DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Wednesday, July 10, 2002

8:30 a.m.

Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland

PARTICIPANTS

L. Barth Reller, M.D., Chair
Tara P. Turner, Pharm. D., Executive Secretary

MEMBERS

Gordon L. Archer, M.D.
David M. Bell, M.D.
Alan S. Cross, M.D.
Steven Ebert, Pharm.D. (Consumer Representative)
Mary P. Glod, M.D.
James E. Leggett, Jr., M.D.
Judith R. O'Fallon, Ph.D.
Jan E. Patterson, M.D.
Julio A. Ramirez, M.D.
Ciro V. Sumaya, M.D.
Ellen R. Wald, M.D.

CONSULTANTS (VOTING)

Monica Parise, M.D.
Theresa Shapiro, M.D., Ph.D.

GUESTS (NON-VOTING)

Donald Poretz, M.D.
Coleman Rotstein, M.D.

FDA

Renata Albrecht, M.D.
Ruthanna Davi, M.S.
Mark Goldberger, M.D., M.P.H.
Rosemary Johann-Liang, M.D.
Leon Sacks, MB.B.Ch.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. RELLER: Good morning. I would like to call the Advisory Committee meeting of the U.S. Food and Drug Administration Anti-Infective Advisory Committee to order. We will begin this morning by the introduction of staff from the FDA and committee members for today's meeting.

We will begin on my right with Dr. Mark Goldberger.

Introduction of the Committee

DR. GOLDBERGER: Mark Goldberger from the Office of Drug Evaluation IV.

DR. ALBRECHT: Renata Albrecht, Acting Director for the Division of Special Pathogens and Immunologic Drug Products.

DR. SACKS: Leonard Sacks, Medical Officer in the Division of Special Pathogens and Immunologic Drug Products.

DR. JOHANN-LIANG: Rosemary Johann-Liang, Medical Officer with the Division of Special Pathogens.

MS. DAVI: Ruthanna Davi, Statistical Reviewer, Office of Pharmacoepidemiology and Biostatistics.

DR. PARISE: Monica Parise, Medical Officer with the Malaria Epidemiology Branch at Centers for Disease Control.

DR. ARCHER: Gordon Archer, Chair of the Division of Infectious Diseases at Virginia Commonwealth University.

DR. LEGGETT: Jim Leggett, Infectious Diseases at the University of Oregon Health Sciences University.

DR. GLODEy: Amy Glod, Pediatric Infectious Diseases, University of Colorado, Denver.

DR. BELL: David Bell, Assistant to the Director for Antimicrobial Resistance in the National Center for Infectious Diseases at CDC in Atlanta.

DR. TURNER: Tara Turner, Executive Secretary to the committee.

DR. RELLER: Barth Reller, Division of Infectious Diseases, Duke University Medical Center, Director of Clinical Microbiology there.

DR. PATTERSON: Jan Patterson, Medicine and Infectious Diseases, University of Texas Health Science Center, San Antonio.

DR. SUMAYA: Ciro Sumaya, Dean, School of

Rural Public Health, Texas A&M University System Health Science Center.

DR. WALD: Ellen Wald, Division of Infectious Diseases, University of Pittsburgh School of Medicine.

DR. EBERT: Steve Ebert, Infectious Disease Pharmaceutical and Clinical Professor at the University of Wisconsin.

DR. SHAPIRO: Terry Shapiro, Division of Clinical Pharmacology, Johns Hopkins.

DR. RAMIREZ: Julio Ramirez, Chief, Infectious Diseases, University of Louisville.

DR. O'FALLON: Judith O'Fallon, statistician at the Mayo Cancer Center, Rochester, Minnesota.

DR. PORETZ: Don Poretz, private practice in infectious diseases in Fairfax, Virginia.

DR. RELLER: Thank you.

Tara Turner, our Executive Secretary, will read the conflict of interest statement.

Conflict of Interest Statement

DR. TURNER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at

this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in forms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

We would like to note for the record that Kenneth Brown, M.D. is participating in this meeting as an industry representative acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interests.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. RELLER: The opening remarks for today's meeting will be given by Dr. Renata

Albrecht.

Opening Remarks

DR. ALBRECHT: Good morning. I would like to welcome everyone to today's advisory committee meeting on artesunate rectal capsules. On behalf of both the Division and the Office, I would like to thank the committee members, guests and consultants for making the time to be with us to lend us your expertise in this deliberation.

May I also extend a welcome to representatives from the World Health Organization and to their distinguished consultants who have not only undertaken the challenge of developing artesunate rectal capsules as initial management in patients with malaria, but have also traveled probably the greatest distance to be here. So, for both of these efforts, you are to be commended.

I believe it would be appropriate to acknowledge as well that we have at this committee meeting representatives from Swissmedic who are also reviewing this application and will be making remarks during the open public hearing.

Malaria is a serious disease, a life-threatening disease with serious social and economic impact. It is estimated to cause perhaps

a quarter of the billion cases of acute disease annually and about a million deaths per year in parts of the world, including Africa, Asia and South America. Although it is not a common disease in the United States, it does impact U.S. travelers, Peace Corps volunteers and the Military who go to those parts of the world.

There are various effective oral and parenteral therapies for the treatment of this disease although resistance has developed to some of these. However, when these therapies are not an option for the initial management of a patient, an alternative is needed. It is with this goal in mind that the World Health Organization has developed and submitted the application for artesunate. We thank them for bringing this application forth and enabling us to present it at the advisory committee for discussion.

Let me turn to the scientific aspects of the application. The proposed indication, as we will hear, is the initial management of acute malaria in patients who cannot take medication by mouth and for whom parenteral treatment is not available. The World Health Organization, their consultants and FDA staff have prepared a series of

presentations to provide information on artesunate including its activity and safety profile.

Much of this information was also included in the background material provided to you before the meeting. As you listen to the presentations, we would like you to keep the following issues in mind. These issues would also be relevant to the questions that Dr. Goldberger will give as the charge to the committee this afternoon.

The first set of issues relate to the differences between the intended population that will receive this product in the actual-use setting and the population that was studied as part of this NDA. Specifically the population studied consisted of patients who were already in a hospital setting and, thus, had access to the medical infrastructure, medical personnel and ancillary management.

The question would be what is the infrastructure that will make artesunate available to the intended population. What education program will assure that patients understand how the product should be used and what provisions will be available to enable patient transport for definitive therapy?

Also, the population that was studied consisted primarily of older children and adults, although the anticipated use may involve children less than two years of age and then the question of what is the potential risk of neurotoxicity in that age group arises.

Also, in clinical studies, the patients had a definite diagnosis of moderately severe malaria established on entry while, in the intended population, patients may have all levels of severity of malaria or they, in fact, may have another febrile illness, for example, bacterial meningitis.

The timing of drug administration may also be significant. For example, what might be the consequences if the drug is administered too soon in the course of disease or, perhaps, too late in the course of disease.

The second set of issues relates to the endpoints used in the study and their clinical implications. These include the 24-hour parasite clearance or parasite-count reduction as a surrogate of clinical success or clinical cure and, also, the clinical significance of the recrudescence at 28 days that we will see, and what

is the impact of such recrudescence on the emergence of resistance to artesunate or other agents.

So these are some of the issues that we would like you to keep in mind as you listen to the presentations this morning. With that, we look forward to your discussion and deliberations of the questions and issues before you.

I now turn it back to you, Dr. Reller.

DR. RELLER: Thank you, Dr. Albrecht.

We will now have the presentation of the sponsor, the World Health Organization, Dr. Melba Gomes.

Sponsor Presentation: World Health Organization

DR. GOMES: Good morning. My name is Melba Gomes. I work for the Special Program for Research and Training in Tropical Diseases in the World Health Organization and am leading a team of experts who come independently to act on behalf of WHO in defending this current submission.

[Slide.]

The first slide essentially repeats what Dr. Albrecht has said that infectious and parasitic diseases constitute a large proportion of causes of death and, of these, malaria is amongst the highest

major killer. About 40 percent of the world's population is exposed to malaria and the death toll is highest in young children.

[Slide.]

The estimates are essentially about 1.5 to 2 million deaths in children under the age of five. If you go to a pediatric ward in most of Africa, Kenya, Malawi, Tanzania, Ghana, half of the wards would be filled with children dying of malaria, the majority having symptoms that would have progressed fast over 24 hours.

[Slide.]

This child would not have been able to take drugs for a period of 24 hours before the picture was taken. As the disease would have progressed, her mother would have needed to choose between taking her child to a hospital or not and would have calculated the probability that they, the mother and the child, would have arrived at the hospital before the child died.

From the data that we have, a small proportion of those who are referred to hospital actually reach hospital with a child that is alive. The rest, essentially, have died en route to hospital or at home. If they have made it to

hospital, the disease would have progressed to a point at which it is in a very acute stage. This would be considered as a medical emergency in a disease considered fatal unless treated and most lives are lost from malaria in this way.

[Slide.]

In 1997, WHO needed to find a solution for these kinds of children. We attempted to respond to this need for a preventable condition by developing an antimalarial--in this case, artesunate--to be given as emergency treatment, emergency management of patients who cannot take drugs by mouth but who cannot get to a hospital where definitive treatment can be given for several hours, where the risk of death is high and we needed to buy them the time to reach definitive treatment.

[Slide.]

We will have presented a dossier which is in the hands of the Food and Drug Administration, the Swissmedic and the medical-control agency in the United Kingdom, the essence of which is in the briefing document that you would have, providing what we believe is a coherent case for the efficacy, safety and quality of this drug,

artesunate, provided in a suppository form for the following indication: to manage initially acute malaria in patients who cannot take medicines by mouth and for whom parenteral treatment is not available.

We see the challenge before us today to defend this indication which we have carefully worded to show that the drug is effective for the purpose and to discuss safety in relation to the way that we propose to give the drug, and to argue that, for this purpose and in the way we propose to give the drug, the safety issues for the narrow indication can be set aside.

We see it as our responsibility to ensure that any reservations you may have regarding safety do not have a bearing on the way we propose to use the drug. We will want to show you a future that, if approval by the advisory committee and the FDA is given, it will release the World Health Organization's energy for implementation with a large public-health benefit.

The WHO has no intention of releasing its responsibility for providing a medicine and undertaking its safe and responsible use following approval. It will not be our primary

responsibility or aim in our presentations to argue on the manner in which the indication applies in the U.S. We will be wanting to discuss and to defend this if the advisory committee wishes to do so.

It is the first time that WHO has developed a drug and submitted it for registration in its own name. In coming to the FDA as a U.N. agency, we come in the confidence that the development will meet the standards of the highest review process that you will ensure.

I would like to be able to introduce the team who have developed this drug. Included implicit in that is the donation of the Chinese who have given us their data and the drug. But the first introduction, and there would be five members of the team, is Professor Nicholas White, Professor Peter Folb, Professor Fred Binka, Sanjay Krishna and Anthony Dayan who is not here with us today.

All have contributed their time on a pro bono basis as independent experts in this development and they are here as independent experts. Professor White and Sanjay Krishna would be the world's experts on clinical pharmacology and severe malaria. Nick White would have devoted the

past twenty years of his life to understanding the pathogenesis of malaria, the pharmacokinetics and pharmacodynamics drugs that can be used in the treatment of malaria.

Professor Peter Folb is normally on the other side, in your position in normal life, but he has spent twenty years critically reviewing all aspects of drug development dossiers submitted for registration in South Africa. He is the person who advised the WHO five years ago that we could build a case for this indication, this new indication for malaria, and potentially save lives. In large part, he was the architect of much of its development.

Fred Binka would have spent the past fifteen years of his life in malaria-endemic communities, in Ghana, mainly, quantifying the risks and benefits of different interventions that have the potential to save lives in malaria.

This is the end of my introduction. I will come back at the end, but I will now hand over to Professor White to take you through the clinical part of the presentation.

PROFESSOR WHITE: Thank you, Melba.

Mr. Chairman, members of the committee,

ladies and gentlemen, I am Professor Nick White. I am Professor of Tropical Medicine at Mahidol University in Bangkok Thailand and Oxford University in England. It is my job this morning to present to you the rationale for rectal artesunate and the clinical evidence of efficacy.

[Slide.]

I don't apologize for repeating the size of the problem, approximately one-fifth of the world's population infected today and various estimates of a higher mortality even than written here of up to 3 million deaths per year. So this is the most important parasitic disease of man and it is caused by a parasite which invades the red blood cell, as you know, and the pathology of malaria is entirely related to that process.

[Slide.]

So malaria, unlike most other infectious diseases, but, unfortunately, as with HIV, has a global mortality that is rising, not falling, and we believe that approximately 90 percent of that burden falls in the African continent upon children.

[Slide.]

This rising mortality is attributed

directly to the loss of affordable and available drugs.

So, briefly, a summary of the epidemiology of malaria. We conventionally define the epidemiology in terms of the entomological-inoculation rate. That is the number of times you are bitten per unit time--in this case, a year--by a mosquito carrying malaria parasites. So you can see that there are places in the world on this logarithmic scale where you may have malaria every day. You may contract this disease every day and everyone has malaria all the time.

In this context of high stable transmission, the burden of severe disease falls largely on young children and it manifests predominantly as severe anemia. This carries, as you have seen, a significant mortality.

As the entomological-inoculation rate falls, the intensity of transmission falls or becomes more seasonal. We see a change in the clinical appearance with a predominant syndrome now of cerebral malaria. That is coma in the presence of falciparum malaria in the blood. We see also other presentations, predominantly metabolic

acidosis. These are all linked.

As the entomological-inoculation rate falls further, then the age range broadens and everybody becomes susceptible and we now see the appearance of different clinical manifestations in adults, notably acute renal failure and, to a lesser extent, liver dysfunction and pulmonary edema.

But this is a multisystem infection with a different clinical epidemiology depending on the intensity and seasonality, to a certain extent, of transmission.

[Slide.]

So this would be your life if you lived somewhere where you had an infectious bite every week. I will show this several times and just go through it. This is a logarithmic scale showing the number of parasites in your body. If I had a 2 percent parasitemia, I would have about 10

parasites in my body. So one is infected all the time. The majority of these infections resolve spontaneously but, very frequently, they cause fever and debility and every so often you have a really serious infection.

[Slide.]

Either you survive if you get effective treatment or, if you don't, you die.

[Slide.]

So, falciparum malaria differs from the other three human malarias in that it kills people regularly and it does that because it induces a phenomenon known as sequestration. What this means is that, once the malaria parasite gets inside the red blood cell, it starts to manufacture a glue, and adhesive protein, and about 16 to 24 hours into 48 hour asexual cycle, these red cells start to stick.

They stick in the microvasculature of vital organs, notably the brain, where they cause microvascular obstruction.

[Slide.]

The mortality of cerebral malaria ranges approximately from 15 to 20 percent, so one in five patients treated with available drugs will die. We believe that the mortality of untreated cerebral malaria approximates to 100 percent.

In adults surviving cerebral malaria, about 3 percent will have some detectable neurological sequelae but, in children, about 10 percent will have detectable neurological sequelae

of which over half will resolve within six months. But, nevertheless, given the cumulative burden of this disease, this is a major problem.

[Slide.]

This may be stating the obvious, but it is very important and it is the basis, really, of the rationale for rectal artesunate, and that is that antimalarial drugs save lives because they kill parasites. Therefore, the reason why people die from malaria is because they don't get effective treatment early enough in the progression towards lethal disease.

[Slide.]

The artemisinins are a fascinating and unique family of compounds discovered, or rediscovered as you probably all know, by the Chinese approximately 30 years ago, a sesquiturpinelactoin peroxides with the business end of the molecule being this peroxide bridge and substitutions here giving us the different derivatives, in this case, a succinate, or hemisuccinate, group forms artesunate.

They are the most rapidly acting of antimalarial drugs. They kill parasites faster than any other drugs. They are extremely potent

and, as I will show you, they have a very important property in that they will kill all the stages that circulate in the blood. They will prevent the progression from the young and relatively less pathological to the mature, more pathological, stages which stick and obstruct the microcirculation.

As a bonus, they reduce transmissibility and, to date, despite considerable effort in the laboratory, it has not been possible to induce resistance and no confirmed evidence of significant resistance has occurred despite use in over 3 million patients. That is not a cry for complacency, but it is reassuring.

[Slide.]

Here we have the 48-hour life cycle of Plasmodium falciparum going from the young, so-called ring, forms which circulate in the peripheral blood and can be counted by the microscopist to the more mature, pathological forms which are sequestered in the microcirculation and cause the pathological processes.

So, perversely, it is the parasites that you can't see in the blood film that are causing the problem, not the ones you can see, and this

explains some of the discrepancies between parasitemia and severity. Nevertheless, there is a general rough relationship between the parasitemia counted peripherally and the overall burden in the body.

