE: I just wanted to follow up                  6 with what Tim just said. Currently, the                  7 monotherapies I don't think will change with the                  8 next generation very much. You have been given                  9 three to seven days to achieve adequate cure                  10 rates.                  11 So if we now follow the experiments and                  12 let's register the drugs as monotherapy and leave                  13 it to the clinicians or the malaria guideline                  14 committee to tell us what would be the adequate                  15 combination, we have artesunate for seven days.                  16 We have mefloquine for three days. What is the                  17 evidence that a three-day artesunate combined                  18 with mefloquine or three days artesunate combined                  19 with piperazine is working?                  20 There would be a lot of work necessary to                  21 actually get the data on your different                  22 monotherapy option and the right dosing and the</p>	<p style="text-align: right;">Page 169</p> <p>1 Jeff brought up an interesting thing                  2 about the priority review voucher and that is a                  3 big incentive. It's one of the great things that                  4 has happened for malaria. It's one of the worse                  5 things that's happened for malaria because                  6 whoever gets first through the gate is the one                  7 who gets a priority review voucher and can sell                  8 it for \$200 million. I think that's the average                  9 latest price. But then nobody else is going to                  10 be able to get it after that.                  11 So all the incentive that came from the                  12 priority review voucher goes away and instead,                  13 they're going to find something else to work on                  14 like Q fever or Zika or Ebola or something like                  15 that and try to get the priority review voucher                  16 so they can get their latest lifestyle drug                  17 through.                  18 So great point, Jeff, but one of the                  19 problems is that whoever is first through the                  20 gate gets and it nobody else gets it afterwards.                  21 DR. KUBLIN: It's a very interesting                  22 discussion because I think, you know, working in</p>

<p style="text-align: right;">Page 170</p> <p>1 HIV, TB, and malaria, I balk at the notion of on                  2 the one hand the development of a single therapy                  3 over time for malaria because of the three                  4 malaria treatment is, of course, most prolific in                  5 the community as ad hoc therapy. And there is                  6 plenty of evidence that fevers of unknown origin                  7 are just routinely treated at the stalls with                  8 monotherapy if it is available, and that's                  9 certainly contributing to the evolution of                  10 resistance.                  11 But if here is medical care and if that                  12 can be directed in such a way, as it clearly is                  13 for TB and HIV, that's a different story. But                  14 given the ubiquitous nature of these                  15 antimalarials in the communities, you know, I                  16 think that's still a major concern.                  17 DR. MURPHY: Just within the context of                  18 keeping possibilities open, we're sitting here at                  19 White Oak and discussing this within the context                  20 of the FDA. I can imagine scenarios by which                  21 medications are used in the United States on                  22 Americans in ways that would be wildly</p>	<p style="text-align: right;">Page 172</p> <p>1 failing in Southeast Asia that a new single drug                  2 might be what gets added to those.                  3 DR. PROSCHAN: So as I understood the                  4 earlier presentation by the regulatory issues of                  5 combination drugs, that superiority of the                  6 combination to each constituent need not be on                  7 the primary outcome, right. It made it look like                  8 you could show that putting them together improve                  9 parasitemia more than either one alone. And that                  10 might be sufficient; is that right?                  11 DR. O'SHAUGHNESSY: That's right. It                  12 could be a number of endpoints. It could be on                  13 fever clearance. It could be on any endpoint you                  14 choose.                  15 PUBLIC COMMENTER: Does it even need to                  16 be on endpoints? It seems to me there are                  17 different levels of evidence for different                  18 things. And clearly you need a high level of                  19 evidence for establishing that a product is safe                  20 or that it is effective in its final form in the                  21 people you're going to use it in. But for just                  22 showing that the different components each have a</p>
<p style="text-align: right;">Page 171</p> <p>1 inappropriate in all these other places. But                  2 that doesn't mean that's not possible, given who                  3 does the FDA approve drugs for. And that may not                  4 be at all the same thing as what do we as a                  5 greater malaria community internationally need to                  6 do. And I can imagine a responsible sponsor who                  7 says this is my pathway. It is going to be a                  8 little more difficult but the same model than                  9 with an approved drug. I can take it back in                  10 there and say now I need to figure out where it                  11 fits in the combinations most appropriately.                  12 Where are we going to put that in and do                  13 some work with that that then becomes the tool                  14 that can be used for the rest of the world. So                  15 at least for me, I can envision that as possible.                  16 And so I'm hesitant to just take off the table a                  17 discussion with the agency that may say this is                  18 our plan. This is our pathway forward.                  19 PUBLIC COMMENTER: And also thinking back                  20 to James's first talk when he was channeling that                  21 as we need to think about adding new drugs to the                  22 ones that the combinations that are already</p>	<p style="text-align: right;">Page 173</p> <p>1 contribution, that could rely on a much lower                  2 level of evidence and need not be clinical at                  3 all. It could rely entirely on MV Pro or                  4 preclinical evidence. And I'm not aware of                  5 anything in legislation that says you need                  6 clinical trials to establish that each component                  7 is having an effect.                  8 DR. O'SHAUGHNESSY: And that's why we                  9 asked the question, you know, what in vitro                  10 studies, what animal studies -- what studies                  11 could help us to show the contribution of both                  12 components. So you're right, it doesn't --                  13 PUBLIC COMMENTER: It's not necessarily                  14 both "and" because I think those can entirely                  15 replace. If we're relying on the argument that                  16 we can't possibly do these factorial studies as                  17 why we need all these other models, I'm not sure                  18 that we have any need for doing the factorial                  19 studies in the first place.                  20 DR. O'SHAUGHNESSY: That's why we're                  21 having the workshop to discuss these issues.                  22 DR. PROSCHAN: Well, I mean, I think it's</p>

<p style="text-align: right;">Page 174</p> <p>1 a good thing that you can have lower levels of                  2 evidence because in a sense, if you find a                  3 combination that just works perfectly, who cares                  4 whether each component is needed or not, you                  5 know, you have something that works.                  6 DR. NAMBIAR: So I think the point here                  7 is how one assesses the contribution of the                  8 components and there are many different ways one                  9 can do it. So it could be clinical if it's                  10 feasible. It could be microbiologic. So I think                  11 there are various ways. And as Dr. O'Shaughnessy                  12 said, that's the purpose of this workshop is to                  13 understand is the science with CHMI studies                  14 there, can we use that information because truly                  15 factorial designs in a clinical setting are maybe                  16 doable but very, very difficult is what we've                  17 heard.                  18 So I think we're trying to see what other                  19 pieces of evidence could we use and CHMI could be                  20 one piece of that. There are limitations, but                  21 there are also limitations with other data which                  22 might be -- so I think that's the purpose of</p>	<p style="text-align: right;">Page 176</p> <p>1 discussion, I'm beginning to think that factors                  2 we cannot control may be removing that from us as                  3 a true viable, long-term option. The parasite is                  4 changing. We understand much little than -- less                  5 than we should about how drug combinations                  6 interact, including the fact that active drugs                  7 put together can occasionally produce a result                  8 which is less than either of them alone. I                  9 wonder if the discussion that's going around                  10 about shifting the paradigm and licensing or                  11 approving the single drugs as is often done in                  12 others parts of medicine is not an idea that                  13 deserves some serious consideration.                  14 DR. COX: So we can work really with                  15 other circumstance, with either circumstance. I                  16 mean, whether it be singles or whether it be                  17 fixed-dose combinations, I think, you know, we                  18 can work through that. You've heard arguments                  19 for. You know we don't want people to be taking                  20 monotherapy. We want to protect the drug. I                  21 think everybody gets that. You've heard                  22 arguments about well, what if somebody is already</p>
<p style="text-align: right;">Page 175</p> <p>1 having this discussion.                  2 DR. WELLS: But if you look at, as you                  3 said, looking at Question 3, the translation                  4 between the scid mouse, because it has the right                  5 parasite and it has human red blood cells through                  6 to the CHMI at least is very good. I mean, we                  7 can point out where there are problems and the                  8 factors of three here and there, but I think a                  9 combination of CHMI data supported by combination                  10 studies in animals would be actually quite solid.                  11 DR. NAMBIAR: Right. So I think the                  12 science is certainly encouraging. It certainly                  13 does appear that there might be some more work                  14 that we need to do and we were hoping that at the                  15 end of today's discussion we would get some ideas                  16 and see how to move forward. I think that's the                  17 intent. I think maybe that could be the comment                  18 before we wrap up. Maybe there is one more                  19 comment from the audience.                  20 PUBLIC COMMENTER: Like many of the                  21 people here I came fixed on the idea of a fixed                  22 dose combination. But as I listened to the</p>	<p style="text-align: right;">Page 177</p> <p>1 resistant to one of the drugs and the combination                  2 and wouldn't it be nice to have singles to be                  3 able to tailor the regiment appropriately. You                  4 can see there's pros and cons on all sides.                  5 One other point of clarification too, the                  6 question about 15 or 20 minutes ago was talking                  7 about the priority review voucher. So I'll                  8 preface this by saying I'm not a lawyer.                  9 I'm not one of the folks that makes these                  10 interpretations. But I think it was about a year                  11 and-a-half ago we issued a guidance document that                  12 described our interpretation of a new chemical                  13 entity.                  14 And there was a recognition that there                  15 were in many fields, infectious disease in                  16 particular, innovation happening where a new                  17 chemical entity, you know, in the old sense, a                  18 new drug, a molecule that had not been previously                  19 approved had been paired with a drug that had                  20 been previously approved. And that guidance                  21 document talks about -- it's more along the lines                  22 of talking about exclusivity, but I think that</p>

<p style="text-align: right;">Page 178</p> <p>1 the issue of pairing a new drug with an old drug                  2 in a fixed dose combination, it certainly has                  3 been addressed from the setting of exclusivity                  4 determinations. Again, I'm not a lawyer, but I                  5 would think that would also have implications,                  6 too, for the priority review voucher for drugs                  7 that are being combined with previously                  8 approached drugs. So that's sort of an evolving                  9 areas, if you will, recognizing the value of                  10 fixed dose combinations in certain settings.                  11 And of course, for a final rule on that,                  12 we'd need to go back to our lawyers to make sure                  13 what I'm saying makes sense and is correct. But                  14 that's at least my understanding.                  15 DR. HAZELTON: John Hazelton, head of                  16 Malaria for GSK, based in Canada. It's actually                  17 my group that actually works with Tim and James                  18 very carefully, in terms of doing a lot of the                  19 animal models specifically around the scid mouse                  20 model.                  21 But just to add some context to Question                  22 3 because that's what we're here for at this</p>	<p style="text-align: right;">Page 180</p> <p>1 informed data from in vivo animal studies, ex                  2 vivo, and also, James, as we've discussed in the                  3 past, retrospective validation of existing                  4 clinical combinations to build that data set and                  5 I think that's what you're asking in terms of                  6 what animal models are relevant out there that we                  7 could use in the future. So that's really just                  8 to add some context to Question 3 there.                  9 DR. MCCARTHY: I just wanted to make one                  10 other comment about combinations. I think if you                  11 go back to my slide on the pipeline for                  12 antimalarial drugs, where I think quite                  13 fortunately that we've got a number of novel                  14 targets that are already in the clinic that we                  15 provided the adverse problems don't occur. We're                  16 likely to have completely new target with                  17 potentially more than one drug available to use.                  18 So the concept of hypothetically only                  19 having one drug to add to already licensed drugs                  20 I think is a little naïve. Jörg spoke about                  21 OZ439 and DSM265. There are other examples there                  22 where I think we really have hopes that in five</p>
<p style="text-align: right;">Page 179</p> <p>1 workshop, actually discussing those at relevant                  2 animal models. As Tim has just suggested, it                  3 would be great to have that combination model in                  4 the scid mouse to be able to test these                  5 combinations. And that's what we do. That's                  6 what we're developing now. We're developing                  7 those assays, both ex vivo PRR, in vivo                  8 combination models, not to look at synergy. And                  9 this answers the question around looking for                  10 contributory. Does A work? Does B work? Is A                  11 plus B better than A or B alone?                  12 Actually, that's not what a combination                  13 scid mouse model will answer. It will tell you                  14 if A plus B works and it works just as well as A                  15 or B that's fine, but what you don't want it                  16 negative interaction. So we are actually looking                  17 at using the in vivo and the ex vivo PRR model to                  18 actually assess which combinations work and then                  19 you will have armamentarium of drugs whereas the                  20 industry can work with the people at MMV, the                  21 Gates Foundation, Well Trust, et cetera, to put                  22 together those right combinations based on</p>	<p style="text-align: right;">Page 181</p> <p>1 years' time we will have these drugs in the Phase                  2 III trial and we need to think about how we're                  3 going to license them and how we're going to put                  4 them together and what appropriate regulatory                  5 environment that we're going to be working to get                  6 those drugs licensed, both here or in the                  7 developed world where malaria is a rare disease,                  8 but in the developing world where there are                  9 millions of cases and hundreds of thousands of                  10 deaths every year. And I think that's where, at                  11 least those of us who work in this community are                  12 highly motivated to try and get those things to                  13 move forward.                  14 DR. COX: So maybe we'll bring the                  15 morning session to a close and break for lunch                  16 here in just a minute.                  17 I do want to say that you've heard a lot                  18 of the complex issues that are dealt with here                  19 and I think the science and the advances and the                  20 science really are impressive and I think that's                  21 really a credit to all the folks in the field                  22 that have really moved things along here. You</p>

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<p>1 know, that scientific information, I think, is                  2 very important, as we start to look at the roles                  3 of combination that would be developed for                  4 treatment of patients with malaria.                  5 There are ways to work through the                  6 combination issue. It shouldn't impose an                  7 impediment to development. It really should be                  8 trying to get at the information that you would                  9 need to use the drug appropriately. So as people                  10 are developing drugs, don't hesitate to engage                  11 us. Don't hesitate to engage us early. I think                  12 that we can work through this issues in a way                  13 that I would hope would be acceptable and                  14 scientifically based to help really address the                  15 question of what's the role of the different                  16 components of the combination.                  17 You know, clearly, we need more drugs for                  18 malaria. And this is an opportunity to try and                  19 work through some of these situations so that                  20 drugs can be developed efficiently and we can                  21 have new options out there for patients, both                  22 here in the U.S. and recognizing the tremendous</p>	<p>1 AFTERNOON SESSION                  2 (1:00 p.m.)                  3 DR. BALA: I'm Shukal Bala with the                  4 Division of Anti-Infective Products, CDER, FDA.                  5 I'll be co-chairing this session with Dr. Ingrid                  6 Felger.                  7 Dr. Ingrid Felger is -- okay -- is a                  8 full-time employee at the Swiss Tropical and                  9 Public Health Institute in Basel, Switzerland,                  10 where she heads the Molecular Diagnostic Unit, or                  11 Swiss TPH. Her research focus is molecular                  12 technology of plasmodium falciparum and                  13 plasmodium vivax. Dr. Felger is a molecular                  14 biologist with a PhD in drosophila genetics from                  15 University of Tübingen in Germany.                  16 During her first job, she worked for                  17 three years at the Papua New Guinea Institute of                  18 Medical Research where she established genotyping                  19 assays for molecular monitoring in malaria                  20 vaccine and drug trials.                  21 So Dr. Ingrid will be giving the first                  22 talk on Molecular Detection, Quantification,</p>
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<p>1 global burden and have drugs for patients where                  2 the larger burden of diseases are so that new                  3 therapies are out there.                  4 So with that, why don't close the morning                  5 session and we'll be back after lunch at 1:00                  6 p.m. So we'll have everyone back at 1:00.                  7 Thanks.                  8 (Whereupon, at 12:00 p.m., a luncheon                  9 recess was taken.)                  10                  11                  12                  13                  14                  15                  16                  17                  18                  19                  20                  21                  22</p>	<p>1 Genotyping of P. Falciparum in in vivo Drug                  2 Efficacy Trials.                  3 Thank you, doctor.                  4 DR. FELGER: Thank you for the                  5 introduction.                  6 Good afternoon, everyone. Thank you for                  7 coming back after lunch in beautiful summer in                  8 Washington.                  9 My talk today will cover three topics --                  10 basically, molecular detection, quantification                  11 and genotyping of plasmodium falciparum in in                  12 vivo drug efficacy trials. So the focus will be                  13 on field work and not so much on the CHMI.                  14 When you talk about molecular detection,                  15 the first thing is what people ask -- what about                  16 the sensitivity. So for me, sensitivity has two                  17 aspects. One, certainly, is the assay. But a                  18 major aspect which is always forgotten, this is                  19 the relationship of the sensitivity to the                  20 sampling methods.                  21 And I would like to point out a few key                  22 things here. For example, if we would take a</p>