The artemisinin derivatives affect all these stages and they will prevent the progression from the circulating stage to the sequestered stage. The other antimalarial drugs, notably the ones that are used for severe malaria, are the cinchone alkaloids, quinine and quinidine. These drugs do not prevent the development of the circulating ring forms to the sequestered pathological stages.

[Slide.]

Again, the paradigm of a person, me, perhaps, with 2 percent parasitemia. This is to illustrate the different properties of the antimalarial drugs. You can treat falciparum malaria with an antibiotic such as tetracycline but it is very weak. It will kill with a fractional killing rate of 10 per asexual cycle which would mean you would have to take tetracycline for about a month to get rid of all the parasites in your body.

We can't detect parasitemia below about 10^8 in the body so, below this level, we certainly have an infection but we are not able to detect it by microscopy. Most of the antimalarial drugs work in this sort of area, fractional killing rates or parasite-multiplication rates of 10^2 to 10^3. So this would be 100-fold to 1,000-fold reduction per asexual cycle.

The artemisinins are the most active. They will cause 10,000-fold reduction in the number of parasites per asexual cycle, so a single dose will cut that parasite biomass by 10,000-fold. Note that it is still necessary to expose that parasite population to these drugs or an effective antimalarial drug for at least a week. Otherwise, we will see recrudescence. So, short-acting drugs need to be present for at least a week.

[Slide.]

In the worst-case scenario of somebody getting a single rectal artesunate administration and then not following up as we believe must be done--in fact, we recommend, of course, must be done--then this is what would happen. You would cut the parasitemia by about 10,000-fold and then there would be an uninhibited multiplication. The

parasite can't multiply more than the number of children it has per cycle. That is about 10 to 20 maximum. In vivo studies would suggest a multiplication rate of 10 maximum per cycle. So it would take nearly ten days to get anywhere near the sort of parasitemias that initially presented by which time host defenses are mobilized.

Of course, the patient has been ill for all this time, so the probability of getting access to antimalarial drugs is much increased. This explains, or this simple cartoon, explains why even a single dose would be very unlikely to be followed by a recurrence of this rare event where one presents with severe or impending severe malaria.

This cartoon is one where there is no mobilization of host defense and yet there is rapid nonspecific mobilization of host defenses which is why we have people living in the tropical areas of the world. Malaria is not uniformly fatal.

[Slide.]

What the artemisinin derivatives do is that they cut the parasitemia more rapidly than any of the other drugs and they remove those ring stages before they progress to the more pathological stages. We can actually quantitate

this by subtracting the parasite-clearance curve after artesunate or another artemisinin derivative from that, from a comparator drug such as quinine.

The difference, the area between these two curves, would represent the ring forms that have been removed from the circulation before they could cause trouble.

[Slide.]

This is a summary slide of the pharmacokinetic properties of the drugs, the artemisinin derivatives, that we might use in the treatment of severe malaria, plasma concentration along here and time. If we have artesunate parenterally, intravenously or intramuscularly, in severe malaria, it is very rapidly and reliably absorbed. We get concentrations well above 1,000 milligrams per kilogram.

The other formulation widely available, in fact the most studied formulation, is artemether, which is an oil-based intramuscular injection, which is much more slowly and erratically absorbed reaching peak concentrations often twelve or more hours after the original injection.

Rectal administration occupies a position perhaps more close to the intravenous or

intramuscular administration where absorption is certainly slower but more rapidly than following artemether. Now, artemether has been subjected to the largest trials ever in severe malaria and it is certainly as effective. In fact, Professor Folb will show you some data. It is certainly as effective, if not more effective, than quinine. It is because the concentration required of these drugs to produce the maximum parasiticidal killing, or minimal parasiticidal concentration--that is the minimum concentration producing the Emax or maximum effect--is very low.

The IC50s would be of the order of 3 to 5 nanograms per ml, IC95s of the order of 10 to 20. So, even though these concentrations may look very low, very low concentrations are all that is needed to produce maximum parasiticidal effect. That is why these profiles are very effective and, certainly, these profiles are reliably effective.

[Slide.]

Let's just briefly examine the relatively unusual, in an individual, but, as I have explained, frequent overall path towards lethal malaria. After receiving an infected mosquito bite, there is about a five- or six-day incubation

day in the liver. Then, somewhere between 10,000 and 100,000 parasites are released into the blood stream.

Then multiplication rates of approximately six-fold to ten-fold per cycle means that the parasites become detectable in the blood approximately eleven to twelve days after inoculation. This also coincides with the time when fever is usually present. The pyrogenic density is quite close to this level.

If no treatment is given and the parasite multiplication continues unabated for several more cycles, we enter the dangerous territory where lethal disease may occur. Things happen at this point very quickly.

[Slide.]

In that next cycle, if we manage to stop development of the parasites at this stage, then lethal events will not occur. But if the parasites mature, sequester and then undergo further schizogony now with a burden of 1012 in the body somewhere, a parasitemia that may be between 1 and 20 percent, then lethal events may occur.

Our objective, therapeutically, is to stop that progression. This is a very short time span

which explains why children die very rapidly once they develop severe malaria.

[Slide.]

So if we are on the threshold of developing severe disease, in Thailand, if you have more than 4 percent parasitemia but no evidence of vital-organ dysfunction, your mortality is 3 percent. That is 30 times higher than in uncomplicated disease with a lower parasitemia but five times lower than once severe disease has developed with vital-organ dysfunction.

[Slide.]

Then, as I have said, things happen very rapidly and we enter, and we very rapidly increase the probability of a fatal outcome.

[Slide.]

So the objective of treatment is to interrupt that process and the earlier we can do that, the better the probability of saving the patient.

[Slide.]

Just to summarize our rationale again, as Melba has presented, it is a treatment for patients who can't take oral treatment. That is a range of clinical syndromes from just repeated vomiting

through to deeply unconscious. Hopefully, we are going to prevent the progression towards deeply unconscious.

The trials were designed to assess the antimalarial activity in vivo in that high-risk group of patients who had not yet developed vital-organ dysfunction. They were on the threshold of developing severe disease. Our focus is the immediate life-saving response. This is not an assessment of a curative treatment. It is an assessment of a life-saving treatment.

[Slide.]

Patients were either those who could not take oral drugs or had, as I described previously, defined increased mortality. They were given a single rectal dose of artesunate and that was followed by the standard treatment in the country at the time which varied from an effective drug to an ineffective drug, as you will see later, and all cases were hospitalized.

[Slide.]

The assessment focused on the reduction in parasitemia which reflects the main pharmacodynamic effect, parasite killing. It was assessed by fractional reductions or total parasite clearance

time and the clinical response was assessed by the standard ways of fever clearance, time to be able to take oral treatment again and, of course, prevention of clinical deterioration or death.

[Slide.]

There are three types of studies. The first two were randomized crossover phase 2b, if you like, dose-finding studies, three phase 3, so to speak, studies, one in Thailand, one in Malawi and one in South Africa, each with a slightly different design. In Thailand, where there was a defined group with a defined mortality, oral artesunate was the comparator because that had been shown to be superior to intravenous loading-dose quinine in patients with hyperparasitemia.

In Malawi, they were non per os and the comparator was parenteral quinine. In South Africa, there were two studies, one in moderately severe malaria where the comparator was quinine and one in severe malaria where all patients received quinine and some received artesunate, while others did not. The randomization was unequal so, in each of these trials, the majority of patients received rectal artesunate.

Finally, there was a comparability study

between the original formulation that was used in these studies and the new formulation, the one that we are submitting for regulatory approval, we hope.

[Slide.]

These studies confirmed the results of all other studies with these drugs and that is that there was a reliable and rapid reduction in parasitemia when compared with the comparator quinine. This is an absolutely consistent finding in all trials with these drugs.

[Slide.]

The beneficial effects in terms of parasitological response would be the different between those two curves, the parasites that were prevented from going on and sticking in these patients' brains, livers, kidneys, lungs and so forth.

[Slide.]

A couple of slides just to deal with this question, really, of the parasitological outcome, the subsequent treatment response which is not the focus of this submission. Once the patients had received the rectal artesunate, they were then given so-called consolidation treatment which, in Thailand, was mefloquine, which was pretty

effective. In most of the other countries, it was sulfadoxine/pyrimethamine which sadly, although it is national policy in many of these countries, is failing fast and also chloroquine which, as you know, in most of the world, is no longer effective. So there were quite a lot of recrudescences in the patients who received these drugs.

The comparator group in Malawi received more quinine than did the artesunate group so they had a better, if you like, consolidation treatment.

[Slide.]

What happened to those patients with the recrudescence infections? Most of them just had a fever and were found to have parasites again when they were retreated and about a third had other symptoms of nausea, vomiting and so forth. One patient was temporarily obtunded but recovered rapidly and there was no development of severe malaria and there were no deaths in the recrudescent infections.

[Slide.]

We have had a question as to how relevant are those studies compared to the ongoing, very large community-based studies. These studies which are, as I said, ongoing have as their entry

criterion that the patient cannot take antimalarial drugs by mouth. But they are not associated-- because they are community-based, we are actually testing how these drugs would be used in real life. They are not associated with immediate availability of diagnosis.

But, generally, the populations appear to be comparable, similar rate of patients being obtunded, similar seizure rates. We would contend that these populations are comparable. But, obviously these patients had to be studied in hospital because we had to provide the data appropriately.

[Slide.]

So, in summary, the basis or the evidence that we would like to provide to you for efficacy of rectal artesunate is based on 310 patients ranging from young children to adults in countries where there were very different background levels of drug resistance and background levels of intensity of transmission ranging from very low transmission in Southeast Asia to very high transmission in Ghana.

The median parasitemia reduction at 24 hours is 99 percent. These drugs reliably cut the

parasite biomass by a huge amount. All but four patients were able to take oral drugs within 24 hours.

[Slide.]

So, in conclusion, we believe that this is a highly effective treatment. It has a particular place, a particular application. It produces consistent results on the main determinate that it kills parasites quickly. That is associated with rapid clinical responses and these benefits are independent of the patient's age. They are independent of their geographic location and, therefore, the intensity of transmission and associated background immunity. They are independent of the patient's ethnic origin and they are independent of the prevailing levels of resistance to the other antimalarial drugs.

Thank you.

DR. RELLER: Thank you, Professor White, for that comprehensive review.

Professor Peter Folb?

PROFESSOR FOLB: Good morning, Mr. Chairman and members of the committee.

[Slide.]

The FDA in its executive document points

out correctly that, under certain exceptional conditions of experimental design, the artemisinins, as a class, are neurotoxic. We deal with the issue of neurotoxicity in the following way; firstly, to draw your attention to the strictly limited indication for which we propose whereby the drug will be used once or, at the most, twice in the dose of 10 milligrams per kilogram body weight.

We argue from a hierarchy of evidence starting with extensive clinical experience of the artemisinins in general and artesunate in particular including artesunate administered in the way that we propose, rectally, moving from the clinical to the experimental. We shall point out that, except under the most exceptional circumstances experimentally, artesunate, given orally is never neurotoxic not even to experiment animals and that no human toxicity, neurotoxicity, has been demonstrated with artesunate given in any formulation or any mode of administration.

We shall also argue that artesunate, within the class artemisinins, is arguably the safest.

[Slide.]

This is the basis for the concern including that concern addressed by the Food and Drug Administration. From animals, mice, rats, rhesus monkey and dogs, there is both symptomatic and observational evidence on the one hand that, with very high doses given parenterally apathy, unsteadiness, collapse, even coma and death have been observed.

Neuropathologically, specific lesions have been described of chromatolysis and necrosis of brain-stem nuclei in particular. These nuclei are identified especially as vestibular, cochlear, the olivary and the red nuclei in the brain stem. As pointed out, it is identifiable in several animal species. So it is reasonable to question whether there is a likelihood that this would apply also to humans.

[Slide.]

Here is an example of an isolated dead neuron in the brain stem in an experimental animal showing enlargement, hyperchromasia, swelling of the neuronal soma and pigmentosis of the nucleus. This is the characteristic lesion that has been identified by those experimental investigators who have described it.

[Slide.]

Moving, as I say, from the experimental to the clinical, I draw attention to the work done in the first instance on mice who have been studied in terms of abnormalities of balance and gait and survival. I wish to point out that dihydroartemisinins certainly are more potent and more potentially toxic antimalarial than artesunate. In human equivalent doses up to 342 milligrams per kilogram produced no functional or neuropathological injury.

Artesunate, in a human equivalent dose of 683 milligrams per kilogram produced reversible abnormality of balance and gait in two of twenty animals in this particular experiment.

Oral artemether, artesunate and dihydroartemisinin have not produced clinical or neuropathological evidence of toxicity in doses below 200 milligrams per kilogram per day given for 28 days. Members of the committee will recognize that this is orders of magnitude greater than the proposed dose to be given to humans.

[Slide.]

In this work done by Nonprasert and Dr. White and others, I wish to highlight the evidence

that oral artesunate has produced--this is the only evidence of its kind--oral artesunate has produced abnormal equilibrium given in table form in doses of 250 to 300 milligrams per kilogram per day for 28 days. These, of course, are exceptional doses compared with what we propose for humans.

[Slide.]

With regard to a study commissioned by the World Health Organization, a 7-day artesunate toxicity study in rat largely designed on the basis of work previously done which had suggested neurotoxicity, designed that way in terms of dose and observation, no neurotoxicity was demonstrated over this range of human equivalent doses. Besides the small number of animals that died in their cage and could not immediately be preserved for autopsy, the brain stems of all the remaining animals were studied and stained with hemotoxinin and eosine and toluidine blue, primary stains for determining neurotoxicity, and were examined by an eminent neuropathologist previously mentioned, Dr. Antony Dayan, in the United Kingdom.
These stains showed no evidence of neurotoxicity.

[Slide.]

Repeat human artemisinin exposure has been

looked at by a number of investigators including Kissinger, Van Vugt, and they have tested in their clinical investigation, clinical neurological investigation--they have included audiometry, brain-stem-evoked potential and auditory-evoked response. This refers to patients in Viet Nam, 240 patients, compared with 108 matched controls.

With artemisinin, a cumulative exposure of artemisinin, median cumulative exposure of 168 milligrams per kilogram. In Thailand, 79 patients were compared with 79 matched controls with a mean cumulative exposure to artesunate of 39 milligrams per kilogram and no clinical or neurophysiological toxicity was identified in these patients.

These tests clearly enable one to evaluate function from frontal cortex through to cochlear nucleus and acoustic nerve.

[Slide.]

The work of Price and others based on 1,971 subjects over the age of five years, 307 of whom received artemether, 1,664 artesunate in artesunate doses of 12 milligrams per kilogram given over three to seven days and investigated clinically carefully by heel-to-toe ataxia, fine-finger dexterity, hearing and assessment for

nystagmus and balance, evaluated at these days from naught to 28 days after admission, showed no evidence clinically of deafness or permanent neurological disability.

[Slide.]

In a randomized, double-blind comparison of artemether and quinine in severe falciparum malaria in work reported by Dayan and Hien, full neurological assessment was done on 560 adults including audiometry and assessment of balance at discharge.

Now, in these patients, there were 36 deaths following artemether treatment and 47 following quinine. The total artemisinin exposure was 4 to 44 milligrams per kilogram which allowed 21 patients who died to come rapidly to autopsy. Of these patients, fifteen who died and who were examined in rapid autopsy, fifteen had received quinine and six artemether and they were compared blind by neuropathologists including those in the United States. There was no evidence of drug-induced neurotoxicity whatever.

[Slide.]

We have referred, and will refer further, to Study 013 which is a safety update conducted at

present in Bangladesh, Ghana, Tanzania, double-blinded, randomized and controlled, in which, of 3,366 patients, there has been a 99.3 percent follow up. Sixteen patients in this follow up had neurological sequelae.

[Slide.]

These were identified on schedule follow up over the period seven to thirty days after treatment. Now, of these sixteen patients, four had confirmed meningitis and we attributed the neurological effects of the meningitis. Six of the sixteen were unconscious at the time of enrollment and we might argue that they largely would be accounted for by cerebral malaria.

Four of the sixteen had focal neurological sequelae, quite uncharacteristic of the drug effect, and two of the sixteen, 0.05 percent of the 3,366, are, we believe, possibly attributable to artesunate. They have not been followed up in the long term. One had unsteady gait. One had generalized weakness and we would not be able to say which of these patients fell in the comparator arm and which in the treatment.

[Slide.]

In the largest study of its kind in the

comparison of artemether and quinine for deaths, if I may draw your attention to the overall result, artemether was on the borderline of being better in terms of preventing death than quinine at this level of significance, 0.08 in the comparison of 961 patients who had received artemether and 950 who had received quinine.

There was lower mortality in the artemether group, as the graphic indicates, but of borderline significance. The question is whether this lower mortality would translate to a higher level of neurological abnormality.

[Slide.]