<p style="text-align: right;">Page 186</p> <p>1 blood -- a whole blood sample on the filter                  2 paper, we normally have a very limited amount of                  3 material which we add into our molecular assay.                  4 In that example here, we have punches -- three                  5 punches, three millimeter punches that                  6 corresponds about to nine microliters of blood.                  7 So if we throw all the punches into a PCR tube,                  8 this -- then we have the equivalent of nine                  9 microliters of blood in the PCR tube.                  10 However, if we extract the DNA by the                  11 Chelex method, which is recommended, we only at -                  12 - infect half -- the equivalent of half a                  13 microliter of blood. So this is very little and                  14 doesn't really compare.                  15 So if we use the finger prick blood                  16 sample where we get about 200 microliters of                  17 blood, we can extract that with a spin column                  18 extraction where it's suspended in 50                  19 microliters. And then we would add about the                  20 equivalent of 20 microliters of blood. So this                  21 is -- the starting material is really very                  22 different.</p>	<p style="text-align: right;">Page 188</p> <p>1 and at the day of recurrence. So with                  2 microscopy, of course, only have a reliable                  3 detection if the densities are above 50 to 100                  4 microliters of blood -- of parasites per                  5 microliter. This, of course, is very likely                  6 sufficient if we have a clinical trial where                  7 there is some -- where we start from a malaria                  8 case -- uncomplicated malaria case.                  9 There are alternative methods to                  10 microscopy -- RDT, PCR, LAMP, quantitative PCR.                  11 I'm not going to talk about these because David                  12 Saunders later on will cover these topics.                  13 I would like to talk about the                  14 alternative methods -- for example, the large                  15 volume of venous blood and the ultrasensitive                  16 multi-copy marker detection method, or an RNA-                  17 based technique where this is applicable in the                  18 field.                  19 In these antimalarial drug trials with                  20 uncomplicated malaria, we quite likely have a                  21 very good sensitivity with live microscopy.                  22 There is a complication that in the day of</p>
<p style="text-align: right;">Page 187</p> <p>1 There is this method which has been                  2 presented in the White Paper that is the high                  3 volume, ultrasensitive method which is based on                  4 collecting a venous blood sample. And there, you                  5 extract DNA from one milliliter of blood, and you                  6 end up with about -- with the equivalent of 200                  7 microliters of blood. So I mean, it is very,                  8 very clear that if there is one parasite in that                  9 volume of blood, it can be detected by the                  10 ultrasensitive method. But it can never be                  11 detected by a DNA, which comes from a filter                  12 paper.                  13 So these considerations are very, very                  14 important when designing a study because the                  15 outcome, the sensitivity of the method, really                  16 very much depends on the sampling and not so much                  17 on the molecular assay. That is just the point I                  18 wanted to make.                  19 Now coming to the sub-microscopic                  20 infections, do they really matter in a clinical                  21 trial? We have -- in a field trial, we have                  22 parasite detections requirements at enrollment</p>	<p style="text-align: right;">Page 189</p> <p>1 recurrence there might be gametocyte presence.                  2 We have heard this already from the human-                  3 controlled trials. Already, James McCarthy has                  4 also detected those gametocytes. And they might                  5 compromise our positivity in the sample. So this                  6 is a threat.                  7 So the decision on the method what we                  8 will use would very much depend on the study                  9 population and the protocol and the facilities at                  10 the field site. How can -- what kind of blood                  11 sample do we take? Can we take a venous blood?                  12 How do we process the venous blood? Or do we                  13 need to take blood on an FDA card on a filter                  14 paper?                  15 So there is some -- is there -- for us,                  16 the question today -- is there a consensus among                  17 the experts on the use of the molecular detection                  18 in field trials? This is a question we need to                  19 discuss later. Do we stay with live microscopy?                  20 Or do we introduce the more expensive molecular                  21 tools?                  22 So what is the most sensitive assay for</p>



<p style="text-align: right;">Page 190</p> <p>1 parasite detection in a finger prick blood                  2 sample? We have two options -- RNA-based                  3 detection or DNA-based detection. In both                  4 assays, we target the 18S ribosomal RNA -- once                  5 the transcript and once the genes. So there are                  6 three to five genes per haploid genome in a                  7 parasite. But the transcripts are highly                  8 abundant. These are millions. So the                  9 amplification is tremendous. We have a much --                  10 potentially, a much higher sensitivity. So the                  11 limit of detection is quite different in both                  12 assays.                  13 So we have used that in a field trial in                  14 PNG DNA-based versus RNA-based diagnosis for                  15 plasmodium falciparum and vivax. And the result                  16 was that the prevalence in those 300 samples                  17 doubled when we used the RNA-based detection for                  18 both species.                  19 And what's even more important -- if we                  20 checked for gametocytes in those samples                  21 positive, we also find -- found gametocyte                  22 carriers in those who were only positive by RNA-</p>	<p style="text-align: right;">Page 192</p> <p>1 we found.                  2 When we checked the plasmodium vivax, we                  3 didn't see this, right? There was not this                  4 trailing off of the -- in the low-density                  5 samples. And we figured out that the reason for                  6 this is an overall, much lower density in                  7 plasmodium vivax compared to falciparum.                  8 So if we compare the two assays, RNA-                  9 based and DNA-based, we have the abandoned                  10 transcripts in one hand, but we only have three                  11 copies which we can target in -- on the DNA-based                  12 assay. So there is extremely high sensitivity,                  13 which we want. On the quantitative PCR-based --                  14 on the gene-based, we only have a standard                  15 sensitivity. But everybody uses that, so we are                  16 -- that is standard. And it's already very good                  17 sensitivity.                  18 So the disadvantage is that                  19 quantification is a little bit imprecise. It                  20 doesn't really match very well to live microscopy                  21 in the RNA-based quantification possibly because                  22 the different parasite cells have different</p>
<p style="text-align: right;">Page 191</p> <p>1 based detection. So we would even also miss                  2 gametocytes if we would only look by the standard                  3 molecular assay by quantitative PCR. So that                  4 argues for RNA-based detection.                  5 When we plotted all our samples, all the                  6 results, we had this funny observation that all                  7 samples basically declined. And -- but here we                  8 have this little neck, and then it seems to trail                  9 off. And it -- the curve, really, there is                  10 something else happening.                  11 We checked this out, what is happening                  12 here, and we identified that there is some --                  13 there are some aerosols which cause                  14 contamination. Because the template is so highly                  15 abundant, this transcript in the tube that during                  16 the RNA extraction, we obviously had problems to                  17 contain this in our system.                  18 So we had to decide to use a cutoff like                  19 in other methods, in other amplification methods                  20 like RNA-based amplification methods. But this                  21 is a bit unusual thing. In quantitative PCR, we                  22 don't have a cutoff. So that was the condition</p>	<p style="text-align: right;">Page 193</p> <p>1 abundance in the transcripts or because the RNA                  2 in some samples was mistreated. And RNA is much                  3 more fragile than DNA. So much care needs to be                  4 taken when sampling RNA. So there are many                  5 explanations for that.                  6 On the other hand, the DNA-based assay                  7 has a very good correlation with live microscopy.                  8 So quantification is certainly possible -- of                  9 course, then the contamination issues, which is a                  10 drawback -- and there have been no contamination                  11 issues, at least what I can see, with the                  12 quantitative PCR.                  13 So this, of course, argues for field                  14 samples which were collected in the field, which                  15 are processed in the field. That is a completely                  16 different thing that, when we use the RNA-based                  17 detection, the highly sensitive detection in a                  18 fully enclosed system where we can contain all                  19 these contaminants -- and I think Sean Murphy                  20 will later discuss about that because he has the                  21 opportunity to have a really safe RNA-processing                  22 infrastructure. And in certain settings in</p>

<p style="text-align: right;">Page 194</p> <p>1 central laboratories, this is very possible, in                  2 my view.                  3 So the lessons learned from RNA                  4 transcripts as a diagnostic marker is that we                  5 normally lose a large proportion of infections.                  6 They are not noticed by the standard methods. We                  7 have to be careful and very cautious and apply                  8 tight controls if we use RNA, the ribosomal RNA,                  9 as a marker.                  10 It's unlikely field-applicable unless we                  11 have a really enclosed system. Quantification is                  12 not that -- as precise as like on the DNA-based                  13 method. That's -- I think we have to -- that is                  14 at least our experience. And the blood volume,                  15 of course, matters very, very much because we,                  16 basically, detect one -- we can detect one                  17 parasite in a huge blood volume because there are                  18 so many transcripts in.                  19 So the ultra-low density infections, they                  20 also carry gametocytes. We have to carry -- keep                  21 that in mind for certain applications. This will                  22 matter.</p>	<p style="text-align: right;">Page 196</p> <p>1 some samples.                  2 And also, when we looked at the                  3 gametocytes here, in those who have been only                  4 positive by the two new assays but negative by                  5 the standard assays, still 40 percent carried                  6 gametocytes.                  7 So do we need the highly sensitive assays                  8 at all in the field trials? On Day 1, the                  9 parasite detection at enrollment, I would say no                  10 because these are all symptomatic people. I                  11 think -- but I don't really think that we need                  12 their molecular methods.                  13 However, for validating live microscopy,                  14 for example, we could use quantitative piece                  15 here. That would be a quality control. It could                  16 be an external quality control done in a central                  17 laboratory. I would find it very good. And                  18 because of blood sample -- or DNA sample is                  19 collected anyway for genotyping, we should                  20 consider that option.                  21 On the Day X of recurrence, there -- I                  22 have two opinions. I mean, no, we don't need</p>
<p style="text-align: right;">Page 195</p> <p>1 So we have developed an ultra-sensitive                  2 DNA-based quantitative PCR, basically, two                  3 assays. One is based on a telomere-associated                  4 repetitive element 2. It has 250 to 280 copies.                  5 And the other is based on the var gene acidic                  6 terminal segment. And there are about 60 var                  7 genes in the 3D7 genome.                  8 So we have checked where this is --                  9 whether they can be used for quantification. And                  10 both methods really correlate very well with the                  11 standard 18S DNA-based quantification, so a very                  12 good correlation. These assays can be used for,                  13 also -- despite having multi-copies, they can be                  14 used for a good quantification.                  15 So the implication for prevalence in a                  16 Tanzanian study where we had more than 400 people                  17 was that we gained 16 percent in prevalence. So                  18 the -- by combining the two assays, so this                  19 already told us that there is much more out than                  20 we thought because the microscopy was very low                  21 and the 18 -- and still compared to the                  22 quantitative piece are the 18S, we still missed</p>	<p style="text-align: right;">Page 197</p> <p>1 that because we have a problem here of                  2 gametocytes who are not affected by the drug we                  3 have been -- which has been on trial. So we will                  4 have false positives.                  5 But I also would say yes because we can                  6 much earlier detect recurrent parasitemia. So                  7 that is a trait often that also needs a decision.                  8 And here, also, we have the chance for quality                  9 control by PCR.                  10 These sensitive methods seldomly have                  11 room in surveillance and in research. They are                  12 absolutely essential. They also just work in                  13 malaria research in the times of elimination.                  14 They will have -- they will be used. And of                  15 course, in vitro drug assays are -- I mean, in                  16 the human challenge trials, I think that's the                  17 way to go, but not -- maybe not in the field. We                  18 should discuss it later.                  19 The next find is quantification. Can we                  20 quantify absolutely? I mean, there has always                  21 been a talk about discrepancy between                  22 quantification by live microscopy or by molecular</p>

<p style="text-align: right;">Page 198</p> <p>1 methods. So I -- these are the different stages.                  2 I would like to remind you that not all parasite                  3 stages are in the circulation. When we take a                  4 blood sample in the field, we primarily have                  5 rings -- light rings -- and maybe early                  6 trophozoites.                  7 And now, the interesting thing is that                  8 the DNA syntheses starts maybe a little bit                  9 earlier than that. Or the maximum is about 30                  10 hours. So it's possible that we have a one-to-                  11 one relationship. But that might not be really                  12 one because there might be some parasites                  13 infected by two rings or there might be, also,                  14 this little overlap, right, that the DNA                  15 synthesis had already started.                  16 So my molecular methods will show maybe                  17 twice -- two signals, basically. It would look                  18 like two genomes instead of one. So we -- this                  19 is a biology, and we cannot resolve this. So                  20 it's likely that in the peripheral blood we have                  21 1 or 2 genomes per parasite, certainly not the                  22 30, which are in the schizont.</p>	<p style="text-align: right;">Page 200</p> <p>1 molecular quantification.                  2 So in the field samples, the relationship                  3 of the density should be, roughly, one to one.                  4 If not, we have to consider or think about the                  5 DNA stability, which can be compromised. The DNA                  6 is nicked. The standard curve, maybe there were                  7 not only rings, but also mixed stages, other                  8 stages. Or the standard curve, maybe the plasmid                  9 was not really digested.                  10 So these are issues which make absolute                  11 quantification a bit of problem. However, in a                  12 clinical trial, we often have two groups. We                  13 have -- you know, we compare two groups. And                  14 then this is much less of a problem because, I                  15 mean, the -- we have a control group. And what -                  16 in the end, what we do is we don't compare our                  17 quantitative results against live microscopy, but                  18 Group A against Group B.                  19 So my last point, a few words about                  20 genotyping -- there, we are using length-                  21 polymorphic markers. And we amplify infogenic                  22 (ph) repeats. And these are the three marker</p>
<p style="text-align: right;">Page 199</p> <p>1 So the essential of -- essentials of                  2 quantification by quantitative PCR is that we                  3 have to validate this in a trend-line, which is                  4 of synchronized ring stage parasite so that we                  5 are sure that this is only one genome per                  6 parasite. We cannot take a mixture of parasites                  7 to evaluate our tests. So if we use those trend-                  8 lines, I think we can validate safely.                  9 Then coming to a standard curve, a lot of                  10 people, including our lab, use a plasmid -- and                  11 as -- instead of a ring stage trend-line because                  12 having a ring stage trend-line is a lot of work.                  13 And not everybody has it available. So a plasmid                  14 is used. When this is in supercoil, how you                  15 extract it from the bacteria, then you                  16 overestimate the copy number eight-fold.                  17 So there is a restriction digest of the                  18 plasmid needed so that then the result is then                  19 that the quantification matches that of the                  20 trend-line. So many people maybe have not                  21 realized this, that this can also be a cause of                  22 discrepancy between live microscopy and the</p>	<p style="text-align: right;">Page 201</p> <p>1 genes -- the merozoite surface protein 1 and 2                  2 and glurp.                  3 These are amplified by nested PCR. And                  4 the standard is now to use a capillary                  5 electrophoresis for absolutely precise sizing.                  6 This has replaced the gel-based sizing.                  7 Now, in the past, we have done a couple                  8 of experiments where we think we need to revise                  9 some of the previous recommendations. For                  10 example, we should stop multiplexing the nested                  11 PCRs because there is some -- sorry -- because                  12 there is some size -- a fragment size bias there.                  13 So the recommendations have been                  14 described in this leaflet. There was a meeting                  15 sponsored by MMV and by WHO. And it's clear                  16 everybody knows that this is a recrudescence                  17 because two fragments are the same. Or even if                  18 one fragment is the same, this is a recrudescence                  19 here. We would see the image -- a gel image of a                  20 new infection.                  21 So the achievements in genotyping are                  22 that the capillary electrophoresis improved the</p>