Here is the examination of the neurological sequelae. In the artemether group, there were 81 of 807, in the quinine group, 91 of 765. The inference is that, with improved survival with artemether, there was no greater incidence, on the contrary, of neurological abnormalities.

[Slide.]

In conclusion, the World Health Organization, in developing this drug, accepts that there is a prima facie case based on experimental evidence of the possibility of the artemisinins as a class being neurotoxic. We point out that

artesunate never in clinical experience, regardless of the therapeutic regimens that have been used, has been neurotoxic in humans.

An expanded use of artesunate would require reconsideration about potential neurotoxicity, but we propose that this is not an issue in the circumstances in which we are to be using the drug.

The FDA may wish to consider with the applicant, the World Health Organization, the neurotoxicity potential in terms of labeling and that, of course, we would have no objection to.

Thank you.

DR. RELLER: Thank you, Professor Folb.

Professor Fred Binka.

DR. BINKA: Mr. Chairman, members of the advisory committee, the WHO has, in the past two presentations, presented its case on the efficacy and safety of rectal artesunate. But, in addition to that, WHO is committed to making sure that this drug is properly deployed if it is registered in a manner that would benefit the great number of people in endemic countries who need this drug most.

In doing this, it has made a firm

commitment to understand some of the crucial issues that need to be addressed in order to deploy these drugs and also has a commitment in trying to make sure that, if the drug is registered, it is properly implemented.

It is currently conducting studies, phase 4 studies, in three countries, in Ghana, Tanzania and Bangladesh, to try to understand some of the crucial issues that are involved. These studies have been alluded to by my previous colleagues. These studies are currently in these three countries. They are double-blind, placebo-controlled trials and they are recruiting patients that we expect this drug to be used for.

Most of these patients are patients who cannot take anything by mouth and have provided consent to be part of the trials. In these studies, the recruited patients are given a single dose of rectal artesunate, 100 milligram in children and 400 milligrams in adults.

They are followed up in hospital and expected to have consolidated treatment for malaria based on the national treatment guidelines. They are followed up for seven to thirty days to measure some of the potential outcomes. In these outcomes,

we are looking basically at survival and neurotoxicity.

[Slide.]

Professor Folb has already presented the issues on neurotoxicity and I am going to concentrate on the other major outcome which is mortality. The studies have recruited about 3,300 patients so far in the three countries, and the slide above shows the distribution in the three countries, approximately about 1,000 in Ghana and Tanzania and the remaining in Bangladesh.

[Slide.]

The characteristics of these patients partly have been shown to you but let me reemphasize who they represent, the target population for which this indication has been proposed. About 11 percent of these patients were unconscious at baseline at the time of recruitment and a proportion of these patients, almost 22 percent, have had repeated convulsions.

I think Professor White has already alluded to the fact that, in these cases, these are community-based trials where enrollment is basically based on being not able to take things orally. 74 percent of these patients have

demonstrated a positive slide for malaria.

The follow up has been very remarkable. 99.3 percent of these patients have been followed up over the period from seven to thirty days prior to recruitment into the trial. So far, the study has recorded 99 deaths.

[Slide.]

The distribution of these deaths is shown in the slide above. I think it is important to know that approximately half of the patients who died were unconscious at the time of recruitment into the study. Also, to demonstrate this indication and the need to work very hard in trying to make sure we have something to help these patients, 87 percent of these patients died even before they reached hospital. A further 43 percent died in hospital. The rest, about 20 percent, died at home after leaving hospital.

[Slide.]

These studies are being closely monitored by the Data and Safety Monitoring Committee. Their plan was to recruit close to about 10,000 patients. The analysis of review of this data in April of this year, the committee basically agreed that there was no reason for the study to be unblinded

or the protocol to be modified.

So these studies are ongoing and we hope that they will provide a large body mass of information on the safety of rectal artesunate.

[Slide.]

This is not the only commitment. The WHO is committed to a plan of implementation if this drug is registered. Basically, there are several crucial issues that need to be addressed. It is committed to a controlled, phased introduction and deployment of this drug in five countries to appropriately understand how we can reach those who need these drugs most.

This controlled phased deployment will include extensive work in trying to train mothers, health workers and, in this case, in these settings, traditional healers to whom most of these cases ascend when they present with these conditions. These training programs and communication programs will ensure the correct use of this drug and also to make sure that patients are provided or are encouraged to have consolidated treatment after the emergency phase.

WHO is also committed to establishing postmarket registration surveillance to continue to

monitor the safety of this drug as it is implemented.

I think these two phases show a commitment not to just register drug and just leave it on the shelves but to make sure that this drug, after it is registered, is properly used for the indication for which we are asking the committee to review the dossier.

I will spend the last few minutes to remind you of the true situation in which these patients in which this drug will be used and the population for which we seek the registration.

[Slide.]

I think you have heard already about the burden, but let me remind you that these mothers who are sitting here with their kids, most of them might not see those kids live to age of five years in most malaria-endemic countries. So they are looking very bright and nice today, but the chances of losing these kids are very great.

Not only that, even if they die, most of them, nobody will know that they are dead.

[Slide.]

Most of these children die at home. Over 90 percent of the cases with malaria die at home

and very few are seen in health facilities, just under 8 percent. I think this is the challenge we face in trying to control this disease.

[Slide.]

Not only that, when these people are sick, all these children are sick, most of them will be sent to traditional healers for any kind of disease at all. If you see the brown slide here, in this pie, about 24 percent of children are sent to traditional healers. But when it involves acute febrile illness, the percentage gets bigger. It is about 27 percent. It gets even bigger when we are talking about acute febrile illness with seizures where almost half of these kids will see a traditional healer for treatment.

[Slide.]

That is not the only problem. The major problem that these people face is that they really have a problem with geographical access to healthcare. Most people live several distances away from a health facility. In a district in Ghana, a huge part of the population live over 10 kilometers away from a health facility. We will say, "Well, that is just 10 kilometers." But the problem is how do they get there.

[Slide.]

The best means of transport would be on a bicycle in most cases if they are fortunate. Unfortunately for them, if it is in the rainy season where malaria occurs most of the time, there might not be even roads.

[Slide.]

They might have a child who is having a serious condition like this and the whole place is flooded in the seasons where malaria is most common. So you can see the problems that these people have and the challenges that they face in trying to get care for their kids.

[Slide.]

I think I want to reemphasize the issue related to the fact that this is a disease that deteriorates rapidly. In a study in Bangladesh, 73 percent of these children under six were found to deteriorate quickly to severe malaria and about 83 percent within 48 hours. So this is a disease that has really grave consequences if there is no immediate intervention.

But if most of these people get to health facilities, what kind of infrastructure do you have?

[Slide.]

In my district, in northern Ghana, with a population of 160,000 people, we have a district hospital and maybe there will be only one doctor, three health centers. You can see the mass of traditional healers, 240. So, obviously, these are the people who will provide the services.

If you go to the facilities, those who get there form the bulk of the work that the health workers are tasked to try and deal with. Malaria is the major problem.

[Slide.]

Over half of these patients are outpatients with cases of malaria and half of the patients on the pediatric wards are certainly cases of severe malaria. I think this gives you a true picture of what is happening in these parts of the world.

Having said that, I think, in the last couple of years, there has been a concerted effort to try to deal with the burden of malaria. It is really a joy to see that we are increasing the tools that we can have to treat this disease.

[Slide.]

In the last couple of years, the World

Health Organization has endorsed full management of malaria as one of the key strategies to try and reduce the burden of malaria. There are several tools in trying to help the families in villages like this to address this problem. First, and the cardinal one, is prompt diagnosis and treatment. Invariably, we think mothers and people in the community can diagnose this disease early.

There is also a big push to try and look at the preventive measures of malaria both in infancy and in pregnancy and also the use of insecticide-treated bed nets to protect against malaria.

We look forward to including another tool which is rectal artesunate to prevent death in cases where we have severe malaria. If we are to do this effectively, we think there will be a big prize at the end of the day.

[Slide.]

Happy little children in endemic countries. Thank you very much.

DR. GOMES: Mr. Chairman, members of the advisory committee, this concludes our presentation and we would be prepared to answer questions.

DR. RELLER: Thank you, Dr. Gomes.

Dr. Bell?

DR. BELL: I want to commend the speakers for their very nice presentations and for the hard work that they are doing to address this terrible problem of malaria. My question is a rather basic one that has little to do with the scientific issues involved.

Malaria is a terrible problem overseas. The artemisinins in all their forms, intravenous, oral, rectal are widely available overseas. In some respects, therefore, I find the discussion we are having this morning to be a little strange. The indication that is being sought for approval by FDA in the United States is a very limited one to address a problem that does not exist in the United States.

We don't have babies who die of malaria before they can get to the hospital. What we do have are concerns about drug resistance that we would, perhaps, like to have this drug available to treat when they do get to medical care. We don't have to worry. We have facilities to give it intravenously but it would require, presumably, repeated dosing.

I guess my question is the FDA has

regulatory authority in the United States where this drug is not available. The FDA is being asked to approve the drug for single-dose rectal--to address a problem that doesn't exist in the United States. I guess I am wondering why that is. There must be some very clear reason that FDA approval is being sought for this indication that would only be applicable outside the areas of FDA jurisdiction.

Could you explain that please?

DR. GOMES: I will provide an initial comment on behalf of WHO but then I would like Nick White, perhaps, to take the nearest microphone and comment in terms of the indication as it applies or would potentially apply within the United States.

We are clearly here with a concern for a public-health issue that is global, not necessarily limited or of wider relevance within the United States. This is a group of compounds which, essentially, have not been taken to registration for the purpose between ten. So we took this submission of a dossier to the regulatory authorities that would have the highest level of review as a global health organization, ourselves.

So our purpose here is actually for the infants and children that are in malaria-endemic

countries but we do believe that this has an implication for the United States. I would like perhaps Nick White to comment on that in more detail.

PROFESSOR WHITE: The currently recommended treatment for severe falciparum malaria in the United States is quinidine gluconate. That was introduced following studies that we did in Thailand because the previously available treatment, quinine, was provided from the Centers for Disease Control and there were undue delays in getting the quinine out to the various parts of the United States where people returned and presented with severe malaria.

So quinidine became the treatment because essentially because of its availability. I will very briefly show you that.

[Slide.]

Quinidine is not a safe drug. It is very difficult to use. It has a very narrow therapeutic ratio. It requires intensive-care monitoring certainly which is available, as you quite rightly say. I think there are serious concerns over the dosage.

[Slide.]

This is the basis for your current recommendation, a study of fifteen patients, multicenter, multi-instance. It was a telephone-directed study from CDC. Only five of them received quinidine alone. Only two of those would have fulfilled WHO criteria for severe malaria. The other ten got quinidine plus exchange transfusion. The three deaths were associated with low blood concentrations.

[Slide.]

This was the original study we did in Thailand with a much higher dose, much higher blood concentrations.

[Slide.]

We don't actually know what the therapeutic range is for quinidine but, by extrapolation from quinine and the available evidence would suggest that the currently recommended dose is relatively low. But that is not my main point.

[Slide.]

My main point is that quinidine is increasingly unavailable. It is no longer widely used as an antiarrhythmic drug. Therefore, it is not stocked in pharmacies. Therefore, there are

delays and that now approximates the indication we are talking about. I think that there is a genuine possibility, if you are admitted in, I don't know, in Nebraska or Nevada or somewhere like that, your hospital would not have quinidine and there would be a delay, a potential lethal delay, instituting treatment. So I think there would be a strong case for each pharmacy having in their refrigerator ten artesunate rectal formulations.

DR. RAMIREZ: May I answer his question?

DR. RELLER: Professor White, if you could stay close for a moment, there will be at least one more question.

Dr. Ramirez?

DR. RAMIREZ: Just to give you my point of view. Even though at the University of Louisville, in Kentucky, we have our Claver Clinic. During the years, I have seen, I would say, several families, all missionaries, that have been in the middle of Ghana, in the middle of Columbia, but mostly in Africa and I have been treating some of the--usually the fathers with malaria.

But they are in areas that they are 10 kilometers from the medical center. This may apply to some American children. When I came here, the

only children that I can see that are going to be in the bush at 10 kilometers from healthcare are going to be children of missionaries.

Sometimes, people look at the FDA to say, "If it is approved by the FDA, I am going to give it to my family." If it is not approved, they have some questions. I don't see that any military is going to be--because, wherever there is the military, there is medical care. But I can see children of missionaries.

If you want to make a case, you want to see American children that may need this drug--at least, if the FDA has any other considerations. I also had your questions before coming to this meeting. That was my only answer, if there was any other issue if we need to address.

DR. RELLER: Dr. Patterson.

DR. PATTERSON: Just to echo Dr. White's comments about I.V. quinidine, we recently had a case at our medical center of a returning traveler with severe malaria who had ventricular tachycardia, was put on amiodarone and really couldn't take I.V. quinidine and had to be treated with exchange transfusion. So it would have been much easier to give them rectal artesunate. So I

think there are cases where we would use it in the United States.

DR. RELLER: Dr. Bell, when the Epidemic Intelligence Service offices are dispatched to the far corners of the earth, Peace Corps workers, et cetera--Dr. Albrecht mentioned this earlier--what is currently in their kits for therapy until reaching appropriate medical care? I would like anyone who wants to comment on that and then I would pose the same question to Dr. White, what role, if any, might this be for those groups.

DR. BELL: Perhaps Dr. Parise knows the question about the Peace Corps, the answer to that.

DR. PARISE: What currently, as far as my understanding of the Peace Corps, they have is a drug for self-treatment. In most cases, that is Fansidar. In areas where there is Fansidar resistance, it would be malarone, I believe. But there is not any rectal or other--I mean, that would be for people who can take oral. That would be for people who can take oral.

PROFESSOR WHITE: So, did you say malarone?

DR. PARISE: I believe. What we are recommending here at CDC is that, in the areas

where there is too much Fasidar resistance like the Amazon, Southeast Asia and parts of East Africa is that people should take malarone as self-treatment. I believe Peace Corps is echoing that.

DR. RELLER: We will let Professor White comment on this when we get all of those comments together. I ask, in particular, because of these issues, because of resistance to some of these agents that was pointed out earlier.

Dr. Archer and then we will hear Professor White.

DR. ARCHER: Actually, I have a question for Dr. Binka but maybe Dr. White can answer if you know the results of the study. In the operational studies that were conducted, so far, that are ongoing, one of the questions is the problem of misdiagnosis of malaria when, in fact, the patients that are severely ill have something else.

How many patients who were unconscious who had severe malaria in the operational study had another infection like meningitis or typhoid? Do you know those data?

DR. BINKA: There are four cases of meningitis out of the 3,000 that were confirmed.

DR. ARCHER: Were those initially

diagnosed as malaria or were they recognized as bacterial meningitis?

DR. BINKA: The diagnosis was mainly for people getting the studies not on the basis of the diagnosis of malaria but the condition that they cannot take anything orally and they are febrile. So there it is not a diagnosis of malaria. It is a clinical diagnosis.

DR. ARCHER: So you really couldn't confirm.

DR. BINKA: Yes; in most of those situations, we don't confirm the diagnosis. We use the clinical diagnosis of malaria.

DR. GOMES: Can I just clarify that point? All of the children of patients who would have been non per os, which is the basic criteria for entry into the study, and likely to be the way in which it happens in reality, would have had a blood smear taken. It is not read and cannot be read at the time they are recruited. They would, following treatment, have been referred to a hospital. At the hospital level, a diagnosis would be made as to the attributable cause of the illness and, in four of those patients, there would be meningitis.

If your question is reaching to a broader

issue which is what is the probability that patients exposed to the drug would have another underlying cause of the disease, this is a general issue. Fred can probably answer this very well, but in malaria-endemic areas where you would have very high inoculation rates, there would be two coinfections. One would be acute respiratory infections and the other would be malaria.

Within the WHO, we had gone to a great deal of trouble to try to separate the two causes, both clinically and parasitologically. It is very difficult, even for a very trained pediatrician to separate the two courses. It is complicated by the fact that you may have acute respiratory infection but you will have parasites as well. But we are dealing essentially with the vast majority who would have malaria but may have another infection. They would be treated for malaria with this particular drug.

Some of them, however, a small proportion, might have meningitis. The issue before us would be that we don't have an alternative for the children that do have malaria and have parasites and for whom parasites would be on board in any case. The likely prospect would be that if you

give the drug, the patient would reach the hospital. If they hadn't responded, then the hospital would treat the patient such as in the case of the children that have meningitis. But the vast majority of the children would have malaria.

DR. ARCHER: Just one follow up while you are at the microphone. A question on the cerebral malaria and the possibility that cerebral malaria might mask neurotoxicity of this drug in some of the studies, is that a possibility? Is there enough overlap that you might have missed some of the toxicity?