<p style="text-align: right;">Page 202</p> <p>1 resolution and the reproducibility of fragment                  2 sizing a lot. It permits comparison of alleles                  3 between separate runs, which is important. And                  4 we can estimate allelic frequencies in the                  5 population to determine the probability of a                  6 reinfection with the same allele.</p> <p>7 But the critical issues in genotyping are                  8 the detectability of clones, of minority clones.                  9 And well, it's really useful in settings with                  10 very low or very high transmission because, in                  11 very low transmission, we have clonal population.                  12 And in very high transmission, we have just too                  13 many examples -- too many clones so that the                  14 amplification bias will only (ph) have a role.</p> <p>15 The detectability -- I show you here some                  16 longitudinal examples -- different msp2 alleles                  17 over time. And so we see there is a little gap.                  18 And here, there are also gaps. In between, the                  19 red dots are the detected dots, and the gray dots                  20 are the blood samples taken. So that means that,                  21 despite that the parasite is still there, the                  22 clone is there, we cannot detect it because it</p>	<p style="text-align: right;">Page 204</p> <p>1 no choice. We need genotyping. The protocols                  2 are optimized. They exist. And the quantity                  3 control is established between the labs. What's                  4 needed is to revise the recommendations and                  5 reconsider these three markers maybe. And also                  6 what's needed is to reassess the usefulness for                  7 all different levels of endemicity.</p> <p>8 And what is really very much to my heart,                  9 that's the quality assurance and external quality                  10 control. This must be reinforced.</p> <p>11 There is some research needed, also. And                  12 the validation on deep sequencing for SNP-based                  13 genotyping that is amplicon -- targeted amplicon                  14 sequencing. This is on the horizon. This can be                  15 used possibly very soon. This might be an                  16 alternative to the length-polymorphism. But we                  17 can discuss that later. That has certain                  18 advantages and certain disadvantages. And we                  19 also need to do research on the improvement of                  20 the SNP-based detection of minority clones, which                  21 we had problems so far to detect these.                  22 So conclusion -- on the molecular</p>
<p style="text-align: right;">Page 203</p> <p>1 might be sequestered or it might be below the                  2 detection limit. It fluctuates.</p> <p>3 So over time, we see these gaps, and we                  4 have -- this is biology. This is sequestration                  5 of a synchronous clone, for example, of                  6 fluctuations in the densities. So there is not                  7 much what we can do about it.</p> <p>8 And here, that is an example of the size                  9 bias that, if we mix one-to-one -- in the one-to-                  10 one ratio two different alleles, we see that                  11 always the shorter allele will be preferentially                  12 amplified. So it's still above here, above the                  13 detection, the cutoff. But there is an effect of                  14 the fragment size.</p> <p>15 And here from our (inaudible 00:25:47),                  16 there is -- it's only one allelic family. And                  17 there is a much dramatic effect, a much more                  18 dramatic effect. So this marker needs to be                  19 reconsidered.</p> <p>20 So as a conclusion, do we need                  21 genotyping? I say, yes, we need it because, in                  22 an area where there's high transmission, we have</p>	<p style="text-align: right;">Page 205</p> <p>1 detection quantification, I think we have very                  2 good protocols. Both in DNA- and in RNA-based,                  3 there is the consensus on the epidemiological                  4 relevance of these methods. What we need is to                  5 build a consensus whether there is a potential                  6 application in field trials and, of course, very,                  7 very important to reinforce the external quality                  8 control for absolute quantification.</p> <p>9 Research is needed, certainly. And there                  10 comes this digital droplet PCR, which can be used                  11 to support this absolute quantification, at least                  12 for external quality control. We might use this                  13 in future, maybe in some central labs to be able                  14 to relate different findings to each other. And                  15 also, research is needed on the contribution of                  16 gametocytes to the positivity.</p> <p>17 So I want to thank my group and my                  18 collaborators and you for your attention. Thank                  19 you.</p> <p>20 DR. BALA: Thank you, Dr. Felger.                  21 We'll save questions to later.                  22 The next talk will be by Dr. Kalavati</p>

<p style="text-align: right;">Page 206</p> <p>1 Suvarna. She's a clinical microbiologist with                  2 the Division of Anti-Infective Products, CEDR.                  3 As a microbiologist, she reviews and                  4 evaluates pre-clinical and clinical microbiology                  5 data submitted in investigation in new drug                  6 applications and new drug -- investigation in new                  7 drug applications and new drug applications for                  8 anti-microbial products, including anti-malarial                  9 drugs.                  10 DR. SUVARNA: Thank you.                  11 Good afternoon, everybody.                  12 Thank you, Dr. Felger, for giving that                  13 very nice overview and setting the stage for this                  14 session.                  15 I'm going to talk about the regulatory                  16 concentrations when detection methods are used in                  17 clinical trials. The outline of my talk --                  18 basically, I'll give you a very brief background                  19 in diagnostic tests in anti-malarial trials. In                  20 the setting of the regulations, these diagnostic                  21 tests are regulated as devices.                  22 And I will talk about what that means for</p>	<p style="text-align: right;">Page 208</p> <p>1 200 or so, to detect malaria parasites, but the                  2 only to point out that that only FDA-cleared                  3 malaria rapid diagnostic test is the Binax NOW.                  4 In clinical trials, it basically has been used to                  5 enrich patients and enrollment of patients who                  6 have falciparum malaria. These tests, however,                  7 have to be confirmed by blood smears.                  8 Clinically, it's being used, of course, to                  9 diagnose patients suspected of having malaria.                  10 So as I mentioned, in vitro diagnostic                  11 tests are devices. Here, I have the definition                  12 of in vitro diagnostic devices, as it's defined                  13 in 21 CFR 809.3. These are reagents,                  14 instruments, systems intended for use in the                  15 diagnosis of disease or other conditions,                  16 including the determination of state of health,                  17 in order to determine cure, mitigate, treat or                  18 prevent disease or its sequelae and also those                  19 that are used in collection, preparation and                  20 examination of specimens.                  21 In vitro diagnostic devices are cleared                  22 by the FDA Center for Device and Radiological</p>
<p style="text-align: right;">Page 207</p> <p>1 use in anti-malarial trials; the various tests                  2 within each context of use -- the two important                  3 contexts of use that we're discussing today are                  4 in Controlled Human Malarial Infection trials and                  5 treatment trials; and what type of information                  6 would be important when you're using an FDA-                  7 cleared versus a non-FDA-cleared test; and then                  8 provide some conclusions.                  9 So in anti-malarial clinical trials,                  10 assessment of parasitological response to therapy                  11 is an integral part of efficacy determination.                  12 Blood smears have been used. They've been used                  13 for the past 100 years and are the gold standard                  14 for malaria diagnosis and are currently used for                  15 enrollment and monitoring treatment outcomes.                  16 However, one of the limitations are that it                  17 cannot be used to distinguish recrudescence,                  18 which is reappearance of parasites possibly due                  19 to treatment failure from reinfection where you                  20 have new infections due to new mosquito bites in                  21 endemic areas.                  22 There are several diagnostic tests, about</p>	<p style="text-align: right;">Page 209</p> <p>1 Health, the CDRH. We in CDER, the Center for                  2 Drug Evaluation and Research, work closely with                  3 CDRH when a sponsor proposes to use a non-FDA-                  4 cleared test in clinical trials.                  5 Clearance of a device by CDRH does not                  6 automatically render it suitable for use in                  7 registration trials. Similarly, lack of                  8 submission to or clearance by CDRH for device                  9 does not render it automatically unsuitable for                  10 use in clinical trials. What's more important                  11 here is the context of use and risk to patients                  12 enrolled in the trial.                  13 To come to the two contexts of use, tests                  14 in Controlled Human Malaria Infection trials are                  15 basically used to monitor parasitemia in healthy                  16 subjects. If designed to evaluate anti-malaria                  17 activity, you have tests also to measure                  18 treatment outcome.                  19 In treatment trials, they're used for                  20 various purposes in enrichment/enrollment for                  21 monitoring the patients, parasitemia in patients                  22 and for measuring treatment outcome. Another</p>

<p style="text-align: right;">Page 210</p> <p>1 important use, which we'll discuss more today, is                  2 about of use of these molecular tests to                  3 differentiate recrudescence versus reinfection.                  4       There's some guidance out there. The ICH                  5 E8 document provides some guidance on general                  6 concentrations for clinical trials. This talks a                  7 little bit about the methods that are used for                  8 measurement of endpoints, both subjective and                  9 objective. It states that these should be                  10 validated and meet appropriate standards for                  11 accuracy, precision, reproducibility, reliability                  12 and responsiveness.                  13       So what are the types of information when                  14 it comes to cleared versus non-FDA-cleared tests?                  15 For FDA-cleared tests, the performance                  16 characteristics of the assays are described on                  17 the package insert. However, if the test is                  18 modified from what it's cleared for its relevant                  19 context of use in a clinical trial, more                  20 information may be needed.                  21       In terms of non-FDA-cleared tests, some                  22 of the molecular tests that we heard today, this</p>	<p style="text-align: right;">Page 212</p> <p>1 we hear -- are going to hear about today because                  2 we believe that this would help with the                  3 development of anti-malarial drugs. So we                  4 encourage you to submit this type of information.                  5       With respect to the FDA-cleared tests,                  6 like I mentioned, the context of use is what's                  7 important. And that will determine what                  8 additional information is required. With respect                  9 to the non-FDA-cleared, we definitely need the                  10 performance characteristics of the test within                  11 the laboratory where testing is performed.                  12       So we heard today a little bit about the                  13 various molecular tests that are used in the                  14 session this morning and also in our previous                  15 talk and how these methods are evolving and                  16 studies that are being done and data that's being                  17 collected to understand the characteristics of                  18 this test. So we really look forward to your                  19 input, scientific input, in how these methods can                  20 be used for its various purposes of use in the                  21 CHMI studies, the anti-malaria trials and also                  22 may need to differentiate recrudescence versus</p>
<p style="text-align: right;">Page 211</p> <p>1 morning, the performance characteristics of the                  2 test in the actual laboratory where this testing                  3 is performed is needed for our assessments. Now,                  4 the extent of validation information may vary,                  5 again, with the context of use.                  6       So for all tests, basically, the context                  7 of use and the ability to rely on these tests                  8 results for the specific purpose of use is                  9 important. Besides performance characteristics                  10 are the quality assurance procedures that are                  11 implemented are also important.                  12       So today, we'll hear some more about the                  13 tests that are used for these two context of use.                  14 Dr. Sean Murphy will elaborate more on tests used                  15 in Controlled Human Malaria Infection trials.                  16 And Dr. Saunders will talk more about tests that                  17 could be used in treatment trials.                  18       So in conclusion, blood smears are                  19 currently the gold standards for malaria                  20 diagnosis. The only cleared FDA test is the                  21 Binax NOW Malaria Test. We are -- really want --                  22 we are open to all the new molecular tests that</p>	<p style="text-align: right;">Page 213</p> <p>1 reinfection.                  2       I -- we heard about the quantitative PCR                  3 assays and how they are more sensitive and may be                  4 very valuable in the CHMI studies in terms of                  5 providing rescue therapy and evaluating anti-                  6 malarial activity. I guess we -- there's also a                  7 lot of interest in looking at genotyping and                  8 assays that can differentiate recrudescence                  9 versus reinfection and how it could be used in                  10 endpoints, outcome measurements and to help us                  11 understand the differences and its effect on                  12 digested cure rates in endemic areas.                  13       So with that, I'm looking forward to a                  14 very rigorous discussion and diagnostic tests.                  15 Thank you for listening.                  16       (Applause.)                  17       DR. FELGER: Any questions?                  18       DR. BALA: No, later.                  19       DR. FELGER: Oh, sorry. In the sake of                  20 time, we continue to our next speaker. This is                  21 Sean Murphy. He's an assistant professor and                  22 assistant director of the Clinical Microbiology</p>

Page 214	<p>1 in the Department of Laboratory Medicine at the                  2 University of Washington. He also serves as a                  3 clinical investigator at the Seattle Malaria                  4 Clinical Trial Center and a medical director of                  5 the Human Challenge Center at the Center for                  6 Infectious Disease Research. Lots of centers.                  7 Dr. Murphy's laboratory studies malaria                  8 diagnostics and malaria vaccine development.                  9 Sean completed medical and graduate training at                  10 Northwestern University Residency Training in the                  11 Clinical Pathology at the University of                  12 Washington and conducted his post-doctoral                  13 studies with Michael Beban (ph) before becoming                  14 assistant professor in 2012.                  15 DR. MURPHY: Thank you very much.                  16 DR. FELGER: Looking forward to your                  17 talk.                  18 DR. MURPHY: Thank you for the invitation                  19 to be part of today's workshop. I have just a                  20 couple disclosures here, some clinical trial                  21 support and consulting for Biofire Defense.                  22 And in my talk, I'm going to talk about</p>	Page 216	<p>1 exactly, you know, the clinical reliability of                  2 this and whether this would be a suitable                  3 replacement for blood smears categorically. And                  4 so I want to show you a bunch of data that kind                  5 of begins to address that. But like all nucleic                  6 acid-based tests, there are a number of steps.                  7 And often, we focus on the last part of this                  8 nucleic acid-based test and forget about the                  9 upstream part.                  10 So just to tell you what a test                  11 comprises, it involves extraction of whole blood                  12 from the patient either to obtain DNA or RNA or                  13 total nucleic acids. If you're going to look for                  14 an RNA marker, then you have to either do a                  15 reverse transcription or do total cDNA synthesis.                  16 And if you're going to look for an unspliced                  17 target like pfs25 for gametocytes, you also have                  18 to destroy the genomic DNA. This isn't necessary                  19 when you do 18S ribosomal RNA testing because                  20 there are thousands of copies of the RNA to the                  21 very few copies of DNA.                  22 And then you go on to what we hear about</p>
Page 215	<p>1 the main target that's being used in                  2 investigational molecular-based diagnostics in                  3 Human Challenge Trials; describe some of the                  4 tests that are being used at our center and other                  5 centers; and then look at how the kinetics of                  6 onset of positivity in these tests vary,                  7 depending on how you give the parasites and what                  8 form of the parasites you give. And at the end,                  9 we'll talk about a couple topics that have been                  10 broached a little bit earlier about recrudescence                  11 and gametocytemia.                  12 So I think it's been clear from the                  13 literature and in our own studies, for instance,                  14 what we call the demonstration trial that we did                  15 in 2009 in Seattle that nucleic acid-based                  16 testing, that detection of the biomarkers that                  17 are used in nucleic acid-based testing accelerate                  18 the time to infection detection as compared to                  19 blood smears. And that's shown -- blood smears                  20 in the dark line and the nucleic acid test in the                  21 dotted line.                  22 And we're working toward understanding</p>	Page 217	<p>1 most, which is the PCR part of this process,                  2 where various labs have quantitative or                  3 qualitative tests. And amongst those, the most                  4 common target is the 18S ribosomal RNA.                  5 And so this is a very useful target,                  6 whether you look at the DNA or the RNA target.                  7 And it allows you to, I would argue, quantify the                  8 parasites with, actually, a considerable degree                  9 of accuracy in the bloodstream for P. falciparum.                  10 And that's because we know that P. falciparum                  11 sequesters in the mature stages where there would                  12 be multiple genomes or increased numbers of RNA                  13 relative to the ring stage parasites.                  14 So the peripheral circulating parasites                  15 are really the ring stage parasites. And in my                  16 group, depending on the assay we've used, we find                  17 3,500 to 10,000 copies of the ribosomal RNA per                  18 individual ring. And we know from the genome                  19 that there are two of the asexual type genes and                  20 two of the sexual type genes and a fifth                  21 pseudogene. So whether you use DNA or RNA, you                  22 can very reasonably quantify the parasites. And</p>

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1 we must remember that nucleic acid-based tests  
 2 are generally viewed with a log base 10 scale.  
 3 And so you know, in my lab, we focus on  
 4 RNA-based methods. And we get a big bump in  
 5 sensitivity for a given volume because of this  
 6 biological enrichment of the 18S ribosomal RNA.  
 7 It's not the only way to do it, and I'll show you  
 8 what other labs have done as well.  
 9 When I reviewed the literature, this is  
 10 23 studies that have compared 18S-based methods,  
 11 be they DNA or RNA, to blood smears. And so this  
 12 graph shows the time to positivity from the time  
 13 of challenge with sporozoites until the onset of  
 14 either molecular-based positivity for the  
 15 biomarker or blood smear-based positivity in the  
 16 circles. And what you'll appreciate is that, in  
 17 all instances here, the nucleic acid-based test  
 18 accelerates the time to positivity compared to  
 19 blood smears.  
 20 We are very confident in this method in  
 21 our center, and we've now embarked on studies  
 22 where we no longer do daily blood smears leading

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1 up to infection detection. And so this study on  
 2 the left shows a trial that we have conducted  
 3 where our molecular-based test has been the  
 4 primary endpoint that has triggered rescue  
 5 treatment in people who have failed the  
 6 therapeutic that we were testing.  
 7 So I'll show you a few tests as they're  
 8 performed at other major centers doing CHMI  
 9 studies. And so we conducted an external quality  
 10 assurance program several years ago and involved  
 11 all of these centers who, by and large, are doing  
 12 vaccine studies. Some of them are also doing  
 13 drug studies. And you'll see that there's  
 14 diversity in the kinds of testing that people do,  
 15 even though we all use the 18S target.  
 16 So there are people who, like my lab,  
 17 look at the RNA. And there are more groups that  
 18 look at the DNA. Within that, you can place your  
 19 PCR targets either in the sexual or the asexual  
 20 genes. And so we really have to make sure we're  
 21 comparing apples to apples when we talk about  
 22 where our targets are.