PROFESSOR WHITE: It is very difficult to be absolutely categorical, but the neurotoxicity in the animals is irreversible. The studies of Professor Folb shown with artemether, I think, is the most illustrative because that is, by far, approximately six times more neurotoxic, intramuscular artemether. That is a very large database of evidence. Specifically, the studies we did in Viet Nam, which was a 600-patient study, about half of them receiving artemether, we looked very carefully for any of the tell-tale signs.

Every patient on discharge had audiometry and a full neurological examination. There wasn't

a hint of any of the aberrances that have seen in mice, rats, adults and monkeys. So I can't be absolutely categorical and say there isn't a transient effect, but it is not detectable.

Also, if you look at the--we do four hourly full neurological examinations in these patients. In the double-blinded study, there was absolutely no difference in the evolution of neurological symptomatology, signs and symptomatology, in target patients who received artemether and quinine, the only difference being slightly faster recovery in the patients who received artemether.

So there is no suggestion. But I can't be absolutely categorical.

DR. RELLER: What is known, if anything, about the interaction between those patients who have malaria and the neurotoxicity of these compounds? Are there any primate studies that address this of primate malaria with and without graded doses of artesunate?

PROFESSOR WHITE: I know there is somebody in the audience who knows a lot more about this than I do but there are studies going on at the moment. But, to my knowledge, there are not good

data to look at that interaction.

DR. RELLER: Before taking other questions, I would like to return to several that were related to your views on the potential role of rectal artesunate for therapy in groups apart from the recognized primary beneficiary, namely children in impoverished and rural distant areas away from healthcare, but the potential ancillary use in selected other populations, be it workers abroad from various backgrounds and for various roles.

PROFESSOR WHITE: I think that the artemisinin derivatives in whichever form you can get them are the drug to have if you are away from medical attention and you are ill because of the rapidity of action and the fact that you don't get vomiting and so on.

Now, the specific role of rectal artesunate hasn't been assessed as a standby treatment, but the oral drugs are widely used as standby treatments. I think they do have a very important role particularly in that group of people who are becoming sick.

If you can take malarone, for example, you have uncomplicated malaria, that's fine. There has never been a good population PK study with

malarone, interestingly. The one that was done didn't address severity. But if we borrow from data with mefloquine, which would be the alternative, it is quite clear that you malabsorb mefloquine in proportion to your disease severity. I would have grave concerns with malarone, a lipophilic drug, in somebody who is developing severe malaria. I think the absorption of that would be unpredictable.

It is an excellent antimalarial drug. It is effective against parasites throughout the world. But I would be concerned about taking that drug. So I think there is a specific benefit for these drugs in people who are becoming severely ill. While I am speaking, I don't think that that provides a resistance generator as some people have said. I think that the proportion of people involved is so small that it doesn't impinge on resistance.

But this is speculative and it has not been formally assessed.

DR. RELLER: Dr. Sumaya and then Dr. Cross.

DR. SUMAYA: My question relates back to the issue on a population studied in the intended

population for use. You had data, in some of the literature I was reading on this, on children but I was still unclear how many children under the age of five, for example, have been studied in the age brackets one, two, three, four and five. I'm sure you have that data but it wasn't presented. I think it would be very useful to have that, not only for efficacy but certainly for safety.

Secondly, related to that, outside of the U.S., presumably, in poor populations, transportation problems, rural areas, who is the intended prescriber? Who would be the intended prescriber of this rectal suppository? Would this be the traditional worker? Would this be, as you had a slide on home management, somebody within the family, or would it be in a more clinical setting?

DR. GOMES: In relation to your first comment, we do have an age breakdown of the patients. One of the trials is in Bangladesh where the majority of people who are exposed to malaria happen to be adults. So a large proportion of what you saw in the 3,366, from just that study, would be adults.

But, on the African continent, because of the studies in Tanzania and Ghana, we are finding

that a significant proportion of the people who are recruited into these trials in the real-life situation tend to be under 24 months.

The irony of the development of this drug is we wanted to be able to do the initial work in conditions in which we could manage the patients very carefully and, therefore, we obviously did all the phase-3 studies and the phase-2 studies in hospitals. The inclusion criteria were very broad. They were six months upwards. But, clearly, the patients that we saw in the hospital-based studies in terms of age don't represent what happens in the community in terms of age.

I think it was Fred Binka that stated that many of the children die and you may never see them in the statistics. So, what we find in the community-based studies in this one that has been referred to is we see a much younger population than we ever see in hospitals. So, although we are not asking for registration for children below 24 months because we have very few that we have studied and, therefore, have been submitted in the dossier, we are, therefore, asking for registration for children above 24 months.

We have in place--we have had to produce a

smaller dosage form for children under 24 months and we have in place studies that would address this issue for the age, the pediatric age, under 24 months.

But, since your question was phrased what proportion, I just want to tell you that, in reality, what happens is we get a much younger population that has never before been described.

If you want further details on the age breakdown, we can provide them, but we would be able to provide them, perhaps, later.

DR. RELLER: Dr. Cross?

DR. CROSS: You showed us neurotoxicity data in mice and rats. I am just wondering whether any of those studies have included a different range of ages of those animals; for example, have you looked at the potential neurotoxicity in very young or newborn rodents or, as a measure of its potential, have you even looked at its potential effect on the developing nervous system in experimental animals?

PROFESSOR WHITE: While Professor Folb is coming to the microphone, I will mention about the pregnancy experience. In Thailand, we don't have such multidrug-resistant parasites that we are

forced to use these derivatives in pregnancy having no alternatives.

If you can show that.

[Slide.]

We basically prospectively followed up all the children born to women who were exposed at any stage in their pregnancy to an artemisinin derivative with a standardized and validated full neurological assessment at birth and developmental milestones. The bottom line is we may not be able to find it in time, but there is absolutely no evidence of any difference between those children and the other children.

I can say that in experiments that we did in mice, we did not specifically address young mice.

PROFESSOR FOLB: We don't have the experimental data on very young rodents or other experimental animals. We are not in a position to answer that part of your question.

[Slide.]

We can draw on human experience, in particular the work of Dr. McGready and colleagues. Here is a study of pregnancy outcomes in women treated with artemisinin compared with those not

treated with artemisinin, compared with the community in general. You will note that the incidence of spontaneous abortion, stillbirth, congenital abnormality, gestational age at delivery and low birth weight do not appear to be meaningfully different. That is the best source of information on which we can draw to give you some assurance about the safety of the unborn child.

DR. RELLER: Dr. Ramirez?

DR. RAMIREZ: Some questions regarding the drug, itself, because my interpretation seems to be that this will be the mother or the traditional healer giving this drug to a child. I imagine that you have to distribute this drug almost to all households to have the drug available. What do we know about the stability of the drug and what do we know about--do we have an expiration time?

Also, this concept of 10 milligrams per kilogram, and then you have to have suppositories for different milligrams, that this is going to be extremely difficult for a mother to figure out, at four years old. I don't know if you even know the weight or the kilograms.

DR. GOMES: I realize that we have not completed our response because you had asked who,

in fact, would be prescribing or making the drugs available. So it is a good point. Our approach, the onset, to it is that we have not formulated exactly how it would be delivered. In the conditions in which we are doing the work, it is what we refer to as Study 013 and the operational studies, these are given by field workers.

This would be the basic indication for delivery of the drug, would be that the child cannot, or the patient cannot, take drugs by mouth. There are several ways in which they are assessed in terms of suspected malaria during the malaria season, and so forth. In those trials, we have an age group. The majority of patients, as I said, have essentially come below the age of five. In those cases, when we have only one suppository now that is for pediatric use which is 100 milligram, the children that are recruited, we gave one suppository and it averages at 10 milligrams per kilogram if you are above 9 or 8 kilograms and below the age of two years.

So either if you have a weight or age, you can work within that group to get the dosing around 10 milligrams per kilogram. But we would like to become much more accurate, particularly for the

younger child. So, as I refered to earlier, we would like to include a 50 milligram suppository that includes the age range from about three months to about a year old so that they have a much more targeted dose that is given to that age group.

DR. RELLER: Do you have any issues to maintain this drug at room temperature--

DR. GOMES: Not so far. In terms of the stability, no. We have taken a great deal of advice from the review team of the Food and Drug Administration in terms of the packaging that we must make the drug available. Our intention is to have at least a two-year stability for the tropical conditions that we, of course, have in mind.

So we have put the drug in that packaging for that period of time to be able to examine the conditions. We are talking about, of course, conditions that are not only hot but humid at the time the drug would be used.

DR. RELLER: Dr. Shapiro?

DR. SHAPIRO: I had two points. The first one is that the artemisinins are arguably the only class of antimalarials we have for which there are not drug-resistant parasites recognized. I can't think of a better scenario for selecting

drug-resistant parasites than to give a subtherapeutic dose of a single agent to people with immature immune responses who are teeming with parasites. To me, that is the ideal recipe for selecting resistant parasites.

The second point is human nature being what it is, if one is treated for malaria and has symptomatic improvement, the incentive for getting in the boat and getting to the healthcare center is very much reduced. If people can't get there when the child is dying, they are certainly not going to get there when the child is better.

So it would seem that this temporizing measure perhaps may provide time for people to get to the hospital but, perhaps, will prevent people from going to the hospital and may result in just repeated doses whenever the parasitemia rises above a threshold of concern.

That scenario plays into both the issue of resistance and the issue of safety; that is to say, repeated subtherapeutic doses.

PROFESSOR WHITE: I quite agree with you. You are quite right. This is the ideal way to induce resistance. Therefore, it is incumbent on us to try and do everything we can to educate

people on the need to provide an adequate treatment. I think I will ask Fred to speak to that, but our approach is, as Fred explained, an integrated approach. But you are quite right. It is a major concern.

DR. BINKA: I think you are quite right. This is a major concern to everybody but the direction now is to try and make sure that when drugs are developed, they are developed in such a way that we take into consideration those who are going to use them. There is an increasing push to try and make sure that we can package these drugs, like in the previous question, and make sure that the mothers can differentiate between the different weights and the amount of drug they have to give them.

So, if they are packaged and labeled appropriately, showing whether a very young child or a middle-aged child, the mothers are able to read these pictures and are able to use this appropriately. This has been ongoing. In fact, currently, the regular antimalarial drugs that are prescribed in most of the countries, WHO is seriously advising countries to package these drugs in such a way that illiterate mothers can

appropriately decide on the dose that is supposed to be given and to appropriately administer the drugs.

So, yes; these are some of the issues why the plan is to have a phased implementation and to address some of these issues that are truly there. But I think this can be overcome.

DR. RELLER: There will be much time for discussion this afternoon so, because we are at the time of our break, we will take brief questions from Dr. Patterson, Dr. Bell and then that's it for before the FDA presentation and our break.

Dr. Patterson?

DR. PATTERSON: The briefing document indicates that the drug is metabolized by the liver. In the clinical studies or in clinical experience, is there any evidence of hepatotoxicity and should the drug be adjusted in patients with liver disease?

PROFESSOR WHITE: That is a good question. Artesunate is very readily hydrolyzed in neutral pH to the dihydroartemisinin which is the main biologically active metabolite. And then the main route of elimination of the dihydro appears to glucuronidation which is impaired in liver

dysfunction.

We have looked at--we have got pharmacokinetic data which are not published and you have not before you and, therefore, I can't really comment, but I can tell you that there isn't a relationship between liver dysfunction, per se. But there is certainly a relationship between overall disease severity measured in terms of metabolic acidosis, renal impairment and so forth and reduced clearance.

But the inter-individual variability actually is greater. So the intrinsic inter-individual variability in pharmacokinetics is greater in the disease effect on contraction volume and distribution and reduction and clearance.

Finally, we haven't found any side effects so we haven't got any side effects to relate to anything.

DR. RELLER: Dr. Bell?

DR. BELL: I would like to ask the presenters if they could to expand their comments on the safety and efficacy of repeated dosing. Again, I am trying to think of the problems we face in the United States and how this drug is actually likely to be used.

I attend, sometimes, on the pediatric infectious-disease service at Emory University. I take the point about the difficulties in acquiring quinine. In my experience, we do have a rare case of cerebral malaria but it is much more common to get a sick infant who is febrile, anemic and we don't know the drug-resistance profile of the parasite.

I suspect the principal advantage here is going to be that there is very low resistance so far to the artemisinins and so it is likely that this drug will be given once, followed by clinical improvement. Then, the question is going to be, "Then what?" I suspect there will be almost irresistible pressures for repeated off-label dosing because you can't argue with success.

You have clinical improvement. What is your experience with this in the field in terms of its safety and efficacy? When do you switch to what? I know this isn't the indication that is being sought but, realistically, this is the problem that we have in the United States and this is how it is likely to be used.

So, could you talk a little bit more about the hazards to the extent of what is known about

repeated dosing and how would you use this? What would you switch to and when?

PROFESSOR WHITE: First the benefits and then the risks. I actually think that the benefit is the rapidity of action. That is so apparent to the consumers in endemic areas that there have been tremendous problems with fake drugs. So, basically, you get better a day quicker, go back to work, back to school, a day quicker than any other drug. So that, to me, is their great benefit.

Certainly, the fact that you don't have to think about resistance is an advantage but I think, operationally, it is the rapidity of the action.

What do you do next? This drug is to stop the person dying. They then have to have a full course of antimalarial treatment, whatever the national recommended program, whatever is available. What do we do? In Thailand, where we have multidrug-resistant malaria, we continue with oral artemisinin in combination with Mithracin. It is whatever you have available, but it must be a full course of treatment. Otherwise we are going to return to the scenario of selecting for resistance. Outside endemic areas, resistance selection is not an issue but, in practice, you

give the full course of treatment.

Repeated treatment, well, that is what people will get. That is what everybody has in endemic areas because of the frequency of infection. But, as Professor Folb has shown, we haven't been able to show any adverse effects associated with that, either in terms of toxicity or induction of resistance.

DR. RELLER: Thanks to the WHO and the committee members for a rigorous discussion. We will return in fifteen minutes at twenty minutes before the hour of 11:00 to hear the FDA presentation.

[Break.]

DR. RELLER: Dr. Leonard Sacks will begin the FDA's presentation of rectal artesunate.

FDA Presentation

DR. SACKS: Good morning.

[Slide.]

I am Leonard Sacks. I am a medical officer in the Division of Special Pathogens. What I will be doing during the next half hour or so is reviewing the clinical efficacy of rectal artesunate as evidenced in this submission.

[Slide.]

Before progressing, I just want to acknowledge the excellent help from the rest of my colleagues in the review team and several other members of the Division who are not listed on the slide.

[Slide.]

I am going to spend a short time recapping some of the background information which, at this point, has been very adequately covered by the previous presenters.

[Slide.]

Just a word about the rationale for product development. I think it has been adequately addressed that malaria carries a very high mortality, especially in children. This is largely due to delays in effective therapy. Malaria patients are often unable to take orally and this may be the result of cerebral involvement. It may be the result of the fact that many of these patients are vomiting.

Finally, parenteral therapy is not available in the bush.

[Slide.]

The goal of a the applicant, in this application, was to develop an effective

antimalarial that can be administered rectally that serves as an emergency treatment until definitive therapy can be reached and, finally, that decreases malaria mortality and morbidity.

[Slide.]

The indication, as provided by the applicant--I will read it out to you. We have covered it in previous slides. The indication is for the initial management of acute malaria in patients who cannot take medication by mouth and for whom parenteral treatment is not available. In the label, there is additional information suggesting that treatment with rectal artesunate must be supplemented and/or followed by effective oral or parenteral drug therapy for malaria as soon as possible.

[Slide.]

The product that was chosen to satisfy these objectives was rectal artesunate. The question is whether this is a suitable candidate. This is just a brief recap of some of the issues in favor and against the product. Artesunate is an artemisinin derivative. We know that artemisinin products are very potent antimalarials. They have been used with a lot of success in areas of

drug-sensitive and drug-resistant P. falciparum malaria.

The downside is that they have a short half life. They have been associated with recrudescences of infection and they carry the potential for some neurotoxicity.

[Slide.]

I want to digress briefly and just to make a few remarks about the clinical pharmacology of rectal artesunate. Artesunate, as we have heard earlier, is rapidly biometabolized to dihydroartemisinin. Dihydroartemisinin is also an active agent against P. falciparum.

When we look at the pharmacokinetics of these products in healthy volunteers, given a single 400-milligram dose, the Tmax for both products is somewhere between 2.5 and 3.5 hours. The Cmax for the parent compound and for the principal metabolites is similar. Note that the elimination half-life is less than three hours for both of these moieties.

[Slide.]

In the course of the product development, the formulation that was used in the clinical trials and the formulation that is to be marketed

were different.

[Slide.]

Attempts were made to establish the bioequivalence between the formulation in clinical trials and the formulation to be marketed. A bioequivalence study, Study 009 in the submission, was performed in healthy volunteers. This study failed to satisfy the regulatory requirements for bioequivalence.