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1 There are various ways to extract the RNA  
 2 or DNA, including manual methods and higher  
 3 throughput methods on automated platforms. And  
 4 the sensitivities that these tests achieve,  
 5 fortunately, are generally in the same range.  
 6 And these sensitivities were designed to be able  
 7 to test the -- to detect the parasites on or  
 8 about the day that parasites emerge from the  
 9 liver following five mosquito bites. And so that  
 10 sensitivity is probably on the order of 10 to 100  
 11 parasites per milliliter.  
 12 You can achieve this off of different  
 13 volumes of blood. And if you use DNA, you need  
 14 to look at more blood than you need to look at if  
 15 you use RNA. And so in our group, we use 50  
 16 microliters of RNA. This is also the volume of  
 17 blood that we can place on a dried blood spot.  
 18 And when we process our dried blood spots in our  
 19 group, we process them with a laser cutter  
 20 because, as Ingrid mentioned, there can be a very  
 21 high copy number of the RNA that could contribute  
 22 to contamination. And so we've had to,

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1 basically, invent a touchless laser cutting  
 2 system for dried blood spots. And when we  
 3 process dried blood spots in that method, we  
 4 completely eliminate any cross-contamination.  
 5 We did an EQA comparison amongst these  
 6 centers knowing nothing about how well the test  
 7 would compare, knowing only what the claimed  
 8 sensitivities and quantification of each center  
 9 was. And what we were very happy to find is that  
 10 we had really excellent qualitative and even  
 11 quantitative correlation between centers that  
 12 placed their targets in different parts of the  
 13 genes or even in our center that did RNA compared  
 14 to everyone else who did DNA. And our results  
 15 put our RNA quantification right in the center of  
 16 all the DNA targets.  
 17 So this was very reassuring. And we know  
 18 that EQA is needed in this program. And the  
 19 World Health Organization is working on an EQA  
 20 program right now that will serve the needs of  
 21 CHMI centers, of field studies of epidemiologic  
 22 groups and sort of cut across that need for the



<p style="text-align: right;">Page 222</p> <p>1 field.</p> <p>2       So one of the questions I was asked to</p> <p>3 address is how do we use these tests when we give</p> <p>4 different parasites or we give them by different</p> <p>5 modes of infection. And so these are our</p> <p>6 experiences and my thoughts on this topic.</p> <p>7       So mosquito bite versus intravenous</p> <p>8 sporozoites -- we don't think that this changes</p> <p>9 the duration of the liver stage by any meaningful</p> <p>10 measure. We don't think that, based on the</p> <p>11 biology of the parasite, that there's any</p> <p>12 indication to test blood during the first five</p> <p>13 days when the parasite is in the liver and we</p> <p>14 don't think that it's in the blood at all. And</p> <p>15 what we've seen in the studies that we've now</p> <p>16 done both by DVI or by mosquito bite is basically</p> <p>17 the same onset in positivity, meaning the</p> <p>18 parasites come out of the liver at the same time.</p> <p>19       If we were to do sporozoites and ask how</p> <p>20 does that differ than red cell infection, I'd</p> <p>21 like to basically go to the next slide to show</p> <p>22 you this. This slide basically says that there</p>	<p style="text-align: right;">Page 224</p> <p>1 people with red blood cells, they give 1,800</p> <p>2 parasites. And if you put 1,800 parasites into</p> <p>3 the body, this is too few parasites to detect on</p> <p>4 the day that he first injects them. It's</p> <p>5 probably too few parasites two days later. But</p> <p>6 after the parasites have gone through two rounds</p> <p>7 of replication, now we're talking about a density</p> <p>8 that's detectable by the kind of assays that I</p> <p>9 have shown you here.</p> <p>10       So with those tests, we have the option</p> <p>11 to accelerate the time that we treat people.</p> <p>12 Historically, we would treat people on the basis</p> <p>13 of blood smears. And so whether you use a</p> <p>14 sporozoite inoculum or a red cell inoculum, the</p> <p>15 previous slide would show you that, because of</p> <p>16 the liver stage, the parasites in the sporozoite</p> <p>17 inoculum in the absence of pre-existing immunity</p> <p>18 will come out on about Day 6 or 7. And they will</p> <p>19 climb in this saw tooth pattern until you become</p> <p>20 blood smear positive and you introduce treatment.</p> <p>21       In the red cell stage, there's similar</p> <p>22 growth kinetics. But the onset is after four</p>
<p style="text-align: right;">Page 223</p> <p>1 are three ways to get someone infected with</p> <p>2 malaria parasites in the red cell stage, which</p> <p>3 is, after all, the diagnostic stage of this</p> <p>4 organism. You can give five mosquito bites, a</p> <p>5 model that's been around for a while. You can</p> <p>6 give 3,500 <i>P. falciparum</i> parasites by venous</p> <p>7 injection. These are both going to go into the</p> <p>8 liver. They're not all going to invade a</p> <p>9 hepatocyte. But those that do, we think, make 20</p> <p>10 or 30,000 merozoites per infected hepatocyte.</p> <p>11 And on about Day 6, these pour into the blood.</p> <p>12       So there's a certain inoculum into the</p> <p>13 blood at that point. And if -- I've just modeled</p> <p>14 this up here for you. If there were 10 infected</p> <p>15 hepatocytes, we're talking about 300,000</p> <p>16 parasites in your total number of red cells in</p> <p>17 your body. So you need a test that might be able</p> <p>18 to detect 60 parasites per mil in order to find</p> <p>19 that. And that's on the order of the sensitivity</p> <p>20 for the test that we designed.</p> <p>21       If you take the third route, which is</p> <p>22 what James is doing in Australia, and infect</p>	<p style="text-align: right;">Page 225</p> <p>1 days because of how many parasites Dr. McCarthy's</p> <p>2 group puts in. And so in general, you can treat</p> <p>3 these people by about -- upon blood smear</p> <p>4 positivity by about Day 10 to 13. And in James's</p> <p>5 group, you can treat people a little bit earlier</p> <p>6 because the parasite load is a little bit bigger.</p> <p>7       If we decide to treat with the nucleic</p> <p>8 acid-based treatment threshold, we have the</p> <p>9 option -- the ability to spare symptoms that</p> <p>10 subjects generally find uncomfortable and still</p> <p>11 to obtain quite a bit of really informative</p> <p>12 quantitative data.</p> <p>13       And so an open question is what should</p> <p>14 those thresholds be because, in a prophylactic</p> <p>15 study where the goal is to completely prevent</p> <p>16 infection, you would argue that, in Seattle,</p> <p>17 there should be no parasites in a person. And as</p> <p>18 soon as you have a reasonable detection of</p> <p>19 parasites, one ought to treat that person and</p> <p>20 clear them with a rescue drug. And so in studies</p> <p>21 that are designed to do that, various thresholds</p> <p>22 are now being used. In our center, we're using a</p>

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1 threshold of 250 parasites per mL. And I'll show  
 2 you how we arrived at that number.  
 3 In the Netherlands, they're using a  
 4 threshold of 100. And you can see some other  
 5 comments about some other centers up here. If  
 6 you're doing a radical cure study, like James  
 7 McCarthy's group, in their most recent paper,  
 8 they initiated treatment -- correct me if I'm  
 9 wrong -- but at a slightly higher threshold. And  
 10 at this threshold, the subjects are completely  
 11 safe.  
 12 Most of them are probably asymptomatic.  
 13 But it allows you to generate a few more data  
 14 points during the clearance phase to allow you to  
 15 calculate what the clearance sort of kinetics for  
 16 that drug are.  
 17 In our center, this is how we arrived at  
 18 our treatment threshold. And what we did was we  
 19 took our quantitative data, and we compared if we  
 20 were to treat people based on even the lowest  
 21 positives for our test. Our test has a  
 22 sensitivity of about 10 to 20 parasites per mil.

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1 And we quantitatively report test results above  
 2 20 parasites per mil.  
 3 So if we were to treat people on the very  
 4 first instance of positivity, we would always be  
 5 treating people before the onset of symptoms and  
 6 before the onset of blood smear positivity. But  
 7 as we ratchet that number up, the so-called  
 8 threshold, eventually, we arrive at a point where  
 9 that overlaps zero. And there would be no  
 10 advantage to waiting that long.  
 11 And we've now modeled that. And what you  
 12 can see is that this is how we arrived at 250  
 13 parasites per mil. We very confidently can avoid  
 14 blood smear positives and symptoms, in general,  
 15 if we use this threshold.  
 16 So there are some other considerations  
 17 about these tests. How often should we sample?  
 18 At one point, we tested people twice a day, and  
 19 we now test people once a day because, in this  
 20 study, there wasn't really an acceleration, a  
 21 really meaningful acceleration for the amount of  
 22 work involved, to do twice-a-day testing. But

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1 here in our center, the question is infection  
 2 detection. It's not really dense modeling in the  
 3 post-treatment phase.  
 4 And for prophylactic studies, most of the  
 5 models really just depend on the density of the  
 6 parasites on the first day that you're positive  
 7 so that you can back-calculate how many infected  
 8 hepatocytes there likely were.  
 9 We also -- even at our center with once-  
 10 a-day testing, when -- this is data on people who  
 11 broke through and required rescue treatment. And  
 12 this shows the kinetics of their clearance of our  
 13 18S ribosomal biomarker in the three days that  
 14 followed that rescue treatment. And what you can  
 15 see is that, within three days, our biomarker  
 16 goes to zero.  
 17 And this is reassuring because we often  
 18 hear that molecular diagnostics have a positive  
 19 tail. And that's true if you let people climb to  
 20 a density where they would be blood smear  
 21 positive or really sick. But if you treat them  
 22 with a molecular marker, they resolve to zero

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1 very quickly unless, as in the case of this one  
 2 subject who had the very highest parasitemia, you  
 3 detect gametocytes.  
 4 In James's group, they do more-dense  
 5 sampling. And he's explained why earlier. And  
 6 that's so that they can more adequately model the  
 7 kinetics of clearance in these radical cure  
 8 studies.  
 9 So I'm going to present just a little bit  
 10 of data on recrudescence versus gametocytemia and  
 11 expand just briefly on what Dr. McCarthy had  
 12 commented on. This is data from a paper they  
 13 published earlier this year, which showed that,  
 14 in some subjects, there was a recurrence of the  
 15 18S ribosomal RNA marker that was shown to be  
 16 asymptomatic gametocytemia. And this  
 17 gametocytemia can persist in the absence of  
 18 treatment with primaquine. And so they followed  
 19 subjects who received no primaquine or two  
 20 different doses of primaquine and followed the  
 21 resolution of the pfs25 target down to zero.  
 22 And so in our center, we haven't seen

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1 this much recurrence of the 18S ribosomal RNA  
 2 target that could be either a recurrence or  
 3 asymptomatic parasitemia. And we believe that  
 4 this is because we're treating people at a much  
 5 lower density. And so there's less -- fewer  
 6 cycles to generate gametocytes, and the overall  
 7 parasite density is lower.

8 Obviously, Dr. McCarthy presented earlier  
 9 this very nice data that uses a gametocyte  
 10 marker, Pfs25, and a ring stage marker to  
 11 differentiate between asymptomatic gametocytemia  
 12 and the additional presence of recurrent and,  
 13 eventually, probably symptomatic asexual  
 14 recrudescence using that ring stage marker.

15 My last comment is about what we need in  
 16 the field -- in the malaria field. And that is,  
 17 for these tests, we recognize that harmonization  
 18 and reagent availability is very important. And  
 19 there's no commercial source of standards. Most  
 20 labs generate infected whole blood. And this is  
 21 okay, but it's not the way a commercial test  
 22 would be run. Nobody -- no commercial test ships

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1 BSL-2 material around as part of the ingredients  
 2 in their test.

3 We also recognize that, beyond standards,  
 4 what we really need are calibrators. And so our  
 5 group has generated some plasmids that we  
 6 linearize. And we have also created plasmids  
 7 that contain both the asexual and sexual type  
 8 gene together on one plasmid. So we have a  
 9 plasmid that, for instance, contains the targets  
 10 of six different CHMI centers so that we can  
 11 distribute this to DNA testing facilities for a  
 12 one-to-one-to-one comparison between centers.

13 And just this week, I also took delivery  
 14 of a full-length 18S ribosomal RNA as a custom  
 15 Armored RNA. So this is a 2,000-based parapesa  
 16 (ph) RNA encapsulated in a verion (ph) that would  
 17 contain the entire sequence of the 18S and would  
 18 be stable from RNAsis (ph). So we hope that this  
 19 will also be a resource. And then as I mentioned  
 20 before, the WHO is working on an EQA scheme that  
 21 will also help all of us.

22 So in summary, the most common target is

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1 the 18S. These tests that target the 18S are in  
 2 use in a number of centers. We think that these  
 3 are useful in a variety of CHMI studies, and I  
 4 touched on a number of issues that we think will  
 5 help to harmonize and pull the field together.

6 I'd just like to thank my group. And  
 7 especially, I'd like to thank the collaboration  
 8 we've had with the other CHMI centers who have  
 9 been very open to harmonization and quality  
 10 assurance, despite the fact that we all have  
 11 different tests.

12 (Applause.)

13 DR. FELGER: Thank you very much, Sean.

14 So we are moving to our next speaker.

15 This is David Saunders. He is a clinical  
 16 pharmacologist and internist currently stationed  
 17 at the U.S. Army Medical Material Development  
 18 Activity.

19 DR. SAUNDERS: All right. Well, thanks  
 20 very much. I'm honored to be the last speaker  
 21 today. And I'll try to keep things punchy  
 22 because I know people are probably a little

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1 sleepy by now.

2 But so I'm just going to talk about some  
 3 practical considerations for detection methods in  
 4 clinical trials, field trials, and expand on some  
 5 of the points from my colleagues earlier this  
 6 session.

7 So we'll just look at some of the  
 8 detection methods as they apply to field trials.  
 9 We will consider how they're used for enrollment,  
 10 and then I'll talk a little bit about how we  
 11 might use it -- how we use them to measure  
 12 outcomes and, really, in three areas. One is the  
 13 use of PCR to correct results of microscopy.

14 The second is how we could use molecular  
 15 methods to look at parasite clearance and,  
 16 finally, how we can use PCR to adjust the  
 17 treatment outcomes. So I use slightly different  
 18 terminology there. And that means  
 19 differentiating new infections from  
 20 recrudescence. And I'll talk just briefly about  
 21 considerations for P. vivax, even though this is  
 22 focused on P. falciparum. In areas where vivax

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1 is co-endemic, there's some important  
 2 considerations there.  
 3 I don't have a disclaimer slide. But I  
 4 should say that these views are my own, and the  
 5 U.S. government is free to disavow them if I say  
 6 anything that they don't agree with.  
 7 So in -- here's my sort of bottom lines  
 8 up front as far as using these methods in field  
 9 trials. The first is that RDT use, really, is  
 10 pretty limited. We use it mostly for screening  
 11 potential subjects, but, really, it doesn't have  
 12 much of a role. And I think this follows on to,  
 13 you know, Kalavati's point earlier that, really,  
 14 RDT results have to be confirmed by a blood smear  
 15 anyway. And for that reason, we don't really put  
 16 a whole lot of stock in them.  
 17 Microscopy is still the gold standard.  
 18 And it has several advantages. Of course, it's  
 19 less sensitive than PCR. So it probably -- these  
 20 days, it's almost routine that we use PCR methods  
 21 to interpret the results of microscopy because  
 22 it's very sensitive and specific.

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1 The limitation, of course, with PCR in  
 2 the field is that onsite use is fairly limited.  
 3 There's not too many centers that can actually do  
 4 PCR in real time making it clinically meaningful  
 5 or -- and producing actionable results.  
 6 The good news, I guess, is that, you  
 7 know, PCR can pretty much quantitate parasitemia  
 8 as well as microscopy now. And so that may  
 9 provide some advantages, particularly when you're  
 10 looking at parasite clearance for resistance  
 11 studies.  
 12 And then finally, I think it's also  
 13 pretty much become the de facto standard that the  
 14 results of trials in a field need to be PCR-  
 15 adjusted to determine whether the recurrence that  
 16 you see represents a reinfection or a true  
 17 recrudescence. And this is important because  
 18 reinfection rates vary quite a bit. It may be  
 19 less than 10 percent in low transmission settings  
 20 like Southeast Asia or Latin America to more than  
 21 50 percent in some settings. And this can have  
 22 significant impact on the interpretation of

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1 efficacy.  
 2 So there's -- starting with RDTs, there's  
 3 a huge variety available. WHO has a table.  
 4 There must be, you know, at least 100, 200 tests  
 5 in there. Only one is FDA-approved. That's  
 6 Binax NOW. It's not necessarily the most  
 7 sensitive or specific among them. Most of these  
 8 are lateral flow immunoassays. And the  
 9 sensitivity of some of these is really  
 10 approaching that of microscopy, although  
 11 specificity is not necessarily as good.  
 12 The limitations here, really, are in red,  
 13 though. They're not useful for follow-up because  
 14 they remain positive after the patient is even  
 15 cleared clinically. They don't give you a  
 16 quantitative result. They don't give you a  
 17 permanent specimen result. So you can't go back  
 18 and read an RDT like you can with a microscope  
 19 slide which you can stick in a box and look at it  
 20 10, 15, 20 years later.  
 21 You also run the risk when you use RDTs  
 22 of ending up with treating people based on false

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1 positives, which can ultimately lead to  
 2 invalidation of trials. And that actually did  
 3 happen in one U.S. Army trial in the past.  
 4 And then for -- you know, so bottom line  
 5 is we really -- they're pretty much unsuitable, I  
 6 think, for clinical trials. And particularly,  
 7 we're talking about, you know, regulated trials  
 8 that you would submit to support an FDA licensing  
 9 application. I think they probably do have a  
 10 role in academic trials and, you know,  
 11 therapeutic efficacy trials that the WHO does,  
 12 but probably wouldn't stand up to allowing you to  
 13 make a GCLP submission.  
 14 Microscopy -- it really is still the gold  
 15 standard. It's probably the most widely  
 16 available method in the field. It gives you  
 17 real-time actionable results. You can identify  
 18 species in parasite stages. You can look for  
 19 gametocytes. You can have your results, usually,  
 20 within 30 minutes to two hours. And it's  
 21 relatively inexpensive, a low-tech method  
 22 compared to PCR.

<p style="text-align: right;">Page 238</p> <p>1 Now, that being said, it is not                  2 necessarily a simple thing to have a cadre of                  3 adequately trained microscopists. It can take                  4 several years to train these folks. There -- you                  5 need to have a good training program. You need                  6 to have a really solid set of SOPs. So not every                  7 center is capable of doing microscopy to a                  8 standard that would support a regulated trial.                  9 In the hands of an expert microscopist,                  10 they might get down to a density of 10 parasites                  11 per microliter. But that's really only sort of                  12 the most skilled and the most patient readers.                  13 But the WHO actually offers a very good external                  14 competency assessment exam program. And when                  15 your microscopists take that, it -- they will                  16 actually get a report that estimates what their                  17 personal sensitivity and specificity is. And so                  18 you can go back and, I guess, do some, you know,                  19 post-talk analysis on your data based on those                  20 estimates.                  21 The other thing with microscopy, you                  22 really need to have, in my view anyway, at least</p>	<p style="text-align: right;">Page 240</p> <p>1 be used to a particular advantage when you're                  2 looking at -- in very -- you know, you're trying                  3 to enroll subjects with sub-clinical infection.                  4 And there are special methods for gametocyte                  5 detection if you're interested in doing                  6 transmission blocking.                  7 But I think the thing to say about                  8 molecular methods is it really requires a pretty                  9 significant infrastructure and, you know, good                  10 training, good quality control. And it's very                  11 expensive if you're going to try to do it onsite.                  12 We only recently at AFRIMS tried to do this, and                  13 it required several years of running -- setting                  14 up the lab; training everybody; developing the                  15 SOPs and making sure that, you know, for the most                  16 part, we were able to produce reliable results,                  17 avoid -- you know, handle situations if there was                  18 contamination and so forth -- to make it                  19 clinically useful.                  20 But overall, you know, qPCR has come a                  21 long way. And you can see there's, literally,                  22 probably hundreds of publications on this. This</p>
<p style="text-align: right;">Page 239</p> <p>1 three readers to look at it. And the readers                  2 should be blinded to each other's results. And                  3 then you really need some expert C -- what we                  4 call C-level readers that do blind over-reads                  5 whenever there is a non-concordance between the A                  6 and B reader.                  7 So that, you know, logistically, is                  8 challenging. You need to amass a sufficient                  9 number of microscopists to be able to get through                  10 a trial, particularly if you're talking about a                  11 large trial.                  12 Okay. So that's microscopy. Now,                  13 molecular methods as far as enrollment goes, it's                  14 tough because if the test is not available onsite                  15 or in real time, you're pretty much going to be                  16 limited to microscopy to determine whether or not                  17 to enroll somebody.                  18 If you do have microscopy onsite -- sorry                  19 -- molecular methods onsite, then it does -- they                  20 do offer the advantage that they're more                  21 sensitive -- usually, several logs more sensitive                  22 than microscopy -- highly specific. So this can</p>	<p style="text-align: right;">Page 241</p> <p>1 is a method that we developed, you know, very                  2 similar other methods looking 18S RNA. But you                  3 can see that there's a really nice correlation                  4 between the, you know, controlled numbers, or                  5 specific dilutions of parasite genomes with the                  6 number of cycle thresholds that have to go                  7 through before the RT-PCR test becomes positive.                  8 There's good assays for general plasmodium                  9 falciparum and vivax.                  10 So this is a fairly well-established                  11 system. And this also compares nicely to                  12 quantitative microscopy and quantitative PCR. If                  13 you compare samples in blinded fashion using both                  14 methods, you actually get fairly good concordance                  15 of results to the point where it would be                  16 reasonable to use these tests to follow out                  17 parasite clearance in studies where you're                  18 particularly interested in resistance and the                  19 rapidity with which your drug is clearing the                  20 parasite.                  21 So bottom lines on enrollment --                  22 microscopy is still the gold standard, and it's</p>

<p style="text-align: right;">Page 242</p> <p>1 rarely going to miss clinically impaired                  2 infections. It may miss sub-clinical infections.                  3 RT-PCR is very good, but it's often not available                  4 -- very rarely available to use in -- for                  5 enrollment. And RDTs, really, are used, I think,                  6 just mostly for enrichment of patients and                  7 initial screening. And often, you know, patients                  8 will come to you from local -- public health                  9 facilities with an RDT. But these always really                  10 need to be confirmed by -- really, by microscopy.                  11 Okay. So I'll switch quickly just to                  12 talk about how do we use these methods to measure                  13 outcomes. And there's three important roles that                  14 molecular tests are increasingly filling. And                  15 the first is looking at parasite clearance. And                  16 we're starting to use PCR to quantify parasite                  17 clearance. But we're also using it to confirm                  18 the results because, often, when a patient comes                  19 back with a microscopic recurrence, the parasite                  20 densities can be very, very low.                  21 And because of that, it can be easy                  22 either to miss or to miss a mixed infection or to</p>	<p style="text-align: right;">Page 244</p> <p>1 infection, whether there's actually no infection                  2 and it was a -- it turned out to be a false                  3 positive -- and so useful to evaluate your                  4 outcomes after the trial is done.                  5 Now, one of the things that it opens up,                  6 though, particularly if you're following, you                  7 know, patients over the course of a trial with                  8 serial blood smears, is it's going to detect a                  9 lot of sub-microscopic infections. And because                  10 of that, you know, potentially, you can open up a                  11 whole new level of issues that you have to deal                  12 with when you have, you know, sub-microscopic                  13 infections persisting after the patient has                  14 become clinically well.                  15 Again, the major challenge of PCR                  16 correction is that it's rarely available in real                  17 time. It's usually done after the trial. And                  18 the clinical significance, particularly a                  19 persistent sub-microscopic parasitemia, is going                  20 to be debatable, I think, in some cases, whether                  21 it affects the patient's health. And it really                  22 sort of has to be died back to what your</p>
<p style="text-align: right;">Page 243</p> <p>1 call the wrong infection, so thinking that                  2 someone has falciparum when, in fact, they have a                  3 vivax infection, which is very common in areas                  4 where vivax is co-endemic. So this is what we                  5 call sort of PCR -- or I call, at least, PCR                  6 correction of the microscopy result. And it's                  7 useful, I think, post-talk in the trial to assess                  8 final outcomes.                  9 And then finally, molecular methods are                  10 useful to distinguish recrudescence from                  11 reinfection and all the other possible things                  12 that can happen as an outcome of a malaria trial.                  13 So PCR correction, microscopy, I think                  14 it's really becoming recognized as a critical                  15 factor for ensuring that you have accurate                  16 outcome measurements. And this is because,                  17 oftentimes, recurrences are detected only sub-                  18 clinically. Patients have no symptoms. They                  19 have no fever. They may have a very low                  20 parasitemia. And so PCR can really help                  21 distinguish whether it's a true P.f. reinfection,                  22 whether it's P.v., whether there's a mixed</p>	<p style="text-align: right;">Page 245</p> <p>1 objectives are when you undertake your trial.                  2 But it's certainly -- I think, for the most part                  3 these days, it's going to be part of a post-talk                  4 analysis of just about any trial that's going to                  5 be done.                  6 So useful also in measures of parasite                  7 clearance, particularly with resistance studies -                  8 - and you know, there's some -- you know,                  9 microscopy is certainly the standard for                  10 measuring parasite clearance. But it can be                  11 inaccurate because microscopy is often --                  12 parasite density is often calculated based on                  13 formulas.                  14 And the formulas -- sometimes we'll just                  15 substitute a standard, you know, white blood                  16 count, for example. So if the readers are                  17 counting based on a number of white blood cells                  18 and they don't know the patient's particular                  19 white blood count that day, 8,000 is often                  20 substituted. But that can lead to wide variation                  21 in the actual parasite densities. So in some                  22 sense, PCR may even be a little more accurate</p>

<p style="text-align: right;">Page 246</p> <p>1 because it's just measuring the overall parasite                  2 burden.                  3 Now, and you can see here in these                  4 figures this is -- and sorry. It's kind of hard                  5 to see. But at the bottom of the screen here,                  6 you can see these bars. These are the, you know,                  7 PCR results where we're looking for parasite DNA.                  8 And then you can see in the red line here is the                  9 microscopic parasite burden. And you can see by                  10 Day 3, Day 4 -- or in this case, Day -- yeah, Day                  11 3, Day 4, the patients have cleared                  12 microscopically, but there's still this                  13 persistent parasitemia that goes on. And in this                  14 case, both of these patients went on to                  15 recrudescence.                  16 But you know, how is this handled in                  17 cases where patients don't end up recrudescing?                  18 Obviously, now you're looking at a much more                  19 sensitive assay, and this could have implications                  20 for how you interpret your study and how you                  21 define parasite clearance -- so some things to                  22 keep in mind as these tools are employed.</p>	<p style="text-align: right;">Page 248</p> <p>1 Asia. We'll see almost one-third of patients in                  2 Southeast Asia where vivax is co-endemic have a                  3 blood stage P.v. infection after they've been                  4 treated for P.f. And you know, it's thought that                  5 the drugs precipitate a relapse of P.v. And                  6 tropical P.v. relapse is fairly often, sometimes                  7 as often as every month. So you know, how do we                  8 interpret that?                  9 And then you know, more complexities --                  10 patients that come in with mixed infections of                  11 P.f. and P.v. then end up with P.f., we still                  12 want to know is that P.f. a reinfection with a                  13 new P.f.? Or is it a recrudescence? And in                  14 cases where we have mixed infections and the                  15 patient then comes back with P.v., is it -- was                  16 it a relapse of the P.v., a reinfection, a                  17 recrudescence of the blood stage P.v.? So things                  18 get fairly complicated very quick -- fairly                  19 quickly.                  20 So it's important to be able to evaluate,                  21 you know, what actually happened. And this is                  22 generally used by, you know, parasite genotyping</p>
<p style="text-align: right;">Page 247</p> <p>1 Finally, we have the issue of PCR                  2 adjustment of trial outcome. So here, you're                  3 really trying to figure out what actually                  4 happened to this patient. Did they come in with                  5 P.f. and then end up with the same P.f. that was                  6 affecting them, which we would call                  7 recrudescence? Or did they come in with P.f. and                  8 end up with a different P.f., which we would call                  9 a reinfection?                  10 So if it's a recrudescence, we hold that                  11 against the drug in terms of efficacy. If it's a                  12 reinfection, the drug gets a pass because most of                  13 these drugs are suppressing the blood stage. And                  14 we wouldn't expect them to prevent a new                  15 infection from another mosquito bite. So there                  16 are -- this is -- it's important to assess this                  17 in the end.                  18 Now, another possibility is the patient                  19 comes in with P.f., and then they develop P.                  20 vivax. And so what do we call that? Is that a                  21 cure? It raises some questions. This is a                  22 common occurrence, particularly in Southeast</p>	<p style="text-align: right;">Page 249</p> <p>1 methods. And I think Ingrid went into the                  2 details.                  3 I think, for the most part, the current                  4 standard is to use the, you know, msp1, msp2 and                  5 glurp. Those three endogens seem to be fairly                  6 reliable. I think there is some -- you know,                  7 maybe some limitations. But for the most part,                  8 they seem to do a fairly good job in helping us                  9 identify patients that come back with either a                  10 recrudescence or reinfection.                  11 Now, you know, one of the challenges,                  12 though, is when we genotype, we often see that                  13 there are polyclonal infections. And these                  14 polyclonal infections may be represented                  15 disproportionately in the recrudescence versus                  16 the original infection.                  17 So things do kind of get complicated.                  18 But it's important to interpret things. You                  19 know, in Africa, up to 50 percent of your, you                  20 know, recurrences of malaria could be a                  21 reinfection. And that's going to have a major                  22 impact on your efficacy if the crude efficacy</p>

<p style="text-align: right;">Page 250</p> <p>1 could go from 50 percent up to 95 or even close                  2 to 100 percent once you adjust the results from                  3 PCR.                  4 And here's just some examples. You know,                  5 we published some of these. And you can see sort                  6 of, you know, here's one pattern of -- here's one                  7 subject, and here's their pattern of msp1, msp2                  8 and glurp. And you can see how, over time, this                  9 stays fairly consistent. And then at the day of                  10 recurrence, the same parasite appears.                  11 And -- but at the same time, you can see                  12 this case. This patient had this pattern of                  13 msp1, msp2 and glurp. And at recurrence, they                  14 had that. But then they had a new organism as                  15 well. So where did that come from? Did they get                  16 a reinfection on top of the recrudescence? And                  17 then some other examples where, you know, a                  18 patient had, you know, a multi-clonal infection                  19 at baseline and then only one of the variants                  20 reappeared.                  21 So doing this also, you know, gives you                  22 some insight into what are -- you know, what are</p>	<p style="text-align: right;">Page 252</p> <p>1 And this was one poor, unfortunate                  2 individual who relapsed three times during a                  3 cohort study that we're doing. You can see each                  4 time they had a different basket of                  5 microsatellite variations -- so very hard to                  6 track what's actually going on with vivax in                  7 terms of efficacy during a trial.                  8 So just to reiterate and sort of go back                  9 to the bottom lines, RDT is limited use.                  10 Microscopy is still the gold standard. But PCR                  11 is increasingly becoming a critically important                  12 factor, or method, to be used for several roles                  13 in trials. And I think, you know, there's going                  14 to be -- as the technology progresses further and                  15 gets more sensitive, there is going to be,                  16 really, I think, a need to determine how these                  17 results are used in a field trial and how much is                  18 required and how much is a sort of a nice to                  19 have.                  20 So thank you very much, and I appreciate                  21 the opportunity to talk to you today.                  22 (Applause.)</p>
<p style="text-align: right;">Page 251</p> <p>1 the dominant variants, what would -- what's                  2 responsible for the resistance. So this is                  3 useful data to have beyond just adjusting your                  4 efficacy result. And then you can see here an                  5 example of a new infection where this patient had                  6 one pattern of msp1, 2 and glurp bands at                  7 baseline. And then at -- reinfection had a                  8 totally different set.                  9 And then just to say with vivax -- and I                  10 know we're not here primarily to talk about vivax                  11 trials -- but in trying to distinguish vivax, we                  12 took a crack at this. It's pretty complicated.                  13 You can see here these are all patients -- you                  14 know, patient numbers. And you can see what they                  15 came in with and then what they looked at -- what                  16 they look like on recurrence using various                  17 microsatellite markers. And it's very                  18 complicated to the point where we can pretty much                  19 say each patient is sort of their own snowflake                  20 of outcomes. So trying to sort all this out in a                  21 vivax trial could be -- prove to be very                  22 challenging, indeed.</p>	<p style="text-align: right;">Page 253</p> <p>1 DR. FELGER: Thank you very much, David.                  2 So I think it's time now for a coffee                  3 break. So we have a 10-minute coffee break, and                  4 we'll reconvene then. We have to be on time                  5 because some people must leave early. So only --                  6 that's why only a 10-minute break.                  7 (Brief recess.)                  8 FEMALE SPEAKER: Good afternoon. After                  9 completing the talks, I think the next step is to                  10 have clarifying questions for the speakers. But                  11 before we do that, I want to give opportunity to                  12 our colleagues from CD8 and well as CDER to                  13 introduce themselves. Maybe we can start with                  14 Noel.                  15 DR. GERALD: Hello. My name is Noel                  16 Gerald and I'm a biologist and reviewer in the                  17 Center for Devices and Regulatory Health. I'm in                  18 the Office of In Vitro Diagnostics.                  19 DR. CHATTOPADHYAY: Hello. I'm Rana                  20 Chattopadhyay. I am in the Office of Vaccine in                  21 the Center for Biologics. And in another life, I                  22 was a malaria researcher for 25 years. That's</p>