A couple of comments on the results of this study. First of all, the point estimates of the area under the curve and for the Cmax for the clinical-trials product and the to-be-marketed product were similar. But the problem was that the 90 percent confidence intervals around these point estimates were too wide for the regulatory requirements.

This was partly ascribed to the fact that there was variability due to difficulties, technical difficulties, in the measurement of both artesunate and dihydro artemisinin in plasma. There was a wide range of inter- and intrasubject variability both in absorption, distribution, m metabolism and elimination. Finally, given all these variables, the study left adequate power to

demonstrate tighter confidence intervals.

To address these concerns, the applicant performed an equivalence study with clinical endpoints, Study 014 in the submission. This was performed in malaria patients. This study showed similar parasite clearance of 24 hours in patients treated with the product used in clinical trials and in patients treated with the product to be marketed.

[Slide.]

In taking all these issues into account, we addressed the totality of the data. We were aware and cognizant of the technical difficulties and the intrasubject variability in the measurement of bioequivalence study. We took into account the satisfactory clinical perforation of the to-be-marketed product in Study 014 and we viewed this in the context of its potential use for a life-threatening illness where really no alternative therapy is available in that particular setting.

[Slide.]

To return to our theme of efficacy, the applicant was faced with the challenge to develop appropriate clinical studies. The underlying

scientific question was as follows: prior to a definitive treatment, is the emergency use of a single dose of rectal artesunate more effective than no treatment in reducing malaria morbidity and mortality.

[Slide.]

To address this question, there were several practical challenges. I am going to go through a couple of them. Firstly, given the high mortality from untreated malaria and the dangers of delaying effective therapy, treatment cannot be clinically withheld for the first 24 hours if effective therapy is available.

So, it was for these reasons that the clinical trials submitted in this NDA have employed active comparators. In the studies in this NDA, provisions are made for the rescue of patients showing an unsatisfactory clinical or parasitological response. We should bear in mind that, while these studies do not directly address the advantages of rectal artesunate over no treatment, they do give a relative idea of the efficacy versus the standard of care.

I have added a point here about Study 013 which was mentioned earlier. This is a trial which

is currently underway to investigate the product under conditions that more closely reflect the intended use. This trial has not been submitted to the FDA and will not be reviewed as part of this efficacy overview.

[Slide.]

There are other problems in modeling the projected use. I have listed them in two columns here. Firstly, in the clinical studies in this NDA, most of the participants in the trials lived in malaria-endemic areas and they had some degree of malaria immunity. We anticipate that, in projected use, this may be used in U.S. travelers, in U.S. military recruits, in Peace Corps participants as well as in residents of malaria-endemic areas. So there is likely to be a spectrum of malaria immunity in the projected use.

In the clinical studies, the diagnosis was confirmed on smear before entry into any of the regimens whereas the diagnosis will not be confirmed before treatment in the field. There were entry criteria in the clinical studies which determined that patients coming into study were diagnosed with moderately severe malaria whereas we anticipate that all degrees of severity will be

seen in the clinical setting.

Patients were hospitalized in all the clinical trials and they will not be hospitalized in the clinical setting at least until they get to definitive care.

[Slide.]

Ancillary treatment was provided to all patients in the clinical studies as needed. This may have included fluids, glucose, anticonvulsants and antipyretics whereas clearly ancillary treatment in the field will not be available.

Suppository retention was supervised in these studies whereas retention may be supervised in the field depending on the abilities and the cooperation of family members. Patients failing on parasitological grounds in these studies were rescued with other antimalarial therapy whereas no rescue would be available during emergency therapy in the field.

Finally, definitive therapy was provided to all study participants at 24 hours whereas, in the field, we anticipate that access to definitive treatment will depend on the local infrastructure.

[Slide.]

There was also another question in the

selection of suitable endpoints. The first problem is although the object is to reduce mortality, mortality is really not a realistic endpoint because deaths are very rare in patients with moderately severe malaria who are properly treated. So we have been left with a number of alternative endpoints to consider. I have listed the most important of these.

Firstly, the response in the degree of parasitemia after drug therapy. Second of all, clinical responses to drug therapy. Finally, an overall evaluation of the success of the regimen in terms of recrudescence rates.

[Slide.]

I am going to move on now to review some of the studies of efficacy in NDA 21-242 in a little bit more detail.

[Slide.]

This is just a quick overview of the studies which were regarded as supportive of clinical efficacy. There were three studies which we designated pivotal studies, 005, 006 and 007. These were comparative, randomized and unblinded studies and they employed the projected dose of the drug for the first 24 hours given alone.

There was a bioequivalence study which we have spoken of a little earlier, 014, which compared three formulations of rectal artesunate used in the projected dosing regimen.

[Slide.]

There were two other supportive studies which were primarily biopharmaceutical studies, or pharmacokinetics studies, 003 and 004. These were crossover dose-escalation studies comparing rectal and intravenous artesunate given sequentially over periods of twelve hours.

Finally, there were a couple of additional studies which were previously published and reanalyzed by the sponsor, Studies 010, 011 and 012. These studies employed twice the recommended dose and they did not, in our view, support the efficacy of the projected dose. I will not review these further.

[Slide.]

This is an overview of the three pivotal studies, the first performed in Thailand, 005, the second in Malawi, 006 and the third in South Africa, 007. As you can see, in the experimental arm, the regimen was the same in all three studies. All patients received a single dose, 10 milligrams

per kilogram, approximately, of rectal artesunate given alone for the first 24 hours of therapy.

The comparator, in the case of the Thai study, was oral artesunate, again given as a single dose for the first 24 hours. In the Malawian and South African study, the comparator was three doses of quinine given parenterally over the first 24 hours.

After the first 24 hours, a consolidation regimen was given, or definitive therapy, was given in each of the three studies. Notice that in the Thai study, the consolidation regimen incorporated several sequential doses of oral artesunate plus two doses of mefloquine. In the Malawian study, the follow-up therapy was a single oral dose of sulfadoxine/pyrimethamine. Parenteral quinine could be given if patients were not yet able to take orally, and the same effectively applied in the South African study where the consolidation therapy was oral sulfadoxine/pyrimethamine given as a single dose.

[Slide.]

In this next slide, I want to mention some comments on the study drugs. First of all, quinine, which, as you may remember, was the

comparator used in the Malawian and the South African studies. Quinine is generally given as a course for seven days in the treatment of malaria. Most would regard 24 hours as inadequate on its own and almost certainly likely to result in recrudescences.

Sulfadoxine/pyrimethamine, which was the consolidation therapy used in the South African and Malawian studies, is a long-acting agent. It is given as a single dose. But sulfadoxine/pyrimethamine resistance is high and exceeds 60 percent in many parts of Africa.

[Slide.]

As far as mefloquine goes, mefloquine is a long-acting agent, has a very long half-life. It may be given as a single dose and it has been used very effectively together with artemisinins for the treatment of drug-resistant malaria in areas of the world where this is prevalent.

[Slide.]

This is just a brief overview of the inclusion and exclusion criteria, to give you some idea of the population in the clinical studies. The noteworthy points here are that in the Thai and the Malawian studies, children were recruited. In

the South African study, the recruited population were adults.

In two of the studies, there was a requirement for a minimal eligible parasitemia with P. falciparum, greater than 4 percent, approximately, in the Thai studies, greater than 0.4 percent in the Malawian study. There was no such criterion in the South African study.

There were some clinical criteria in two of these studies. In the South African and the Malawian study, patients had to be unable to eat or drink. As far as exclusion criteria go, for obvious practical reasons, diarrhea was an exclusion criteria. Previous antimalarials in the 24 hours before therapy were also an exclusion criterion.

Attempts were made to exclude patients with severe or complicated malaria based on the presence of the factors I have listed here; acidosis, severe anemia, jaundice, bleeding, shock, decreased consciousness, et cetera.

Patients were also excluded if they had excessive levels of parasitemia, either greater than 20 percent in the Thai study or greater than 10 percent in the South African and Malawian study.

I just want to mention before going on to the next slide that the South African study also incorporated another arm which attempted to look at patients with severe and complicated malaria. In this particular arm, all the patients were to be given quinine together with or without concurrent artesunate.

For this reason, the fact that all patients were treated with another effective antimalarial medication, we regarded this as not valid evidence of the efficacy of rectal artesunate alone, so I am not going to discuss that section of the study in any more detail other than to say that, among those complicated patients, there were three deaths that were probably due to malaria and they will be addressed later in the safety discussion presented a little bit later.

[Slide.]

The baseline characteristics of the study patients: first of all, study numbers. We see that there were 46 patients in the artesunate arm of the Thai study, 87 in the artesunate arm of the Malawian study. This was the biggest study. 27 in the South African. Comparator numbers were substantially smaller, 17 in the oral artesunate

arm of the Thai study, 22 in the quinine arm of the Malawi study and eight in the quinine arm of the South African study.

The mean age; children, again in the Thai study and the Malawian study, adults in the South African study, a slight preponderance of male patients across the board. Entry parasitemias, again, with P. falciparum in the artesunate arm. First of all, in the Thai study, entry parasitemias were the highest. These were the median counts, 245,000 in the artesunate arm, 376,000 in the comparator arm.

I have to add that these were statistically significantly different, the median, or at least the parasitemia, in the comparator arm was higher. Slightly lower parasite counts on entry in the Malawian study, 183,000 to 230,000. These were not significantly different and even lower counts in the South African study of 51,000 and 58,000.

I have included the platelet counts here just as an indication of the disease severity. Suffice it to say, there were no statistically significant differences between the arms in terms of the parasite in each of the three studies.

[Slide.]

I wanted to mention the criteria for rescue therapy within the first 24 hours. This was during the first 24 hours when rectal artesunate had been given alone. If the parasite density, after the first twelve hours of observation, had not fallen to below 60 percent of the baseline count, then patients were eligible, in some of the studies, for alternative antimalarial therapy.

If there was frank clinical deterioration with development or features with severe malaria or repeated convulsions or coma, patients were also eligible for rescue therapy. Rescue therapy was not equitably applied. In the Thai study, rescue was available to both arms. In the Malawian study, rescue therapy was only available to the rectal arm and not to the quinine arm. In the South African study, some form of rescue therapy was available to both arms.

[Slide.]

The primary endpoint defined by the World Health Organization was the fractional remaining parasite count at 24 hours. There were difficulties with this endpoint in terms of the ability to incorporate data from patients who were

rescued or had failed because, once they been rescued or once they had failed prior to the first 24 hours, some of the effect would have had to have been attributed to the rescue therapy.

So, on this basis, we derived a couple of other endpoints which we thought would best represent the clinical efficacy of the product. The first was the 24-hour clinical success rate. This referred to all treated patients who were evaluated after 24 hours on study drug, who had not received rescue therapy or alternative antimalarial therapy and who neither died nor deteriorated clinically since the baseline evaluation.

We then defined the 24-hour parasitological success rate as all 24-hour clinical successes, as referred to here, whose 24-hour parasite count was less than 10 percent of the baseline parasite count; effectively, those patients who had cleared 90 percent of their baseline parasitemia.

Finally, as an indication of the overall efficacy of the regimen, we looked at the 28-day recrudescence stroke reinfection rate. This referred to any patient who received study drug and was found to have a recurrence of parasitemia

between the time that there was stopped and Day 28.

[Slide.]

Just a synopsis of the important study-related events with an impact on the clinical results. Again, a recap of the number of patients enrolled. There were small numbers of exclusions in all three studies and these were based on technical difficulties, problems with a mistake in drug administration. As you see, there were five and three in the Thai arms, three and one in the Malawian arms and one in each of the South African arms.

In terms of the patients rescued for failing to reach 60 percent at baseline parasitemia within twelve hours, in the Thai study, there were seven patients in the rectal-artesunate arm, four in the comparator arm. In the Malawian study, three patients were rescued in the artesunate arm and, just to remind you, there were no provisions for rescue in the comparator arm among these 22 patients.

In the South African study, one patient rescued in the artesunate arm, two in the comparator arm. In terms of clinical deterioration, one patient was designated clinical

deterioration in the Thai study rectal-artesunate arm, four in the rectal-artesunate arm in the Malawian study and none in the South African study.

There was one death in all these three studies. The death occurred in the artesunate arm of the Thai study and it occurred in a three-year-old child who evidently was admitted ambulant to the study, was given rectal artesunate, showed a response in the parasitemic counts but was given rehydration, subsequently developed Type-O neutremia, mental deterioration. The death was ascribed to overhydration and not to malaria. That death will also be dealt with further in the safety study.

There were a couple of other sundry failures for reasons of expulsion of suppositories. That really covers the study-related events.

[Slide.]

What this slide shows are the 24-hour clinical success rates for each of the three pivotal studies. What you see here are 76 and 71 percent success rates in the Thai study where both arms, remember, were treated with artesunate, rectally in the yellow bar, orally in the blue bar. 24-hour clinical success in the Malawian study was

91 percent in the rectal arm and 100 percent in the quinine arm. Bear in mind that there was no provision for rescue in this arm and, in fact, had rescue been implemented for patients failing to reach 60 percent of the baseline parasitemia at twelve hours, the success rate in this arm would have been 14 percent.

In the South African study, again, 96 percent clinical success rate, 24 hours in the artesunate arm, 75 percent in the quinine arm. Between all these arms, there were no statistically significant differences.

When we look at the 24-hour parasitological success rates, we see the same figures for the Thai study where both arms were treated with artesunate rectal and oral. When we look at the Malawian study, there is a very impressive difference between the 24-hour parasitological results, 88 percent success rate according to the defined criteria for the rectal-artesunate arm and only 14 percent success rate in the Malawian arm. A similar picture in the South African study where, bear in mind, the numbers of patients were very much smaller. For example, there were only eight patients in the

comparator arm here.

The point really is that again this illustrates the very rapid decline in parasitemia that we can attribute to artesunate.

[Slide.]

The next slide shows the 28-day recrudescence rates for each of these studies. Now, this slide refers to blood smears that are positive within the follow-up period from the end of therapy to 28 days. For those of you who have a briefing package, you will notice that there is a difference in the figures for the South African recrudescence rate. That is because those reflected in the briefing document show the results of PCR analysis where this is restricted to smear-positivity. I will go into that in a little bit more detail.

Suffice it to say that, in the Thai study where the consolidation regimen incorporated repeated doses of artesunate plus mefloquine, there were no recrudescences on blood smear. However, in the Malawian study, there was an enormous rate of recrudescence in both arms but significantly higher in the rectal-artesunate arm. Almost half the patients had a recrudescence of a positive smear

within the 28 days of follow up. 23 percent of those treated with quinine in the initial 24 hours had recurrence of positive smear. Very high recrudescence rates.

Bear in mind that, in this study, a single dose of sulfadoxine/pyrimethamine was used as the consolidation therapy and also, I guess, one should be cognizant of the fact that high rates of sulfadoxine/pyrimethamine resistance are prevalent in Africa. So the geographic location may have some impact on this result.

In the South African study, among the 27 patients in the artesunate arm, there was only one patient who had a smear-confirmed recrudescence or reinfection. There were none in the quinine arm.

Just to complete the thought on patients with PCR-detected recrudescences, in this particular study, there were a couple of patients who presented during the follow-up period with clinical symptoms and PCRs were performed on these patients. There were two in each arm which were found to be PCR-positive. But these were not confirmed on smear owing to the fact that we really haven't established the validity of PCR diagnostics. In this setting, I have really

confined the analysis to those who are smear-positive.

[Slide.]

What can we conclude from these three pivotal studies? First of all, at 24 hours, the clinical success rates for rectal artesunate are similar to those seen with oral artesunate or quinine. Secondly, at 24 hours, the parasite clearance is significantly more rapid with rectal artesunate than with quinine.

In terms of recrudescence, by Day 28, recrudescence rates are high when sulfadoxine/pyrimethamine was used as definitive therapy and recrudescence rates may be higher in artesunate-treated patients than in quinine-treated patients. Again, this may depend on the geographic location.

[Slide.]

What can we not conclude from the pivotal studies? First of all, we cannot conclude that we have adequately characterized the impact of rectal artesunate on malaria mortality. Secondly, we cannot conclude that the same result will be seen in the field where hospitalization, supportive therapy and laboratory diagnostics are unavailable.

[Slide.]

I want to raise a couple of other sources of data from some of the supportive studies. This is the equivalence study with clinical endpoints, Study 014, which aimed to compare the efficacy of the product used in the clinical studies with two formulations of the product to be marketed.

[Slide.]

The next slide shows the study regimens. In this study, all patients in the study were given a single rectal artesunate dose of 400 milligrams, one of the three preparations. The follow-up treatment in this study was oral artesunate given daily for three days and two doses of mefloquine.

[Slide.]

The study populations; the study was performed in Thai hospitalized adult patients. The patients were diagnosed with uncomplicated moderately severe malaria and there were 23 patients in each of the three arms.

[Slide.]

The 24-hour clinical success rate in this study was 100 percent for all of the arms. None of the patients were given rescue therapy. In terms of the parasitological outcome in this study, this

was the clinical product and these were the two products to be marketed. These were the admission parasitemias, somewhere between 30,000 and 47,000 on admission.

Within twelve hours, a rapid fall, which we see with most artemisinin products, somewhere between 3,000 and 13,000. By 24 hours, effectively the parasites were below 100 in all three arms. At 48 hours, they were virtually undetectable recognizing that, by this stage, consolidation therapy had already been given, so, again, showing a rapid decline for all three arms with effective elimination by 24 hours.

[Slide.]

In terms of recrudescence, or new infections in the study, unfortunately, this is data that we do not have. Data was not collected beyond seven days in these patients.

[Slide.]

So our conclusions on Study 014; this study showed equivalent efficacy of the three formulations in the 24-hour parasite clearance. The study also served to demonstrate the noncomparative efficacy of rectal artesunate given alone for the first 24 hours to 69 adult patients

with moderately severe uncomplicated malaria.

Among these 69 patients, none were judged by the study physicians to require rescue therapy or made an uneventful clinical and parasitological recovery. But, of course, the outcome beyond seven days in these patients in terms of recrudescence or new infection is not known.

[Slide.]

Just a brief comment on Studies 003 and 004. These were pharmacokinetic studies. They were crossover studies between rectal and intravenous artesunate given at two different dosing strength. The patient population; again, patients with moderately severe uncomplicated malaria. 003 was performed in hospitalized Thai adults. 004 was performed in hospitalized Ghanaian children.

[Slide.]

These were the treatment arms. As you can see, in intravenous therapy given for the first twelve hours followed by rectal artesunate, 10 milligrams per kilogram in this arm. This was the reverse; rectal artesunate, 10 milligrams per kilogram followed, after twelve hours, by intravenous. In these two arms, intravenous

followed by a double-dose of rectal and double dose of rectal followed by intravenous after twelve hours. Approximately twelve patients per arm. This arm was not represented in the Ghana study.

[Slide.]

Consolidation therapy in this study, in the Thai Study 003. Mefloquine was used at 36 and 48 hours. In the Ghana study, chloroquine was used over the first three days although a proportion of patients unable to tolerate chloroquine was given sulfadoxine/pyrimethamine.

[Slide.]

The next slide shows the inclusion criteria. The Thai study was conducted in adults. The Ghana study was conducted in children. Entry parasitemia; the minimum parasitemia for entry in the Thai study was high, was greater than 100,000 per microliter. In the Ghana study, it was substantially lower, greater than 10,000. Patients were non per os. Patients with severe or complicated malaria were excluded. Patients with diarrhea were excluded.

[Slide.]

The 24-hour clinical success rate was high in all the arms, twelve out of twelve in the

intravenous followed by projected dose of rectal, 23 out of 24 in the reverse. In the double-dose rectal, 22 out of 23, 22 out of 24.

I have just made a note that it was these two patients that were diagnosed with clinical deterioration whereas the failures in these two arms were for reasons of inability to retain the suppository or to receive intravenous therapy. So there were two clinical failures across the four arms of the studies.

[Slide.]

The parasitological success rates; more than 90 percent clearance at baseline parasitological at twelve and 24 hours. We looked at two endpoints here. The 90 percent clearance at twelve hours was low but, by 24 hours, a very large percentage of all treatment arms had achieved 90 percent clearance, eight out of twelve, 21 out of 23, 20 out of 22 and 21 out of 23.

[Slide.]

In terms of recurrent parasitological during the two to three weeks following therapy, I have pooled the two studies and divided them according to the consolidation regimen they received. What this shows is that recrudescence

rates were clearly highest in the patients who had chloroquine as consolidation therapy, 30 product of the 23 patients. They were lowest in the patients who received mefloquine, 15 percent, seven of the 48, and they were intermediate in the patients who received sulfadoxine/pyrimethamine, 22 percent.

[Slide.]

What did we learn from Studies 003 and 004? Well, first of all, there was no clinical advantage in using 20 milligrams per kilogram of rectal instead of 10 milligrams per kilogram of rectal. We saw a confirmation of the rapid reductions in parasitological with artesunate. The other thing to note is that, despite the twelve hourly regimen in these studies, recrudescence rates were still high.

[Slide.]

So, in summary, among the 229 evaluable patients with moderately severe malaria treated with 10 milligrams per kilogram of rectal artesunate over the first 24 hours, we saw one death which was probably due to fluid overload. The 24-hour clinical success rates were similar to comparator. The 24-hour parasitological success rates were superior to the comparator and the

28-day recrudescence rates ranged between 0 and 45 percent for the rectal-artesunate arms and from 0 to 25 percent for the comparator arms, bearing in mind that follow-up rates were rather low, and we will address this further.

[Slide.]

Some considerations which I wanted to raise were, first of all, delays in therapy are one of the most important contributors to malaria mortality. Given the potent effect on parasitemia and the good short-term clinical perforation of rectal artesunate, does this imply that it will reduce malaria mortality? Second of all, are there any potential hazards in the empirical use of rectal artesunate for emergency treatment?

[Slide.]

I just want to finish off by drawing your attention to some statistical issues. First of all, in the evaluation of these studies, there are difficulties in interpreting the parasitological responses based on the fact that patients were rescued before the 24-hour endpoint. Second of all, due to significant losses in follow up at later time points, the recrudescence rates that we calculated may be inaccurate.

To help us out with these, I am going to turn over the podium to my colleague, the statistical reviewer on the review team, Ruthanna Davi. She will discuss the statistical implications of these problems.

Thank you.

MS. DAVI: Thank you, Dr. Sacks.

[Slide.]

As Dr. Sacks told you, I intend to discuss the interpretation of the parasite-count measurements in light of the rescue of subjects.

[Slide.]

Secondly, I would like to address the issue of the recrudescence rates that we are seeing in the artesunate arm in light of some of the missing data in lost-to-follow-up. Finally, I will present an exploratory analysis looking for any other risk factors that may be predictive of recrudescence.

[Slide.]

Let's start by looking at the parasite-count endpoint. You have seen, so far, that artesunate-treated subjects seem to experience a significant decrease in parasite counts from the 0 to 12-hour time point. I first want to motivate

you to look at this endpoint rather than the clinical or parasitological success type endpoints that we have seen so far which are dichotomous endpoints giving a response of success or failure.

The parasitological endpoint, however, is a numerical endpoint allowing a continuum of responses and therefore allowing statistically more chance of seeing a difference between treatment arms.

In considering the parasite-count analyses, though, we have problems with the rescue subjects. To handle that, we will consider three cases. First, we will consider the case where we exclude subjects who were rescued. This is problematic, however, because this would exclude subjects who were doing poorly and the resulting analysis would, therefore, look at the success of the successes.

The second possibility is that we could agree on some method for imputation of the data beyond the point at which subjects were rescued. Again, this is a biased analysis because we would be considering data that would was not actually observed.

Finally, we could ignore the fact that

subjects were rescued and look at their actual observed parasite counts, but this analysis would have the problem of attributing the efficacy of the rescue therapy to the randomly assigned treatment.

The truth about this endpoint probably lies somewhere between these three analyses.

[Slide.]

I want to start with presenting Study 007 to you. You will notice I am doing these studies in reverse numerical order. That is not to confuse you. That is merely because there were a smaller number of subjects in Study 007 and it is advantageous to see the plots with a smaller number of subjects first.

This is the South African study. What is displayed in the top plot is one line per subject illustrating the parasite count across time for artesunate-treated subjects. So, on the X axis, we have the time variable from zero, twelve to 24 hours. On the Y axis, the parasite-count response.

Here you will see a rapid decline in parasitemia from zero to twelve hours and that continuing, then, from twelve to 24 hours. The plot below that is the similar plot for the quinine subjects. Again, there is a decline in parasitemia

from zero to twelve hours but, perhaps, not so rapid as that observed in the artesunate group.

If we add, now, the rescued subjects, plotting their observed parasite counts, ignoring the fact that they were rescued, we can see that it would not, in all likelihood, make a substantial impact on the analysis of that data being that there is only one rescued artesunate subject and two rescued quinine subjects. I intend to quantify that statement later in the presentation.

Finally, I would like to show you one last presentation of the data and that is including the rescued subjects as what we refer to as last observation carried forward meaning that, at the point at which they were rescued, we took that observation and carried it forward through the rest of the trial.

So, since they were rescued at twelve hours, their twelve-hour measurement was carried through to the 24-hour time point.

[Slide.]

If we continue, then, to Study 006, these plots are a little harder to look at because of the number of subjects, but the same trend is evident. This is a Malawi study and we see a rapid decrease

in parasitemia in the artesunate group from the zero to twelve-hour time point and that continuing from twelve to 24 hours.

There is, again, a decrease in the quinine group but not as rapid as that seen in the artesunate group. We quickly can illustrate the rescued subjects with their actual observed values. Again, remember subjects in the quinine group in this trial were not eligible for rescue so we make modifications only to the artesunate plot.

Finally, I will show you the results including these subjects as last observation carried forward.

[Slide.]

We will now go on to the Thailand study where the comparator arm is oral artesunate. We observed the same rapid decrease in parasitemia from zero to twelve hours and continuing from twelve to 24 hours in both the rectal and the oral artesunate plots.

We will illustrate now how the rescued subjects impact and this is with their actual observed values and finally with their last observation carried forward.

[Slide.]

At this point, I will show you the numerical results for what you have seen in the plots. These are median fractional remaining parasite counts at twelve and 24 hours. What we can see is that, in both Study 007 and 006, the median remaining fractional parasite count is statistically significantly lower for the rectal artesunate group than the quinine group. In Study 005 we observed no statistically significantly difference in that endpoint between oral and rectal artesunate.

Again, this is the analysis excluding patients who were rescued.

[Slide.]

Let's move now to the analysis where we include rescue patients with their observed values. You will notice there are not substantial differences in the qualitative conclusions. The statistical significance of the results remain. There is a statistically significant result in favor of rectal artesunate in both Studies 007 and 006 and no statistically significant difference between the oral and rectal artesunate in Study 005.

[Slide.]

Finally, just for completeness, let's consider the analysis where patients are--we use their last observation carried forward. The results are much the same. The statistically significance remains with only minor changes in the magnitude of the difference.

So I think, in conclusion, regarding the parasite count endpoint, you can feel comfortable that the data we are seeing is not an artifact of the rescued patients.

[Slide.]

Let's move now to an endpoint that is longer-term follow up, and that is recrudescence with artesunate. As Dr. Sacks told you, we did observe a fairly high recrudescence rate in one of the studies and that is the motivation for the presentation of this.

Subjects' malaria status was assessed at seven, 14 and 28 days post-treatment in all three of the pivotal studies. After a positive result for malaria was found, that subject was given additional malaria treatment. Therefore, we are considering cumulative failure rates in this analysis being that, after another treatment is given, the results can no longer be applied to the

randomly assigned treatment.

Part of the challenge in examining this endpoint is that the follow up of these patients was quite difficult. The missing values, as you will see, were quite rampant. Again, I am going to consider three cases. The first will be where we consider missing values as success; in other words, they did not have malaria.

The second will be if we consider them failures; in other words, they were positive for malaria. The third case will be that we will ignore the missing values, not counting them in either the numerator or the denominator of the recrudescence rates.

[Slide.]

First, this is an overview of the recrudescence rates in each of the three studies. There were no, or very small, recrudescences observed in Studies 005 and 007 and, in contrast to that, Study 006 in Malawi, we observed a much higher recrudescence rate and much higher even in the rectal-artesunate arm than that which was observed in the quinine arm. This was our motivation for exploring the data in Study 006 further.

[Slide.]

If we continue, then, the results for Study 006 are displayed in this table at each of the time points assessed. In this analysis, we are considering missing observations a success.

At Day 7, we observed a 16 percent recrudescence rate in the rectal artesunate group and no recrudescences in the quinine group. Continuing to Day 14, there was a 29 percent recrudescence in the rectal artesunate group and a 9 percent recrudescence in the comparator group. Finally, by Day 28, the results you have already seen were evident, a 45 percent recrudescence in the rectal artesunate group and a 23 percent recrudescence in the quinine group.

[Slide.]

Let's move now to consider the missing observations of failure. Perhaps this is the least likely of the three cases that I will present to you. This analysis relies on the assumption that patients who did not return to their follow-up visit were positive for malaria. Here we see much higher recrudescence rates because of considering the missing data failures but we still see a discrepancy between the rectal-artesunate arm and

the quinine arm in terms of the recrudescence rates.

Continue, then, to the analysis where we ignore missing observations. This analysis makes the assumption that subjects who did not return for their follow-up visits would have similar recrudescence rates to those who did return for their follow-up visits.

Again, we see an early discrepancy between the arms in terms of recrudescence rates. At Day 7, there was a 16 percent recrudescence rate in the rectal-artesunate arm and no recrudescence in the comparator arm. Day 14, there was a 29 percent recrudescence rate for rectal artesunate, 9 percent for the comparator and, finally, 45 and 23 percent at Day 28.

[Slide.]

Having said that, we took one more approach to the analysis of this endpoint and considered a time-to-event-type response where we looked at the time to recrudescence. This analysis afforded us the luxury of considering missing data as censored data. We found that there was a statistically significant result, that recrudescence appeared earlier and more frequent in

the rectal artesunate group.

In that same type of analysis, we aimed to identify other covariates that might be impacting recrudescence rates. In particular, we were trying to see if there might be some imbalance in the treatment groups in some other covariate that was impacting the recrudescence rates and could explain the possible treatment effect that we were seeing.

We considered several demographic factors such as age and gender. We also considered numerous baseline disease-status endpoints such as baseline parasite count and baseline temperature. None of the endpoints we considered were found to be statistically significantly predictive of whether or not someone would recrudesce with the possible exception of the Blantyre coma score. However, the result was not statistically significant and this was an exploratory analysis of numerous variables.

[Slide.]

So, in summary, I would like to leave you with three thoughts. First, you can feel comfortable with the results of the parasite-count analysis because, regardless of how we handled the rescued patients, the results still were highly

statistically significant in favor of rectal artesunate

[Slide.]

The second point is that we did see statistically significantly earlier and more often recrudescence in the rectal-artesunate arm than in the quinine arm in Study 006. Finally, an exploratory analysis of that data did not reveal any other covariates that were important in the prediction of whether or not a patient would recrudesce.

At this point, I would like to introduce Dr. Johann-Liang who will address the safety review of rectal artesunate.

DR. JOHANN-LIANG: Good morning. It is a pleasure to address such a distinguished and global panel this morning.

[Slide.]

My task is to present the integrated safety assessment by the FDA of NDA 21-242, rectal artesunate.

[Slide.]

Once again, the proposed indication is single, 10 milligrams per kilogram dose of artesunate, rectal capsules, in the initial

management of acute malaria in patients who cannot take medication by mouth and for whom parenteral treatment is not available.

[Slide.]

As we go through this talk, please keep in mind the implications of the indication that is being proposed. These are, use in the field, use as empiric therapy. Patients with other severe febrile illnesses such as meningitis, pneumonia, bacteriemia, et cetera, will be exposed, use in patients with severe disease who are at least unable to take PO and use in mainly very young children.

[Slide.]

Three sets of information relevant to the safety evaluation of rectal artesunate was submitted to this NDA by the applicant. They are the WHO-sponsored studies consisting of thirteen study data and reports, the safety review of published and unpublished safety information on studies of artesunate derivatives and a summary of the data on artesunate injection presented to the Chinese regulatory authorities in 1989.

This was reviewed for the sake of completeness but will not be part of this talk. I

will go through an overview of these two safety submissions. I would also like to touch upon the issue, the important issue, of neurotoxicity.

[Slide.]

Let's start with the overview of the WHO-sponsored studies.

[Slide.]

The WHO-sponsored studies consist of a total of 501 patients, 435 with malaria and 319 of that 435 in clinical studies. I have broken out for you here the types of trials and the numbers of patients by disease severity populating those studies. So there were two bioavailability and two bioequivalency studies and then the six clinical studies, three in adults and three in pediatric, of which Studies 5, 6 and 7 were the three pivotal clinical studies that were presented to you in the efficacy evaluation.

There were 66 healthy volunteers, 344 moderately severe disease patients and 91 severe malaria patients making up this application. There were 166 children in total in this safety database all of whom had moderately severe disease. I want to point out that only eight patients out of this 166 were less than two years of age and only five

in this group of severe malaria patients were from the clinical studies.

[Slide.]

This table accounts for all the patients enrolled into the six WHO-sponsored clinical studies separated out by numbers in the adult and children. All six clinical studies were open-labeled. This table illustrates the lack of comparative control data in this application.