<p style="text-align: right;">Page 254</p> <p>1 it.</p> <p>2 DR. BALA: Thank you. So at this time,</p> <p>3 any clarifying questions for the speakers from</p> <p>4 the panel? Yes?</p> <p>5 DR. MCCARTHY: I'd like to make two</p> <p>6 points of clarification. The first is about the</p> <p>7 expenses of QPCR. I think that's -- always I've</p> <p>8 talked about. But when you think about it, the</p> <p>9 cost of maintaining a high quality microscopy</p> <p>10 service that's got all the staff available to do</p> <p>11 -- whether it be CHMI or a randomized clinical</p> <p>12 trial -- I think, greatly underestimated is the</p> <p>13 cost of keeping the staff trained and making them</p> <p>14 available.</p> <p>15 And at our center, the QPCR is</p> <p>16 logarithmically less expensive and more</p> <p>17 convenient. And I think that we really need to</p> <p>18 consider the opportunity cost of having high-</p> <p>19 quality microscopy routinely available in terms</p> <p>20 of these clinical trials and recognize that logic</p> <p>21 problems of executing a trial where you're</p> <p>22 infecting, particularly in the CHMI setting,</p>	<p style="text-align: right;">Page 256</p> <p>1 We've had the opportunity in a clinical</p> <p>2 trial with a company that was doing an</p> <p>3 experimental study where people start out with</p> <p>4 extremely high levels of parasitemia. And what</p> <p>5 was apparent when we did analysis of their blood,</p> <p>6 right at the enrollment period, they had</p> <p>7 gametocytes present in their blood and the drug</p> <p>8 wasn't killing the gametocytes.</p> <p>9 I had consistent positive PCR with their</p> <p>10 asexual parasitemia. And everybody was saying</p> <p>11 oh, look at the drugs failed or there's free DNA</p> <p>12 around or we can't associate one with the other.</p> <p>13 But when you went and did Psf25 PCR for</p> <p>14 gametocytes, what you were seeing was all their</p> <p>15 asexual parasites being cleared by the drug, and</p> <p>16 you had a persistence of gametocytemia.</p> <p>17 So I think it's a gross over-estimation</p> <p>18 of the situation to make a claim that persistent</p> <p>19 DNA signal after cure of treatment represents</p> <p>20 anything other than persistent parasites, and</p> <p>21 more often than not in this situation, it's</p> <p>22 persistent gametocytes. So I don't know if ours</p>
<p style="text-align: right;">Page 255</p> <p>1 we're infecting people to be able to do, in my</p> <p>2 case, twice daily QPCR and have a reliable and</p> <p>3 reportable and reproducible data back within four</p> <p>4 to six hours in cohorts of eight to ten people is</p> <p>5 much more feasible than trying to run a</p> <p>6 microscopy service.</p> <p>7 In my hospital, I wouldn't rely upon the</p> <p>8 ability of my pathology department to reliably</p> <p>9 diagnose malaria because they see it so rarely.</p> <p>10 So I really think that we need to put that into</p> <p>11 consideration when we weigh up the pros and cons</p> <p>12 of QPCR versus microscopy.</p> <p>13 The second point I'd like to make goes to</p> <p>14 the point of residual DNA and persistence of DNA</p> <p>15 I hear quite commonly talked about that</p> <p>16 volunteers in clinical trials or subjects in</p> <p>17 studies endemic settings where people have high</p> <p>18 level of parasitemia and parasites after</p> <p>19 treatment, that that is representative of a</p> <p>20 residual free-floating DNA, DNA that are</p> <p>21 associated DNA, who knows where, but doesn't</p> <p>22 represent viable parasites.</p>	<p style="text-align: right;">Page 257</p> <p>1 would come in on that, I've had experience. But</p> <p>2 I think it really gets in the literature and</p> <p>3 tends to compound people's thinking that what</p> <p>4 we're seeing is really somehow or other something</p> <p>5 other than viable parasites. And therefore, cast</p> <p>6 aspersions on the reliability of the QPCR and</p> <p>7 clinical trials.</p> <p>8 DR. BALA: Thank very much, James. This</p> <p>9 is really spoken from my heart because I have</p> <p>10 encountered these reports and meetings,</p> <p>11 conferences and so on as well. And I always</p> <p>12 commented on gametocytes and people have not done</p> <p>13 tests for gametocytes on RNA level and I think we</p> <p>14 have to watch out for that.</p> <p>15 And eventually, if we are reviewing</p> <p>16 papers and stuff, point it out because that is</p> <p>17 brought out in the scientific community some</p> <p>18 doubts and some people are puzzled.</p> <p>19 So I think we really need to make a</p> <p>20 strong statement about that. But also for us, it</p> <p>21 has, of course, consequences because we encounter</p> <p>22 this eventually also in field trials, so we have</p>

<p style="text-align: right;">Page 258</p> <p>1 to consider this.</p> <p>2 And coming back to my point, if we want</p> <p>3 to apply the QPCR in a field setting, we might</p> <p>4 pretty well detect gametocytes. And then what do</p> <p>5 we do then? How do we treat it? So that's why</p> <p>6 my argument would be not to go to the ultimate</p> <p>7 sensitivity level but stay with microscopy and</p> <p>8 then, either you see the gametocytes or you can</p> <p>9 ignore it.</p> <p>10 I know David is thinking possibly along</p> <p>11 different lines. But I think we could still use</p> <p>12 it, as he suggested, as sort of a quality control</p> <p>13 at the end of a trial if you have doubts about</p> <p>14 the microscopy because we keep the blood spots,</p> <p>15 and that is very easily done.</p> <p>16 DR. MCCARTHY: And to add to that, the</p> <p>17 other possibility is to give a small dose of</p> <p>18 primaquine that will clear the gametocytes, then</p> <p>19 that would take that off the table.</p> <p>20 DR. MURPHY: So I have a comment and a</p> <p>21 question for Dr. McCarthy. So the first thing I</p> <p>22 want to say is I would like to go with what Jim</p>	<p style="text-align: right;">Page 260</p> <p>1 community. And they don't have microscopy to</p> <p>2 look at the virus so this is how it was from the</p> <p>3 beginning for them and we think it's very</p> <p>4 effective.</p> <p>5 My question to Dr. McCarthy has to do</p> <p>6 with recrudescence. And what I'm wondering is, if</p> <p>7 you were to treat people at a low density and go</p> <p>8 to zero with a molecular test quite promptly, is</p> <p>9 there a certain number of days beyond which you</p> <p>10 would be very unlikely to have a recrudescence?</p> <p>11 That is, if you had three or five or</p> <p>12 seven days of negative molecular tests, would it</p> <p>13 be more likely that in the field, if someone came</p> <p>14 back with malaria, that it's a new infection</p> <p>15 rather than a recrudescence. Do you have any</p> <p>16 data on that?</p> <p>17 DR. MCCARTHY: I don't have any data on</p> <p>18 that. I think the key issue there is the drug</p> <p>19 half-life.</p> <p>20 As soon as you get below what would be</p> <p>21 considered to be an inhibitory concentration of</p> <p>22 drug, you're going to then be in a situation</p>
<p style="text-align: right;">Page 259</p> <p>1 McCarthy said, which is that these tests, though</p> <p>2 they're often called to be expensive, have been</p> <p>3 actually very cost-effective in our center.</p> <p>4 For instance, we used to domicile all the</p> <p>5 subjects in a hotel. The hotel phase is a well-</p> <p>6 known feature of human challenge studies,</p> <p>7 historically. And because we now treat people on</p> <p>8 the basis of molecular tests at low densities</p> <p>9 where they're at asymptomatic, we have no need</p> <p>10 any longer to spend two weeks basically of hotel</p> <p>11 costs in every study for every subject. And this</p> <p>12 is a tremendous savings.</p> <p>13 It also is much better for the subjects</p> <p>14 who start the trial thinking it will be great to</p> <p>15 be in a hotel with a pool and, two weeks later</p> <p>16 are going crazy, basically.</p> <p>17 And so now they come to the clinic every</p> <p>18 morning and they go about their business for the</p> <p>19 rest of the day. So this has been very cost-</p> <p>20 effective. And these kind of molecular tests are</p> <p>21 used in HIV trials all the time.</p> <p>22 We've learned a lot from the HIV</p>	<p style="text-align: right;">Page 261</p> <p>1 where your parasites are going to begin to</p> <p>2 multiply. So a very short half-life artemisinin</p> <p>3 then you're going to quickly see recrudescence.</p> <p>4 At that's certainly been the experience</p> <p>5 with one of the ATPA four inhibitors that we had</p> <p>6 some experience with that we saw very rapid</p> <p>7 reappearance of parasites, early recrudescence</p> <p>8 where a drug such as mefloquine or piperaquine</p> <p>9 for example, when we used in it low dose, we saw</p> <p>10 that it took a couple of weeks before the</p> <p>11 recrudescence took place.</p> <p>12 I think we could model that, but I think,</p> <p>13 experimentally, one would be very cautious to</p> <p>14 take somebody out of the study with a long half-</p> <p>15 life drug saying that they have been cured,</p> <p>16 unless you followed them up for quite a period.</p> <p>17 DR. BALA: Thanks very much, Sean and</p> <p>18 James.</p> <p>19 DR. NAMBAIR: Any other questions from</p> <p>20 the audience?</p> <p>21 PUBLIC COMMENTER: I have two questions,</p> <p>22 and actually, I'm going to read them. One of the</p>

<p style="text-align: right;">Page 262</p> <p>1 most important things in clinical trials is                  2 selection of the candidates.                  3 I was a little worried this morning that                  4 we wouldn't get to this point of enrollment but                  5 I'm glad that we got here. I wonder if in                  6 selecting candidates, if two important tests                  7 would be one, the selection test; for example, a                  8 PCR or microscopy. And from what is being said,                  9 I guess the PCR is going to be the more effective                  10 test for screening.                  11 The other test I suspect that we might                  12 need is an immunological test to determine                  13 whether or not the subject has antibodies to one                  14 or the other parasites, one of the other species.                  15 I wondered has anybody looked at the                  16 possibility of Duffy in respect to identifying                  17 candidates with P. vivax. That's number one.                  18 The second question is, in mixed species                  19 infection, when you're doing a PCR, if you have a                  20 very high count in one of the species, for                  21 example, falciparum, does it mask a low infection                  22 of vivax? Have you seen that?</p>	<p style="text-align: right;">Page 264</p> <p>1 necessarily easy to tell a mixed infection by                  2 microscopy, particularly if one of the species is                  3 a very low density compared to the other. So I                  4 think that's where PCR really is essentially, at                  5 least in your post-talk analysis to figure out                  6 what the patient actually had at the time.                  7 I'm not sure I understood the question                  8 about the Duffy antigen though.                  9 PUBLIC COMMENTER: Yes. You know Duffy                  10 affects plasmodium vivax. So I'm wondering if                  11 it's important in determining whether somebody                  12 has vivax or had vivax, if it would be important                  13 to check to see if there were antibodies for                  14 Duffy. Duffy antigen is a receptor for --                  15 DR. WEINA: So I can try to answer that                  16 question. My only experience in this is some                  17 studies that Ruben Wang did in Colombia to look                  18 at immune responses in subjects to vivax and to                  19 falciparum, and they categorically tested people                  20 for Duffy and split the data along the lines of                  21 Duffy positive and Duffy negative individuals.                  22 So yes, it's true that if you were</p>
<p style="text-align: right;">Page 263</p> <p>1 Thank you. Those are my questions.                  2 DR. MURPHY: So I think those are all                  3 good questions. I think your first point of                  4 whether you should use PCR microscopy, I think                  5 the point I was trying to make is that PCR for                  6 enrollment is rarely available in real time, and                  7 you're probably going to be limited to microscopy                  8 in most center.                  9 Immunological test of antibodies are                  10 notoriously not helpful in choosing candidates to                  11 enroll. Because most of the tests that we use                  12 don't tell you about functional immunity. They                  13 can tell you maybe about past exposure but they                  14 don't necessarily tell you how immune somebody                  15 is, per se, to malaria at that moment.                  16 And they also do not necessarily                  17 correspond to a clinical response. So those have                  18 been challenging to quantify and use in a                  19 clinically meaningful way.                  20 And then masking mixed species infection,                  21 mixed species infections can mask one or the                  22 other and often confound microscopy. It's not</p>	<p style="text-align: right;">Page 265</p> <p>1 looking at P. vivax, you would probably want to                  2 know whether people were Duffy positive or                  3 negative. So yes, it's true that if you were                  4 looking at P. vivax, you would probably want to                  5 know whether people were Duffy positive or                  6 negative.                  7 I was going to comment on your second                  8 question which was about mixed infections. So                  9 for instance, in our group, we built our test to                  10 have a P. falciparum specific channel, a pan                  11 plasmodium channel that detects the 18S not just                  12 from the human species, but also from Simenon and                  13 Myriam species. So it's a real bona fide pan                  14 plasmodium target. And when we do mixing                  15 studies, we can detect one part of P. falciparum                  16 in the presence of 10,000 parts of P. vivax. So                  17 we felt that that was an important thing to be                  18 able to show.                  19 Obviously, if it's P. falciparum as the                  20 overwhelming component, we can't find one part P.                  21 vivax in that setting because the pan target is                  22 overwhelmed by the P. falciparum but we could</p>