For adults, there were 153 patients, 148 with moderately severe disease and five with severe disease. Comparative statements are not possible for adults because, in the comparator group, there were only 14 patients and they were all categorized as having severe disease, all receiving I.V. quinine.

Comparative statements may be possible for the children which consisted of about 166 patients all categorized as moderately severe disease in the rectal-artesunate arm as compared to the comparator arm where there were 39 patients all, again, with moderately severe disease, 17 who received P.O. artesunate and 22 I.V. quinine.

[Slide.]

Looking at the comparative adverse-event

counts in children, the overall adverse events was 20 percent for the rectal-artesunate group versus 26 percent for the comparators. Looking at the adverse events by systems, the most common complaint was gastrointestinal consisting of nausea, vomiting, abdominal pain. The rates were similar in both groups.

Next, the CNS adverse events consisted of headaches, impaired consciousness and convulsions and the rates were again similar between the two groups. Also, to point out, the impaired consciousness or convulsion complaints was not attributed to the drug.

[Slide.]

Due to the noncomparative nature of the data in this application, plus the fact that patients received subsequent antimalarials shortly after the rectal artesunate and the difficulty in sorting out what is disease effect versus drug effect, definitive conclusions are hard to make about adverse events in the safety datasets.

Moving on to deaths on study, in total there were seven deaths across the thirteen studies. There was that one pediatric death that Dr. Sacks had pointed out earlier. This was a

three-year-old boy who received a rectal-artesunate dose of 11.5 milligrams per kilogram times 1. The site investigators and the WHO attributed the cause of death to iatrogenic water intoxication.

While in agreement with this conclusion as a plausible etiology, I want to point out that this little boy's dihdryoartemisinin, the serum levels at two hours and post hours were quite high, remembering that this boy died right after this four-hour time point.

I want to also show you the reference mean and the standard deviation for a similar age group taken from the Ghana children. So, what contribution, if any, did the high DHA level make in the demise of this child? I don't think we have that answer.

The three adult deaths in the clinical studies, and these are three deaths coming from the South African study, Study No. 007, were all in patients with severe malaria. The one death was an artesunate arm and the two other deaths were in the I.V. quinine arm. The WHO concluded these deaths were due to underlying malarial disease and we are in agreement with that.

The three additional studies are coming

from the reanalysis studies, Studies 010, 011 and 012. Actually, these three deaths were all from Study 010 and patients all had severe malaria.

The thing to point out about these deaths is that all three deaths occurred at a time point when these patients were cleared of their parasitemia. So the cause of death in these three patients were not determined.

[Slide.]

Laboratory monitoring was limited in the clinical studies of the WHO-sponsored program. Only one study, Study No. 003, had comprehensive labs recorded including CBC chemistry and LFTs. In the 250 patients with malaria who had hematocrits monitored, overall, there was a transient decrease at twelve to 24 hours with rise to baseline by Day 7 and normalization by Day 28.

Four the 48 patients monitored for liver-function changes in Study 003, there were three patients whose amino transferase levels rose to three times upper limit of normal after starting with normal baseline levels peaking at Day 7 to 14. It is possible that this lab abnormality may be drug effect.

Again, only one study, Study No. 003, had

EKG monitoring and no significant abnormalities were noted.

[Slide.]

The majority of patients in PK and clinical studies received one rectal-artesunate dose of 10 milligrams per kilogram with a range from 6.8 to 22.2. In the reanalysis studies, repeated rectal dosing over three to four days with mean doses between 25 to 32 milligrams per kilogram total dose occurred. So the maximum dose exposure for adults was 45.7 milligrams per kilogram total dose given over four days in eight divided doses.

The maximum exposure for children was 21.4 milligrams per kilogram. This was the exposure of seven days where one rectal dose was followed by multiple oral dosing. It occurred in Study No. 005.

[Slide.]

Some specifics to point out about special populations in this safety data. Only eight of the 166 children, again, were less than two years of age. Only six of the 153 adults in the clinical studies or 269 adults with malaria in total were older than 50 years of age. Neither renal nor hepatic-insufficient patients were specifically

studied. Pregnant patients were also not included in these studies. However, looking at what information is available from preclinical evidence or in the literature, the overall impression from the preclinical evidence is consistent findings of impaired fetal survival but no evidence of teratogenicity in the babies born following first trimester exposure to artemisinins in the animal studies.

From the clinical studies in the literature, there is no evidence of fetal injury or impairment of maternal health over and above the effects on reproductive health or malaria, itself.

[Slide.]

So, then, in summary, about the WHO-sponsored studies, this was a very small safety database. Studies were all open-labeled with multiple drugs and mainly noncomparative. It is hard to differentiate safety issues between disease and drug effect. Furthermore, safety assessment was not available for special populations, in particular the very young children.

The dose exposure was mainly one rectal dose around the 10 milligrams per kilogram dose. Overall, no unusual or serious pattern of adverse

events was identified but, again, minimal numbers were available for comparison. Overall, no unusual or serious laboratory abnormalities were reported but, again, monitoring was sparse.

The deaths on study were few but not all had clear etiology.

[Slide.]

Let's turn our attention now to a different set of safety submission. I would like to present an overview of the applicant's submission safety review of the published and unpublished clinical studies on artemisinin derivatives. Once again, highlighting as I go along, some issues that particularly relate to the implication of the proposed indications of the proposed indication.

Please also note that this safety submission did not contain any source data for the FDA to review. This was really a summary report by the applicant of the clinical experience to date with this class of compounds.

[Slide.]

151 published and eighteen unpublished studies were reviewed by the WHO and safety information was available on 130 studies consisting

of 13,639 patients. I have broken out for you how the applicant broke out the data of different study types. The numbers are quite impressive when you look at the comparative and randomized trials. There were 7,848 patients in this safety information.

However, with the implications of the proposed indication in mind, I want to draw your attention to the fact that when these same patients are recategorized by the level of disease severity, we get the following picture.

[Slide.]

On the left side is a pie figure showing artemisinin derivatives taken together. It is around 13,000 patients. The majority of patients included in this safety information were patients with uncomplicated malaria here in the yellow. The patients with moderate or severe malaria, the red and the little blue here, was really 16 percent, a much smaller percentage of the whole safety information.

A similar picture applies even when just the patients treated with artesunate, around 6,000 patients, are pieced out. The number of patients with moderate and severe malaria, again in the red

and this sliver in blue, is a much smaller percentage when compared to the uncomplicated malaria patients.

[Slide.]

The applicant makes several conclusions regarding adverse events from their safety review. For comparative studies, the safety review states that the most common adverse event in the order of less than 1 percent, were mild GI events like nausea, vomiting, diarrhea and abdominal pain.

For severe malaria patients, the applicant concluded that fewer incidents of hypoglycemia, skin reactions, tinnitus, dizziness, occurred as compared to quinine. For uncomplicated malaria patients, the conclusion was that less pruritus than chloroquine, less nausea, dizziness, tinnitus than quinine and less vomiting than mefloquine.

Again, it is important to keep in mind that this pooling of adverse events across many studies is quite problematic, especially in light of the fact that there were no source data reviewed either by the applicant or by the FDA.

[Slide.]

Laboratory abnormalities noted by the applicant in the order of 1 percent included

neutropenia, reticular cytopenia, eosinophilia, anemia, transaminitis, culture-negative pyuria, hemoglobinuria and a few cases of elevated bilirubin. EKG abnormalities in the order of 1 percent included bradycardia, prolongation of QT interval and a few cases of first-degree AV block, atrial extrasystoles and T-wave abnormalities.

[Slide.]

The vast majority of studies included in the safety review did not have neurological assessments. Of the available information, dizziness appears to be the most common adverse event. The paper by Price, et al., is the article that the applicant refers to largely for the clinical neurologic safety of artemisinin derivatives.

In keeping with what the implications of the indication that is being sought here, I want to point out that, in this particular clinical experience, patients with uncomplicated malaria were assessed. In the author's own words in the paper, neurological examination could be performed reliably only in patients greater than five years of age.

Dr. Folb, in his earlier presentation,

also pointed out two other papers in the more recent literature by Kissinger and Van Vugt from Viet Nam and Thailand. When you look at the age brackets and the neurological assessments that were done in those patients as well, I think there were only two patients for each of the papers that had children that were less than actually five years of age.

The human histopathology experience in all the safety information really is just six patients treated with artemether from Hien, et al., in Viet Nam. Here, the slides were looked at at autopsy and no neuronal necrosis was seen but chromatolysis was frequently seen.

[Slide.]

So, in summarizing the second safety submission, we agree with the applicant that this was a comprehensive effort to examine the available safety information on artemisinin derivatives. Relatively few side effects were noted overall and mainly mind and transient. No patterns of adverse events were seen.

For comparative studies, the safety review did not find that patients receiving artemisinin derivatives had an increase in adverse events over

comparators. In fact, the safety review concluded that artemisinin derivatives showed a better tolerability profile over comparators that are available.

Moreover, there was a lack of clinical evidence to suggest an association between the artemisian derivatives and increased neurotoxic adverse events, neurotoxic sequelae or death.

[Slide.]

What are some of the problems with the safety review? There are the obvious methodological deficiencies of pooling all different types of studies together, particularly in this case when the safety parameters examined may be a result of either drug or disease effect and the uncertainties of pooling adverse events across studies become magnified.

As I have pointed out, although the number of patients in the collective safety information appears to be large, the relevant assessments in relevant populations are not as large.

One other issue that is worth mentioning is the issue of the quality of the active ingredient. The application has pointed out that apart from two WHO-sponsored studies, the rest of

the safety data derived from studies which used artemisinin active ingredients not produced to good manufacturing practices and that this supports how remarkable the safety of artesunate is.

I would submit that this issue could be looked at in a different light. It is possible that the many years of actual-use safety that we have is based on drugs that contain subpotent content of active ingredient. Moreover, there is at least one article, if not more, in the literature that discusses the relative abundant use of counterfeit drugs which contains really no active ingredient.

[Slide.]

I would like to focus now on the important safety issue of neurotoxicity and spend a few minutes discussing what we do know at this point and what we do not know at this point.

As you have heard neurotoxicity is considered a class effect of artemisian derivatives in animals. Dose-related patterns of neuropathologies starting with chromatolysis, the necrosis of specific neurons in the brain stem of rats, monkeys, dogs and mice have been described with artemisinin, artemether, arteether and the

principal metabolite dihydroartemisinin.

[Slide.]

The conclusion from the WHO sponsor expert consultation by Professor Dayan, et al., stated that only limited information was available for artesunate but no neuronal necrosis was seen at 420 milligrams per kilogram IM or 200 milligrams per kilogram per day PO over five to seven days.

The applicant concluded in their briefing document that, for artesunate, a total of 210 to 300 milligrams per kilogram by I.V. or PO did not result in neurotoxicity. They further concluded that this is 21-fold to 30-fold greater than the proposed human dose and, thus, a wide margin of safety.

If we accept this dose of 212 to 300 milligrams per kilogram as the best available approximation for no adverse-effect level for artesunate, the body-surface-area convergent from the animal model to human equivalent dose would be 35 to 50 milligrams per kilogram which is only 3-fold to 5-fold greater than the proposed dose, giving us a small safety margin.

[Slide.]

If we take a more conservative approach to

the available preclinical evidence, the safety margin gets even more narrow. For artemether and arteether, Professor Dayan's expert review of the neuropathology materials concluded that the NOAEL for neurotoxicity in rats was 45 to 75 milligrams per kilogram.

This dose by body-surface-area conversion would translate to a human equivalent dose of 7.5 to 12.5 milligrams per kilogram parenterally. For artesunate, looking down the right side of this schema, the seven-day rat in the study in the WHO Committee Toxicology Program was not specifically targeted enough for the determination of neurotoxicity NOAEL.

Furthermore, there were unexplained death in one of 16 animals on Day 4 on the 75 milligrams per kilogram dose and two of 16 on Day 3 of 150 milligrams per kilogram dose. So, for the overall NOAEL, the human equivalent dose calculated from adjusting for body-surface area from this rat model is 12 and 25 milligrams per kilogram if we use the dose at which the unexplained deaths occurred.

This human equivalent dose is right around the proposed 10 milligrams per kilogram rectal dose not giving us any margin of safety.

[Slide.]

Having said all that for the preclinical evidence, what about neurotoxicity and clinical experience in humans? The WHO-sponsored studies contain neurological assessments in the three pivotal studies, Studies 5, 6 and 7, which gives 164 rectal-artesunate recipients out of the total safety database of 435 patients with malaria.

However, these data were problematic due to the many missing data, especially in young patients who could not be reliably assessed. Nevertheless, no pattern of neurologic abnormalities were identified. In the literature on the actual-usage experience regarding neurological safety, the applicant has stated that there is a large body of safety experience with artesunate.

Again, I point out to you that the actual safety information in patients with severe disease, especially the very young with severe disease who actually underwent systematic neurological assessment, is a very small percentage of the actual usage experience.

What about the highest doses used in humans? From the literature in adults, it was the

45.7 milligrams per kilogram given over three to four days in eight divided doses. For children, the highest dose found in the literature was 57 milligrams per kilogram given over three days in daily divided doses.

I just want to tell you that, for both of these experiences, the numbers are very small again, both less than 30 patients.

[Slide.]

In trying to put together our current collective knowledge about neurotoxicity, what do we know of the artemisinin compounds? We know that the neurotoxic lesion occurs in dose-dependent fashion in animal models and that the most neurotoxic substance from this group of compounds appears to be the major metabolite, the DHA.

So why are neurotoxic lesions seen more with the lipid-soluble artemether and arteether than the water-soluble artesunate when, actually, artesunate is converted to DHA the most. This is probably because the lipid-soluble agents artemether and arteether are eliminated more slowly than water-soluble compounds like artesunate and thus producing much longer periods of DHA activity.

Hence, the critical factor leading to

neurotoxicity appears to be sustained levels of DHA rather than peak levels.

[Slide.]

With that in mind, what about what we do not yet know and thus causes us concern regarding neurotoxicity. The safety margin from preclinical to clinical has not been determined yet for artesunate and may not be as wide. So, for now, one rectal dose of 10 milligrams per kilogram probably is okay but it is unclear with higher and repeated dosing.

We know that artesunate elimination is faster for I.V. over PO over rectal. So, with repeated dosing, could rectal formulation also act as a depot-type of compound like artemether and arteether causing sustained levels. Rats and dogs show damage to the olfactory and auditory nuclei whereas monkeys more to the vestibular nuclei.

What nuclei in humans? We don't yet know. We could be doing the wrong types of neurological assessments. Also, in the animal neurotoxicology studies, it has been all done in non-disease models. In humans with malarial disease, using artemisinins, could the tissue distribution of DHA to parasitized cells act as buffers routing the DHA

away from CSF and vulnerable neurons.

If this is a theoretical possibility, then could the empiric use in febrile children which includes children without malarial disease potentially result in high enough sustained levels of DHA in the CNS to cause toxicity?

[Slide.]

So, finally, starting to summarize our view of the integrated safety, I want to once again touch upon the gap in populations. In the NDA application which constitutes the WHO-sponsored studies, the studies were all done with hospitalized patients, all with proven malaria and mainly in patients with moderately severe disease and mainly in adults and older children.

The implications of the actual usage in the proposed indication would impact a very different population, those in the field with severe disease unable to take PO and mainly very young children receiving rectal artesunate as empiric therapy. This is a population we have very little information on, even in the large body of clinical experience, to draw upon for safety evaluation.

Could we make this link at this time?

[Slide.]

In the end, what we have to make is the benefit and risk balance assessment. The applicant has stated that artesunate has a highly favorable safety profile and that the number of adverse events are small and no consistent pattern of toxicity has been identified.

I have tried to highlight for you some of the uncertainties about safety, particularly the as-of-yet-unknown safety margin of neurotoxicity especially in the very young children and the as-of-yet-unknown safety parameters of the population implicated in the proposed indication.

[Slide.]

Given all that, we are mindful of the impact of the disease malaria due to the individual human suffering and to global public health. Based upon our collective current knowledge, the proposed rectal dose of 10 milligrams per kilogram for one dose we feel is within the safety limits.

However, uncertainties and concerns expand if higher doses or repeated dosing becomes an issue.

I thank you for your attention.

DR. RELLER: Dr. Albrecht?

DR. ALBRECHT: Thank you. As the last speaker of the morning, I intend to keep my remarks quite brief. While my slides are coming up, I just wanted to comment that I think now, having heard the presentations from this morning, you are familiar with the indication that the WHO is requesting.

[Slide.]

It is for the use of a single dose rectal-artesunate capsule in initial management of malaria.

[Slide.]

Having heard the presentations by the speakers, I think I would like to refer to some of the comments I made in the opening remarks and say we have now identified for you some of the difference in the populations that were studied.

[Slide.]

The patients that would receive this drug in the actual-use setting of the rural community compared to the patients who received these products in the hospital setting with available medical infrastructure.