<p style="text-align: right;">Page 266</p> <p>1 find a needle in a haystack when it's falciparum                  2 in the presence of something else.                  3 PUBLIC SPEAKER: Thank you.                  4 DR. BALA: All right.                  5 PUBLIC COMMENTER: How good are we at                  6 distinguishing reinfection from recrudescent                  7 infection?                  8 The reason I'm asking the question is                  9 that if somebody has initially a polyclonal                  10 infection and is a minority species, can we find                  11 that early on? Recrudescence could be the                  12 minority species popping up at some later point                  13 in time, as opposed to get a new mosquito bite,                  14 new infection. Do folks have insight into that                  15 or is there data that helps to address that                  16 issue?                  17 MALE SPEAKER: Well, I think there's some                  18 and part of the problem is often, you know,                  19 recrudescent infections -- recurrent infections                  20 have very low parasitemia. So it would be                  21 possible to miss, you know, very low minority                  22 variance if they were to occur.</p>	<p style="text-align: right;">Page 268</p> <p>1 clones would be resistant. So you can expect to                  2 see that one. Of course, there are new clones                  3 coming in, which will be competing. But I mean,                  4 it has been a very, very good, very robust                  5 methods so far.                  6 There is much advancement in the                  7 methodology. We have started by gel                  8 electrophoresis where you could hardly really --                  9 the two bands have the same height. But now, I                  10 mean, really, with a couple of electrophoresis,                  11 we can size it to one base pair and it's very                  12 precise. So there has been a huge advance and I                  13 think we are still improving because we are                  14 learning more.                  15 The field is moving and thank God the                  16 field is moving. It just shows that we make                  17 efforts to optimize. So I think we can now, for                  18 example, stop multiplexing reactions. It is a                  19 little bit more expensive, but we reduce the                  20 competition between clones very much. So that                  21 simple, really simple method can sort out the                  22 problem to a certain degree but there is always a</p>
<p style="text-align: right;">Page 267</p> <p>1 I think for the most part, it's fairly                  2 useful, fairly predictive. I don't know, though,                  3 that anyone has really gone to the trouble of                  4 quantifying exactly how use it is. And I think                  5 that might actually be a little bit challenging                  6 to do.                  7 DR. FELGER: May I comment on that                  8 quickly? I would say it has been quite robust                  9 technique, despite the fact there are polyclonal                  10 infections and that is the rule for P. vivax                  11 normally. And plasmodium falciparum in African                  12 samples, there are infections, about five co-                  13 infections. So when you compare the pretreatment                  14 and post treatment sample, we don't need to find                  15 all the genotypes in both samples. If we see                  16 one, which is the same, then we would say this is                  17 recrudescence. So we don't need to redetect all                  18 the clones, right. So that is the definition.                  19 Normally, if that is a resistant                  20 parasite, it would come up. It would have                  21 selective advantage very often and will expand                  22 because not all clearance are -- not all baseline</p>	<p style="text-align: right;">Page 269</p> <p>1 biological handicap. I mean, because the biology                  2 of the parasite is quite amazing with the                  3 sequestration and absence in the peripheral plat                  4 of a cell clone. We cannot overcome that even                  5 with the best method, we cannot because we only                  6 can sample 200 microliters maximum. That's the                  7 problem.                  8 DR. BALA: With that, I think we can move                  9 to questions for discussion here. The first                  10 question is please discuss the detection methods                  11 to be used in CHMI studies, when infected by                  12 different routes, or with the different state of                  13 the parasite such as bites with the infected                  14 mosquitoes, injected with the sporozoites                  15 intravenously, or infected erythrocytes.                  16 Please discuss the assays, their                  17 performance, and threshold for positive findings                  18 to identify patients that need rescue therapy.                  19 MALE SPEAKER: So my talk attempted to                  20 kind of provide some data and some perspective on                  21 what other centers are doing. I do think that                  22 there is not agreement over -- amongst the</p>

<p style="text-align: right;">Page 270</p> <p>1 centers. There is some disagreement about                  2 whether we should endorse a specific threshold or                  3 whether thresholds should be specified within                  4 each clinical trial protocol.                  5       So for instance, some centers advocate                  6 getting more data points in order to model to                  7 look for things like partial immunity. In our                  8 center, when we do mostly prophylactic studies,                  9 the goal is to prevent infection emerging into                  10 the blood stream, virtually in every subject that                  11 we've ever seen, there is really -- once the                  12 parasites are in the blood stream, they are free                  13 to multiply, even if the therapeutic or the drug                  14 was intended to block something upstream of                  15 there.                  16       So in our sense, this means that these                  17 shouldn't be there and it's time to treat the                  18 patient. And so I showed the data on that and                  19 we've selected a threshold that is not rated at                  20 the limit of detection, so we're not sort of                  21 struggling with the test at all. Not so high                  22 that the patients are symptomatic. But that is</p>	<p style="text-align: right;">Page 272</p> <p>1 each other. And if your goal is to mitigate                  2 symptoms and declare people failed for liver                  3 protection, that's reasonable. I guess one of                  4 the questions along these lines that I have for                  5 Dr. McCarthy has to do with if you're testing a                  6 radical cure, what are the most important                  7 parameters?                  8       Obviously, you have to be safe, but in                  9 order to adequately challenge a drug, is it                  10 enough to have a few days of exposure and                  11 clearance to zero, or do you want a biomass that                  12 is 10 or 100 times higher than the threshold                  13 we're talking about in order to be a little                  14 closer to what really symptomatic patients who                  15 are coming into the hospital are like?                  16       Are you trying to mimic symptomatic                  17 disease or do the curves, you showed earlier, two                  18 curves that had the same slope. If they have the                  19 same slope, might you treat earlier or do you                  20 need to go later?                  21       DR. MCCARTHY: First of all, it's a                  22 statistical issue in terms of getting enough data</p>
<p style="text-align: right;">Page 271</p> <p>1 not a view that is held by some of the centers,                  2 some of which are not represented here today.                  3       So there could be some disagreement in                  4 the field over that. But I think for                  5 prophylactic studies, at least in our center,                  6 we've endorsed this. Gradually, we've seen the                  7 implementation of a threshold because if you're                  8 going to do a molecular test that's quantitative,                  9 you must have a threshold if you're not going to                  10 treat at the very first positive.                  11       For instance, one of the centers that                  12 was on the slide is the NIH Clinical Center,                  13 which has a very good assay, but it's a                  14 qualitative assay. They know the approximate                  15 limit of detection. And for them, their                  16 threshold is two positive tests because they                  17 can't describe a specific quantitative value.                  18 And so they similarly can avoid most but not all                  19 of the symptoms in that setting.                  20       So for them, two positives equals rescue                  21 treatment. At the moment, that's what we have is                  22 a bunch of different thresholds that hover around</p>	<p style="text-align: right;">Page 273</p> <p>1 points to be able to draw a line between data                  2 points, but that's not particularly reliable. So                  3 the more data points you get, the better off you                  4 are. I don't think we have a good understanding                  5 of what the symptom threshold is in falciparum                  6 that I see enormous variation in symptom in my                  7 volunteers and some are actively collecting data                  8 on that some volunteers can be symptomatic in                  9 what I would consider to be trivial levels of                  10 parasitemia.                  11       DR. CHATTOPADHYAY: Right. If the                  12 sponsor of the trial they are saying we will be                  13 using PCR, if that country's accommodation is no,                  14 you'll have to -- whenever a person has a fever,                  15 you'll have to first do a blood smear with RDT.                  16 So they kind of go by that also. So it is kind                  17 of, you know, like depending on what the trial                  18 is. So we sometime look into those things, too.                  19       DR. MURPHY: I'll just make a comment                  20 about our own application from the biomarker                  21 qualification program.                  22       The FDA has a program called the Drug</p>

<p style="text-align: right;">Page 274</p> <p>1 Development Tool program. It's through CEDR.                  2 And my group has submitted a -- we submitted a                  3 letter of intent and then an additional briefing                  4 package.                  5 And the focus of this -- our project is                  6 to qualify the that 18S ribosomal RNA and/or the                  7 ribosomal DNA as a biomarker to replace                  8 microscopy for whatever the context of use that                  9 was specified.                  10 So the initial context of use that we're                  11 hoping to submit later this year has to do with                  12 replacing microscopy in CHMI studies in non-                  13 endemic regions like in Seattle. And then it's                  14 our hope that if we can proceed with that, we                  15 might extend that eventually to other contexts of                  16 use, for instance, CHMI in the endemic regions                  17 and potentially down the road, you know, more                  18 like field acquisitions. Then each of those                  19 benchmarks would have different questions.                  20 Obviously the non-endemic study in                  21 Seattle is the most highly controlled and most of                  22 the questions have to do with, you know, the</p>	<p style="text-align: right;">Page 276</p> <p>1 gain experience with different types of tests and                  2 approaches, we can memorialize those, too, in                  3 guidance documents. So you sort of see sort of                  4 the progression here over time.                  5 DR. MCCARTHY: Well, I mean, the main                  6 reason I bring this up is kind of just thinking                  7 through the whole thought process and direction                  8 of the conversation because, you know, we're                  9 using one of these tests and you spoke about                  10 thresholds.                  11 If you have a threshold that's too low,                  12 you know, picking up, you know, the idea of                  13 moving the product forward is to, you know, see                  14 how it's going to be used in real life. I mean,                  15 that's, you know, part of the argument that we                  16 have for doing the phase threes, right?                  17 And if you're always picking somebody up                  18 before they even have any kind oof symptoms                  19 whatsoever, so the idea is to try to stay as safe                  20 as possible hanging back, are you really giving                  21 them a fair trial because you haven't -- the drug                  22 a fair trial because we're treating before the</p>
<p style="text-align: right;">Page 275</p> <p>1 validity of the biomarker as evidence of                  2 infection and the performance characteristics of                  3 the test.                  4 As you move to the field, there's                  5 obviously issues of strain diversity, reinfection                  6 and recrudescence. And so those are things that                  7 we might have to deal with in the future.                  8 It's my understanding that the                  9 qualification program is not a categorical                  10 approval of any one test. It's a qualification                  11 of the target. But along those lines, if we                  12 qualify the target, then there would be test                  13 characteristics that are required to meet that                  14 qualification that one would have to meet.                  15 Now, that could mean you could use our                  16 test or you could use another test that meets                  17 those qualifications. We thought this was a good                  18 pattern because recognizing that there are a                  19 number of centers that have different and good                  20 tests that this may be a way to streamline things                  21 and yet provide a guidance.                  22 DR. WEINA: And in general, too, as we</p>	<p style="text-align: right;">Page 277</p> <p>1 patient's even being symptomatic, where in the                  2 real world the patient feels crappy for a day,                  3 maybe two days, maybe three days before they even                  4 bother to come in, and then you've got to have a                  5 clinician actually being astute enough to                  6 recognize what's going on and test them.                  7 Next thing you know, it's three or four,                  8 maybe even five days of parasitemia and being                  9 symptomatic before the drug even comes onboard.                  10 So now you've got a huge biomass as opposed to                  11 what you were testing in -- originally and                  12 exposing it to in which there was -- biomass was                  13 so small because the person was asymptomatic                  14 recognizing, of course, there's tremendous                  15 variability among patients. And some of them are                  16 going to be pretty wimpy and come in early and                  17 other ones are going to be John Wayne and have 10                  18 percent parasitemia before they even start to                  19 complain, so.                  20 DR. MURPHY: I'll just comment on our                  21 approach to the (inaudible) and I suppose                  22 approval process for our qPCR in conjunction with</p>

<p style="text-align: right;">Page 278</p> <p>1 MMVR approaches being to validate RSA, to develop                  2 a strong quality system. It's well documented                  3 with all the appropriate tests that one would                  4 use; work with our local regulator in Australia                  5 to have our tests registered under our local                  6 regulator and then participate in an EQA program                  7 with other centers doing CHMI and also doing a                  8 qPCR for clinical trials.                  9 And I suppose with that platform,                  10 although we've not tested it with a regulator in                  11 terms of a drug registration process, we're                  12 hopeful that all our efforts won't be in vain.                  13 DR. FELGER: I mean, we could also add --                  14 it's just an idea -- but at some additional                  15 external quality control that would define                  16 certain center which would perform a highly-                  17 alkaloid assay, for example, digital droplet PCR                  18 which could then process 10 percent of all                  19 samples from a clinical trial just to validate                  20 that against something which is unbiased because                  21 a digital droplet PCR doesn't need a standard,                  22 internal standard.</p>	<p style="text-align: right;">Page 280</p> <p>1 greater than the asexual form. But we don't know                  2 that definitively. And so investigating that                  3 further, I think will be, you know, very helpful                  4 for the centers as we monitor those                  5 gametocytemias, you know, post rescue therapy.                  6 MALE: I mean, it's a good point. We                  7 have been talking about developing a standard                  8 because we have thoughts about having copies of                  9 pfs25 where there are per gametocyte, and we have                  10 a process in place where we're sharing samples at                  11 the moment.                  12 I think those numbers are really based                  13 upon transcripts numbers per mil against a                  14 standard curve and not the number of gametocytes                  15 present.                  16 DR. MURPHY: James, can I ask a quick                  17 question about the gametocytes? When you look at                  18 the 18S for gametocytemia, it is always a                  19 fraction of the 18S content that was the maximum                  20 of the asexual, right? The 18S never rises above                  21 what the max was in the asexual stage.                  22 DR. MCCARTHY: I think the curves were</p>
<p style="text-align: right;">Page 279</p> <p>1 It's just basically gets a very alkaloid                  2 quantification independent of some external                  3 standard trend line or whatever. So this will                  4 take out some of the viability and that could be                  5 maybe one idea to have one center who could run                  6 this for clinical trial just to be on the safe                  7 side if there are concerns on quantification.                  8 But I think your concerns were more on is                  9 that relevant, is -- that very low threshold, is                  10 that very relevant at all? This, I mean, from                  11 the lab side we cannot really -- I mean, that                  12 needs to be discussed.                  13 MALE SPEAKER: An additional issue I                  14 think for the performance of these assays is when                  15 we do start, you know, and when we're evaluating                  16 these drugs, some of them are kicking out higher                  17 parasitemias than others.                  18 And it looked like, you know, from your                  19 data, James, for example, the quantification of                  20 those gametocytes may have been higher than the                  21 actual parasitemia, and that is likely due to the                  22 transcripts of the gametocytes perhaps being</p>	<p style="text-align: right;">Page 281</p> <p>1 reversed and that was an issue related to                  2 standard curves. I think our gametocyte curve on                  3 that particular graph was higher than the 18S                  4 graph. And I think that's just an artifact of                  5 how we set the standard curves and not the fact                  6 that we've got more gametocytes present than we                  7 have.                  8 PUBLIC SPEAKER: So in well, you're                  9 doing DNA. We find the RNA content of the                  10 gametocytes is about four times higher than it is                  11 for rings, which isn't surprising. They're a                  12 little bit larger. Okay. Thanks.                  13 DR. FELGER: Any other questions from the                  14 audience? Can we have the next question?                  15 DR. BALA: The next question would be                  16 that we discuss --                  17 DR. FELGER: Just one moment. I think we                  18 have someone else.                  19 DR. BALA: Oh, sorry.                  20 PUBLIC COMMENTER: Hi. This question is                  21 about regulatory strategy. Okay. So assume the                  22 -- as I understand it, the thick blood smell is</p>

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1 the gold standard, right? That being so, if I  
 2 develop a drug and I use the gold standard and  
 3 have an in-house developed tests, which I  
 4 correlate with the blood smear and I submit to  
 5 CEDR, and through discussions the product is  
 6 approved based on my tests, (inaudible).  
 7 Now, if after approval I went to market  
 8 that test, for market purposes, what is CEDR  
 9 going to say about that? Is that a lab-developed  
 10 test or what is it?  
 11 DR. GERALD: So yes. In general, if you  
 12 wanted a separate application for marketing your  
 13 test now for in vitro diagnostic use in the US,  
 14 that would be a separate application to CDRH.  
 15 DR. COX: Yeah, and it is possible to do  
 16 both. And one of the things we talk about is  
 17 that, you know, a clinical trial and, you know,  
 18 the patient specimens that are obtained in a  
 19 clinical trial, you know, with appropriate  
 20 consent when planning ahead of time, it may also  
 21 be an opportunity to study and/or develop a  
 22 diagnostic test. So it can happen, you know,

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1 concurrently.  
 2 DR. FELGER: And then the other thing  
 3 that I would mention is that, you know, for CDRH,  
 4 for diagnostics, everything is focused on the  
 5 intended use and how you define that. And so the  
 6 parallel here that we're talking about in this  
 7 workshop is, you know, performance  
 8 characteristics of the context of use.  
 9 And so being very specific with your  
 10 context of use, and when we talk about issues of,  
 11 you know, performance characteristics for  
 12 quantification, you know, you're going to need to  
 13 know, you know, just as an example, you know, in  
 14 CDRH, you know, the accuracy of your test itself,  
 15 the imprecision of the test itself becomes  
 16 important if that's near the clinical decision  
 17 points of what you're going to use that for.  
 18 So it all, you know, has a lot to do with  
 19 the intended use in CDRH, and parallel  
 20 considerations come into play with context of  
 21 use.  
 22 DR. BALA: Thank you very much.

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1 Now we are moving to the second question.  
 2 We are going to discuss whether the molecular  
 3 assays are a tool for enrolling subjects in a  
 4 field trial and the different section of  
 5 recrudescence from new infection and the ability  
 6 to differentiate multiple strains including those  
 7 present in low density.  
 8 I think we have quite discussed a little  
 9 bit on that, but we haven't reached a conclusion  
 10 on the first point. Is it a tool for enrolling  
 11 subjects in a field trial?  
 12 We have concluded that on the spot we  
 13 have light microscopy, which clearly needs in  
 14 some instances a confirmation by molecular  
 15 speciation, molecular methods. I mean, I think  
 16 we all agree on that. There could be cryptic  
 17 vivax there and that is a problem in some areas.  
 18 But yeah, I don't know. I mean, are  
 19 there any further opinions here on the panel or  
 20 in the audience on that topic? Yes, please?  
 21 MS. HIGGINS: I have a question about  
 22 recrudescences and reinfections and when they're

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1 typically discovered in a clinical trial.  
 2 Dr. Saunders, I noticed in your talk it  
 3 looked like they were found pretty much near the  
 4 end of a trial, let's say if the test of cure was  
 5 Day 28. And in that case, I'm a little less  
 6 concerned about using an adjusted cure rate as  
 7 opposed to if a new infection was found early on  
 8 and then the subject was treated for that new  
 9 infection such that it might suppress the  
 10 recrudescence that they couldn't be captured.  
 11 So would you say that most recrudescences  
 12 and reinfections are found at the end of the  
 13 trial?  
 14 DR. SAUNDERS: Yeah. I mean, it's fairly  
 15 rare. Because of the incubation period, if a new  
 16 infection is unlikely to occur until after about  
 17 two to three weeks, that's the earliest we would  
 18 see it. And I would say, you know, again,  
 19 there's no hard and fast rules here, but the  
 20 recrudescences also tend to occur usually a few  
 21 weeks later, so Week 3, 4, 5, if you're doing a  
 22 six-week follow up. That's when the majority are



<p style="text-align: right;">Page 286</p> <p>1 seen.</p> <p>2 You know, the way things are defined, if</p> <p>3 somebody occurs -- recurs earlier than that, you</p> <p>4 know, within the first week, that's usually</p> <p>5 called an early treatment failure, and oftentimes</p> <p>6 they've never really, truly cleared, and they may</p> <p>7 have submicroscopically -- they may have cleared</p> <p>8 down to a submicroscopic level. But the clinical</p> <p>9 infection becomes apparent within a couple of</p> <p>10 days.</p> <p>11 But, no, I think for the most part they</p> <p>12 tend to occur later in the follow-up period.</p> <p>13 DR. BALA: Thank you. I have a question</p> <p>14 for Dr. Saunders. Did half-life of the drug have</p> <p>15 anything to do with the time and recrudescence</p> <p>16 would occur?</p> <p>17 DR. SAUNDERS: Yes, it has -- it can have</p> <p>18 a lot to do with it. It just depends on, you</p> <p>19 know -- and that's highly variable. I mean, it</p> <p>20 depends on what drugs you're using and what</p> <p>21 combination and what the properties are and so</p> <p>22 forth. So I think that can have a significant</p>	<p style="text-align: right;">Page 288</p> <p>1 real time during the trial, recurrences are, if</p> <p>2 they occur, are only going to be discovered</p> <p>3 microscopically.</p> <p>4 PUBLIC COMMENTER: Sure.</p> <p>5 DR. SAUNDERS: So, you know, generally</p> <p>6 speaking, in field trial, we don't hunt for</p> <p>7 submicroscopic recurrences. But now because</p> <p>8 increasingly PCR is being used to correct the</p> <p>9 microscopy result, we discover after the fact</p> <p>10 that, you know, there was a persistence of</p> <p>11 microscopic infection.</p> <p>12 The other problem, though, is, you know,</p> <p>13 at the level where you only have submicroscopic</p> <p>14 infection, there is often not enough DNA to do an</p> <p>15 adequate PCR or adjustment using msp1 or msp2</p> <p>16 where that is convincing.</p> <p>17 And even sometimes in very low</p> <p>18 parasitemia recurrences, it's challenging to</p> <p>19 actually adjust the results. So there are</p> <p>20 occasionally, you know, recurrences that we</p> <p>21 cannot genotype adequately and determine.</p> <p>22 FEMALE: Maybe a comment to genotype, to</p>
<p style="text-align: right;">Page 287</p> <p>1 impact.</p> <p>2 DR. BALA: And the second question I had</p> <p>3 was regarding the msp2, msp1 glurp markers which</p> <p>4 you used, did you do them sequentially or were</p> <p>5 they done -- all three were done on -- which is</p> <p>6 baseline at the time recrudescence occurred?</p> <p>7 DR. SAUNDERS: Yeah. No, you have to</p> <p>8 take parent samples and run all three tests on</p> <p>9 them at each time point.</p> <p>10 DR. BALA: So all three were done.</p> <p>11 DR. SANDERS: Oh yes. Yes.</p> <p>12 DR. BALA: Okay.</p> <p>13 DR. FELGER: Can I ask a follow-up</p> <p>14 question about your recrudescence data?</p> <p>15 So when you say recrudescence, I think</p> <p>16 you mean microscopic recrudescence. Is that</p> <p>17 correct? At Day 28 or 56, those -- because in</p> <p>18 order to detect msp1 and these things, there</p> <p>19 would have had to have been molecular detection</p> <p>20 at all of those time points in between.</p> <p>21 DR. SAUNDERS: Right. And generally,</p> <p>22 because the molecular methods are not used in</p>	<p style="text-align: right;">Page 289</p> <p>1 detect clones, which are at very low density.</p> <p>2 This is quite possible if there is one clone</p> <p>3 only, which is extremely low density and we</p> <p>4 perform next the PCR on that. You have no</p> <p>5 problems to detect it.</p> <p>6 So this is also only a problem in</p> <p>7 competition with other clones, of course, and</p> <p>8 currently methods are underway and the idea is</p> <p>9 that you don't use length-polymorphic markers</p> <p>10 anymore but markers which have a stretch, which</p> <p>11 have a lot of single nucleotide polymorphisms in</p> <p>12 a stretch of about 300 bases.</p> <p>13 And then these fragments are sequences</p> <p>14 with next-generation sequencing, and there it</p> <p>15 should -- there should be no bias anymore, and</p> <p>16 the detection of that part -- of a particular</p> <p>17 minority clone would only depend on the depths of</p> <p>18 the sequencing, right, so how many fragments,</p> <p>19 individual single fragments are sequences.</p> <p>20 And, of course, the depths of the</p> <p>21 sequencing depends very much on the costs or</p> <p>22 affects the costs. If we want to do it cheaply,</p>

<p style="text-align: right;">Page 290</p> <p>1 we multiplex 100 or 200 different samples in one                  2 run because this is quite expensive, costs more                  3 than \$1000 one run. So it's only feasible with                  4 many, many samples, which are run at the same                  5 time with sort of nucleotide identifier index so                  6 you can deconvolute individual samples later on.                  7 So there is a possibility but this is                  8 currently under evaluation whether this method,                  9 the amplicon sequencing method will be better in                  10 determining the minority clones because we also                  11 learn from HIV, again, that has been in HIV                  12 exactly the same question, the minority clones,                  13 and they also try to address this with next-                  14 generation sequencing.                  15 So the methods are in development and I                  16 am pretty sure we will see that later. But this                  17 would clearly be, you know, done in certain                  18 centers which have the bioinformatic expertise.                  19 This is not something what can be done anywhere                  20 in the world.                  21 Right now what we do so far, there are                  22 many places who do recrudescence typing all over</p>	<p style="text-align: right;">Page 292</p> <p>1 would say those are two essential pieces.                  2 FEMALE SPEAKER: I would like to add                  3 something along the lines of the targeted                  4 amplicon sequencing. Our hope is that we could                  5 there include, because we are multiplexing highly                  6 and indexing each sample, that we would include                  7 amplicons of, for example, Kelch 13 or, I mean,                  8 we could -- depending on the drug we are                  9 interested in or the drugs we are using, we could                  10 use known molecular markers of drug resistance.                  11 We could use all of them without any additional                  12 costs.                  13 So then we would gain the currently                  14 available information and drug resistance                  15 markers, blast the genotyping and maybe other                  16 things. So we have multiplexed 10 different                  17 fragments already and we can deconvolute them                  18 later without any problem, so it is feasible.                  19 But I mean, it's really a question should                  20 -- because we can do it, should we do it all?                  21 DR. SAUNDERS: Well, I think the other                  22 thing to say is it's a rapidly evolving field.</p>
<p style="text-align: right;">Page 291</p> <p>1 Africa and in Asia, South America. So that                  2 possibly will be restricted because there the                  3 challenge is certainly the bioinformatic and the                  4 analysis.                  5 DR. FELGER: Any other questions from the                  6 panel or the audience? So maybe then we can move                  7 on to the next question.                  8 What did these two information should be                  9 collected besides genotyping to confirm                  10 resistance to the drugs in an endemic area?                  11 DR. SAUNDERS: Well, I suppose it depends                  12 on what resistance you're concerned about in that                  13 endemic area. But, you know, I mean, there's                  14 pretty well-defined markers for most drugs now.                  15 And so those markers are obviously helpful and                  16 pharmacokinetic data is helpful.                  17 You know, someone brought up unity data.                  18 You know, we still don't completely understand                  19 the interactions between unity and apparent                  20 resistance and drug resistance. I think maybe                  21 that's less so. But those, you know, known                  22 markers of resistance, pharmacokinetic data I</p>	<p style="text-align: right;">Page 293</p> <p>1 You know, K-13 just a couple of years ago was                  2 thought to be the (inaudible) and resistance                  3 marker and now we realize maybe that's just a                  4 setup for other markers. So the understanding of                  5 resistance, particularly with the has changed                  6 very rapidly.                  7 One other thing I would mention, I think                  8 when you're looking in an endemic area, one of                  9 the issues -- one of the big issues -- and this                  10 is often overlooked in trials -- is preexisting                  11 use of antimalarials by the subject. So that's                  12 often an exclusion criterion for trials and one                  13 that is notoriously unreliable based on clinical                  14 history.                  15 So identifying what drugs a patient may                  16 have taken in the last 30 days or longer that may                  17 still have some anti-malarial activity or may                  18 have influenced the resistance of the parasite                  19 that you're treating now are critically                  20 important.                  21 And there's a couple of ways you can do                  22 that. There is -- you can take the patient's</p>

<p style="text-align: right;">Page 294</p> <p>1 plasma and incubate it in vitro or, you know, ex-</p> <p>2 vivo against known parasite clones to determine</p> <p>3 whether there's anti-malarial activity in the</p> <p>4 blood before you treat the patient. So it's</p> <p>5 important to get a baseline sample.</p> <p>6 There's also, you know, pharmacokinetic</p> <p>7 methods that have been worked out, bioanalytical</p> <p>8 methods that can scan a patient's blood sample</p> <p>9 pretreatment and look for a series of known</p> <p>10 antimalarials, I think up to 14 or 15 in one run.</p> <p>11 That was published by the Swiss Tropical</p> <p>12 Institute several years ago, a very helpful thing</p> <p>13 to do to see what preexisting antimalarials the</p> <p>14 patient may have taken because that could, one,</p> <p>15 you know, influence the results of the outcome of</p> <p>16 your trial, could exclude the patient, you know,</p> <p>17 based on what were the stated enrollment criteria</p> <p>18 in the study.</p> <p>19 And it could certainly influence</p> <p>20 variables like parasite clearance and so forth,</p> <p>21 and it could inform, you know, particularly</p> <p>22 inform the results if you have a clinical failure</p>	<p style="text-align: right;">Page 296</p> <p>1 you go from the initial specimen to what grows in</p> <p>2 culture.</p> <p>3 So what comes out of culture will often</p> <p>4 give you a less accurate idea than what the</p> <p>5 panelists have been talking about, which is using</p> <p>6 the genotype approach.</p> <p>7 MALE: Yeah. I actually don't think the</p> <p>8 genotyping as we were describing it is</p> <p>9 particularly useful. It's certainly not the</p> <p>10 primary variable for resistance. I think it's</p> <p>11 just sort of a crude adjustment of your efficacy</p> <p>12 overall, but there can be many factors</p> <p>13 contributing to that lack of efficacy and not</p> <p>14 just resistance.</p> <p>15 PUBLIC COMMENTER: Talking about low-tech</p> <p>16 technology providing that we merge with the</p> <p>17 microscopy or PCR seems to be something that we</p> <p>18 should not forget, especially when we don't know</p> <p>19 which marker we want to look at. This has been,</p> <p>20 at least in the way we have detected falciparum</p> <p>21 resistance.</p> <p>22 DR. BALA: Any other comments, questions?</p>
<p style="text-align: right;">Page 295</p> <p>1 by, you know, indicating, well, oh, gee, that</p> <p>2 patient actually had taken that drug already and</p> <p>3 if we had looked at their blood we would have</p> <p>4 known that.</p> <p>5 MALE: So a much more low-tech answer to</p> <p>6 your question, so before genetic resistance</p> <p>7 markers are identified or validated, prophylaxis</p> <p>8 failures in travelers, treatment failures as well</p> <p>9 can help detect your drug resistance in the</p> <p>10 endemic area.</p> <p>11 PUBLIC COMMENTER: Just a brief comment,</p> <p>12 which I think reaches the same conclusion as the</p> <p>13 other comments here, and that is one tends</p> <p>14 intuitively to say to oneself if you could grow</p> <p>15 the parasite from that blood sample when the</p> <p>16 patient had their recurrent illness and then test</p> <p>17 that in the lab, maybe that would be optimal.</p> <p>18 And in our experience, that's really not</p> <p>19 been the case because so many of these</p> <p>20 infections, especially in Africa have multiple</p> <p>21 clones. And if you use your markers carefully,</p> <p>22 you usually see an attrition or loss of clones as</p>	<p style="text-align: right;">Page 297</p> <p>1 No?</p> <p>2 So with that, I turn it back to Dr. Cox.</p> <p>3 DR. COX: All right. Well, I want to</p> <p>4 thank everybody for a very productive day and a</p> <p>5 chance to, you know, discuss clinical trial</p> <p>6 issues, methods of detections.</p> <p>7 And really I think, you know, the reason</p> <p>8 that everybody is here is really to, you know,</p> <p>9 move forward the field of therapeutics for</p> <p>10 malaria, recognizing the patient needs out there.</p> <p>11 I also, too, just want to reflect back to</p> <p>12 and, you know, the many folks that had this, you</p> <p>13 know, as an idea and something we ought to do, I</p> <p>14 want to thank in particular Wendy Samhain (ph)</p> <p>15 for helping to push this along and also the folks</p> <p>16 from MMV for all their participation, folks from</p> <p>17 industry academia, the government colleagues and</p> <p>18 Sania Shukla (ph) from our office, too, who also</p> <p>19 was key in planning all this.</p> <p>20 So we thank you all for your efforts and</p> <p>21 for all that was done to make the opportunity to</p> <p>22 get together here so productive.</p>

1 We recognize there's a tremendous amount  
2 of work that goes on in preparation for these  
3 workshops and all that was done, and I think that  
4 been apparent in the discussions today and really  
5 the fine presentations.

6 So you know, clearly, you know, this is  
7 an area of drug development that's important. I  
8 think the workshops provide an opportunity for us  
9 to get together and understand, you know, the  
10 current state of where the field is with regards  
11 to clinical trials and drug development and also  
12 areas for additional development and questions  
13 for the future. But I do think it's a great  
14 opportunity to push things forward, and I look  
15 forward, as we all do -- our colleagues in CEDR,  
16 our colleagues CEBR (ph), our colleagues in CDRH  
17 -- to talking about development of new therapies,  
18 whether they be drugs, diagnostics and/or  
19 vaccines.

20 So with that, I'll thank you, wish  
21 everybody safe travels, whether you're going near  
22 or far, and look forward to future opportunities

1 to meet with folks and continue to push forward  
2 the field of anti-malarial drug development.

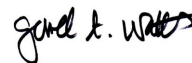
3 Thank you all. Have a good day.  
4 (Whereupon, at 4:02 p.m.,  
5 The public meeting was adjourned.  
6 was concluded.)

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1 CERTIFICATE OF NOTARY PUBLIC

2 I, GERVEL A. WATTS, the officer before whom  
3 the foregoing deposition was taken, do hereby  
4 certify that the testimony that appears in the  
5 foregoing pages was recorded by me and thereafter  
6 reduced to typewriting under my direction; that  
7 said deposition is a true record of the  
8 proceedings; that I am neither counsel for,  
9 related to, nor employed by any of the parties to  
10 the action in which this deposition was taken; and  
11 further, that I am not a relative or employee of  
12 any counsel or attorney employed by the parties  
13 hereto, nor financially or otherwise interested in  
14 the outcome of this action.

15  
16 

17 GERVEL A. WATTS

18 Notary Public in and for the  
19 State of Maryland

20  
21  
22 My Commission Expires: June 7, 2020.

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