[Slide.]

The differences in the age

representations. The certainty in the diagnosis in the study populations with some uncertainties possible in the actual-use patients as well as issues on timing of drug administration.

[Slide.]

I think we have now heard about the endpoints of the studies. There is convincing evidence of parasite-count reduction at 24 hours. The question is does that serve as an effective surrogate for clinical success and perhaps, as importantly, is that an appropriate surrogate for the desired endpoint of mortality reduction in these patients.

We have also seen the statistical difference in recrudescence, particularly in the Malawi studies at 28 days. What is the clinical significance of this finding and, importantly, what impact might this have on the emergence of resistance to the artemisinins?

[Slide.]

So I think what we would like you to think about is what is the impact of these differences, what is the significance and the possible limitations, how much of the available data can, in fact, be generalized to the proposed target

populations and how much probably needs additional investigation or, perhaps, studies.

Thank you.

DR. RELLER: Thank you, Dr. Albrecht. We will look forward to continuing our discussion before the questions are posed later in the afternoon.

It is eight minutes after 12:00 by my watch. Let's reconvene at 1:10 just over an hour from now. We will begin with the Open Public Hearing and a presentation from Swissmedic.

[Whereupon, at 12:08 p.m., the proceedings were recessed to be resumed at 1:10 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:15 p.m.]

DR. RELLER: Welcome back to today's committee meeting. We will begin the afternoon session with the Open Public Hearing. Our scheduled speaker is Dr. Kemmler from Swissmedic, the regulatory group for Switzerland.

Dr. Kemmler.

Open Public Hearing

DR. KEMMLER: Mr. Chairman, members of the advisory committee, ladies and gentlemen. First, I want to thank you that I have the opportunity to speak here to you.

[Slide.]

As you know, the artesunate rectal capsules are for this indication which has been mentioned several times now. This application is somewhat unusual in several ways because, first, the applicant is unusual, the WHO. Second, it is a little bit unusual that an application has been submitted to three regulatory agencies simultaneously, the FDA, the MCA from the United Kingdom and to Swissmedic, the Swiss regulatory authority.

There are several other unusual issues

which I will refer to in the next minutes and which give us some headaches for the decision.

[Slide.]

First, I want to show you what we have done in Swissmedic up to now or the time line which we adhered to. We received the submission in April, 2000. We had our first discussion in our advisory committee in November, 2000 and sent our first comments to the WHO in December, 2000.

That was also a little bit an unusual procedure because we agreed to make some kind of rolling review. Also, we knew at the time in April that the documentation would not be complete. We agreed to receive additional material and we got it in March and August, September of 2001 and the last one just last month.

We also obtained advice from external experts, from Swiss external experts, in tropical medicine, first in December, 2000 and the last one in January this year. We had, apart from the comments we sent to the WHO, discussions with the WHO and the last one was in December, last year.

[Slide.]

The main issues after our clinical evaluation which we have to consider are very

basic. To obtain an approval, a drug must provide more benefit than harm when used and there has to be a little bit of a distinction. Of course, it has to provide more benefit than harm when used as intended but, in addition, it should also have a positive benefit-risk relation when it is used in the actual setting; here, in this case, in the bush or in the field.

So we are aware of the fact, all of us are aware of the fact, that some extrapolation is always necessary. This extrapolation can normally be based on some recent experience.

[Slide.]

This is the normal cascade of the benefit/risk evaluations or the benefit/risk extrapolations. We assess the benefit/risk in the clinical trial, make some extrapolation to the target population and see the benefit/risk in the intended use. Then we have some experience on difference of intended versus actual use and can guess what the benefit/risk and actual use will be.

[Slide.]

So the usual situation is that from the clinical trial to the intended use that the clinical-trial population and administration

circumstances are not too different from the intended use. Then we have a quite good experience on the unlabeled use to be expected which I don't know if you are aware of that. It is sometimes rather important, maybe up to approximately 50 percent unlabeled use. But, in most cases, the indications of this unlabeled use are at least near the labeled use.

[Slide.]

For rectal artesunate, the situation is a little bit different. We have, from the Studies 005, 007 and 007, which are considered as pivotal studies, only a relatively small line of evidence to the intended use because the clinical-trial population and administration circumstances are very different from the intended use as you have heard already in the last presentation about the safety of rectal artesunate.

In addition, we have, in this case, very little experience on the unlabeled use to be expected. So this is clearly a little bit more problematic than the usual situation.

[Slide.]

In addition, we have one further problem which makes things even more complicated. We have

the pivotal studies of with Formulation 2 and intended use is with Formulation 3 and the actual use, of course, will also be with Formulation 3. The bioequivalence between these galenical formulations is not shown up to now.

[Slide.]

This is the situation already mentioned several times, Study 013 will drop in. At least I hope so.

[Slide.]

Study 013 is, at least as far as we know up to now, somewhere between the intended use and the actual use, maybe not directly between the two but somewhere in this field which comes near to the intended or the actual use.

[Slide.]

If we already knew what Study 013 could show us, then we would have also have one problem less because Study 013 is done with the Formulation 3 and bioequivalence would no longer be an issue. So, what do we know, or what is Study 013? It has been mentioned a little bit. I want just to repeat that.

[Slide.]

It is a placebo-controlled, randomized,

double-blind study and the projected enrollment was 10,000 patients of approximately, at least, the target population. This study, in contrast to the studies which have been submitted up to now, has very clear efficacy-related endpoints.

One caveat of this study was it should be halted by the independent monitoring committee if proved beyond reasonable doubt that rectal artesunate is indicated or contraindicated.

[Slide.]

This study is still ongoing and blinded and we know some data already through the 120-day safety update. Another 3,366 patients have been enrolled as of March 22, 2002. 56 percent of the patients in the African studies are age below twelve months. That relates, as has already been mentioned, to an intended use in children beginning with 24-months old.

We have 74 percent positive smears but, as also has already been mentioned, these 74 percent positive smears do not exclusively mean that all of these patients have fever from malaria but it could also be that they have a positive smear and the actual problem of their fever and their non per os status was another one. But, most probably, at

least more than half of the patients had malaria.

99 of these 3,356 patients have died. This is 2.9 percent, 4 percent of them children and 1 percent adults. We have at least four cases of bacterial meningitis as was also mentioned already. But this fact we have to keep in mind that it was a very low number of patients which have been investigated if they have bacterial meningitis, but laboratory analyses have been done.

[Slide.]

The monitoring committee did not stop the trial after 3,366 patients, after the second interim analysis which the monitoring committee had the unblinded data available which are not available to us, to the regulatory authorities, and not available to the WHO.

At least they did conclude that the study can go on. So the questions which arise then are is the advantage of using rectal artesunate as important as the results of the study which have been already submitted would suggest. After 3,300 patients, it is not clear whether rectal artesunate provides a real benefit or poses a special risk.

The second question relating to the 56 percent of patients in the African studies with an

age below twelve months and also to other issues is it inappropriate and possibly counter productive use, even in this clinical-trial situation so widespread that a possible beneficial effect of artesunate is diluted.

If the use in young children is so high even in this trial, is there any point in restricting treatment to those aged twelve months and over. This relates clearly also to safety issues because those children obviously will receive much higher doses on a milligrams per kilogram body weight basis than the patients we have had in the clinical trials, 005, 006, 007 and the other ones.

[Slide.]

Our current considerations are that we don't have any major concerns about toxicity if used as intended. If a single dose is given, even if it is given to an eight or six-month-old child, we don't have too many concerns because all we know up to now, the therapeutic margin is high.

But, of course, we have to have to keep in mind that, most probably, at least outside of the clinical-trial situation as it is in Study 013, for example if we assume that a mother has rectal

artesunate available for an adult with 400 milligrams and her little baby gets sick and she thinks that it may be malaria, given the situation we have already in Study 013, can we assume that she will not give the 400 milligrams to her baby, if it has helped especially, and the child becomes feverish again or the artesunate was not indicated because it has a fever of another origin, will she, perhaps, then use such a capsule again.

These are the things we don't know and are clearly the risks which are accompanied by this possibility of giving the rectal artesunate.

One other consideration; the bioequivalence of the clinical-trial formulation and the market formulation is not shown. But this, of course, is also an issue because of the relatively broad margin of rectal artesunate that it may be that this is less important even if we don't have Study 013 available. At least in the oral dosage, the maximum effect is already reached with 1.6 milligrams per kilogram and we can assume that at least even a single dose with 20 milligrams is not possible for the difference between the two galenical formulations

Even at doses, 20 milligrams was

tolerated, so it may be that this is less important given the overall picture of this application.

[Slide.]

Where we really do have concerns is about the benefit/risk relation in the actual use. I want to cite what our critics from the FDA have written in the briefing document. Patients in the field might get a false sense of security after rectal treatment and fail to present for definitive treatment or therapy and may use another capsule and still another.

This is especially difficult or, perhaps, a difficult situation if you consider that the diagnosis of malaria will, in a substantial part of the population, not be correct and they will be treated with artesunate for another febrile illness.

Perhaps it is even a little bit more complicated than in Study 013 because these are highly endemic countries where you have a high prevalence of malaria. But this may be a little bit different in other areas where the malaria makes only about 10 or 20 or 50 percent of all children which will be treated.

So we have still the question which we

have had already two years ago in our first assessment and the results, so far as we know up to now, of Study 013 only add a few more question marks to this question.

[Slide.]

What it not be wiser to wait for the results of Study 013 before taking a decision?

Thank you very much.

DR. RELLER: Are there any questions for Dr. Kemmler?

Dr. Kemmler, would you be willing to answer some queries from the committee?

Dr. Glod?

DR. GLODE: I just had two clarifications questions about the study design. I just wanted to confirm that the placebo is a true placebo. It is not a comparator; it is just a rectal suppository containing no active ingredient?

DR. KEMMLER: Yes; this is a placebo-controlled study.

DR. Glod: My second question was is the study design to be essentially done under what would be considered to be sort of real-life considerations so that distance and time to getting to a hospital is kind of what we would be thinking

about in the actual use of this, do you know, in those locations?

DR. KEMMLER: I didn't totally understand the question. This is a real-life situation. This is given--at least near a real-life situation. But, certainly, the representative of the WHO could answer that much clearer. As far as we understood, it is provided from a healthcare worker in the villages and then the child is transported to a healthcare facility.

DR. GLODE: With distance and time delays being sort of about what one might anticipate if this were used widely.

DR. KEMMLER: Yes.

DR. GLODE: Thank you.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: A point of clarification. On the bottom slide on Page 4, you state about your conclusions; is the inappropriate and possibly counterproductive use even in this trial so widespread that a possible beneficial effect of artesunate is diluted. Are you referring to the widespread use of counterfeit artesunate or are you talking about the misdiagnosis and, therefore, malaria only representing 20 percent of febrile

illnesses or something of that--

DR. KEMMLER: I assume that the product which is distributed in this study is the real drug and is not a counterfeit. I mean the unlabeled use, the use outside the indication which has been applied for.

DR. LEGGETT: So you are talking about the problem of diagnosis of malaria.

DR. KEMMLER: Yes.

DR. RELLER: Any other questions specifically for Dr. Kemmler? Dr. Bell?

DR. BELL: You probably said this and I apologize because I missed it, but artesunate given in the study, is it the single dose or is it repeated dose?

DR. KEMMLER: Single dose.

DR. ARCHER: Assuming that the study goes to completion and all 10,000 patients are enrolled, how long would you predict that it would take to finish the study, on the basis of how long it has taken so far?

DR. KEMMLER: You should ask a representative of the WHO.

DR. RELLER: With the questions specifically for Dr. Kemmler, I was going to--any

others? I think if someone from Dr. Gomes, others from the WHO, realizing this is an ongoing blinded study, No. 013, could you share with the committee what the design is and what the endpoints being monitored are and what the expected time table is.

DR. O'FALLON: Can I ask one more question? How is the drug being distributed "in the bush?" Who gets it? That isn't clear to me.

DR. RELLER: This is what I hope we will hear with the study design.

DR. O'FALLON: That is another thing I want to hear addressed.

DR. RELLER: Dr. Binka?

DR. BINKA: Thank you, Mr. Chairman. I will start with the last question first. The drug is being distributed within the communities by field workers that are recruited and working with the study. This provides the distribution of the drug and encourages the mothers to apply the drug. So the mothers insert the drug and it is supervised to make sure that the children do not expel the rectal artesunate.

So it is both a learning process for the mothers to be able to do that. This has been distributed within the community in the different

settings. There has been quite some innovation in the way this is done.

In Ghana, the distribution sometimes takes place at places where you have herbals. They refer these cases to the field workers. The field workers are working in close collaboration with the herbalist to whom people principally tend to refer these cases. So we are recruiting the patients from where we expect to find them. So that is the first one.

[Slide.]

The second one is to do with the design. As I alluded earlier on, this is a double-blind controlled trial. The study was designed in such a way that we were expecting to have approximately 10,000 patients as alluded in the previous presentation, but with an estimate of a mortality prevalence of about 5 percent.

You can see from what we have shown so far in the recruitment of 3,300 patients the mortality rate is about 3 percent.

[Slide.]

So, if you work out those figures already, we would expect that, to achieve the same level of difference that we expect, the original thinking

was to have a reduction from 5 percent to 3 percent.

That will quickly increase the numbers of patients that need to be recruited to be able to demonstrate a similar effect; I'm sure almost fourfold. So we have to keep that in mind because this is just looking at mortality as the major endpoint.

So we really have a problem with the low mortality rates that we are demonstrating now. That study will need to be largely expanded or to take a much longer time to be able to demonstrate the survival benefit.

I just wish to remind us that this study, in the way it was designed, was basically trying to look at some of the personal issues. I have just alluded to some of them, working with people who actually see these patients and see how we can work with them and to find the results and to look at a real-life situation and address the issues of survival and also of toxicity.

I am not sure this study will add greatly to some of the endpoints that were discussed today. We agree with the FDA in their submission that a selection of endpoints, especially mortality, is

not really appropriate in this setting and that the most likely alternative endpoints are looking at its effect on both response to parasitemia and also the clinical responses that we are measuring in this case. The mortality endpoint would be very, very difficult to demonstrate.

Study 013 will not provide additional information on these two endpoints. In some cases, we are not even taking initial blood slides so that we cannot compare the two.

Briefly, just to look at the indication for which we requested, that this drug should be used, then Study 013 definitely will not be adding additional information to what we have already presented.

DR. RELLER: Dr. Ebert?

DR. EBERT: Just to confirm what you said a minute ago, are you saying that--you said 74 percent of the patients were parasitemic so those samples are not always taken prior to therapy?

DR. BINKA: No. The bulk of most of these studies, I mean the bulk of the patients that were recruited initially were having a blood film and then given treatment, and they are referred to the clinical facility for the final treatment. We have

been trying to increase the numbers recently. At least in one location, some of the patients didn't have initial blood slides.

DR. RELLER: Dr. Archer?

DR. ARCHER: You basically said that, the mortality rate being 3 percent instead of 5 percent, that your 10,000 patient endpoint is no longer appropriate, that you would have to go to two or three times that many patients? Is that what you are saying?

DR. BINKA: What I am saying is that the initial thinking was that this mortality rate would be about 5 percent and the intention was possibly to reduce this to 2 percent. We were aware that this was an estimate and that the Data and Safety Monitoring Committee would review this very closely because nobody really knew what the estimates were.

Currently, from the number of patients that we recruited, you can see the mortality rate is about 3 percent. Obviously, if we needed to demonstrate the same level of effect, then we need to increase the study much more, three or four times.

DR. RELLER: Dr. Folb?

PROFESSOR FOLB: We need to deal with two

points of possible confusion in the last presentation, one relating to the discussion that has just happened. Study 013 will not address further the evidence of efficacy that we have presented and on which we are in agreement with the Food and Drug Administration.

Study 013 is designed with two principal objectives. A primary objective is to show that in the field this drug, the efficacy of which has been demonstrated, will translate to a reduction in mortality. Our papers and our datasheet do not suggest yet that there will be a reduction in mortality as a result of this intervention.

So we do not want the confusion that Study 013 simply adds to the body of evidence that we have brought before the FDA and this committee.

The second point I wish to make relates to the question of bioequivalence.

[Slide.]

I would like to share this slide which was referred to by the Food and Drug Administration. Our understanding is that we are no longer at issue with the Food and Drug Administration regarding bioequivalence, that we are in agreement. We had a formulation that needed to be upgraded for general

application once this medicine is approved.

Now, that is, we had to show that Formulation F2 is equivalent in activity to Formulation F3. At the start, I must say that the artesunate content, the active principal content and the excipients, are identical. This is not at issue. But the content is different.

We had the possibility of doing one of three things; the first was comparative dissolution. Clearly, that would not have impressed ourselves and certainly not yourselves. The second was to make a comparison of pharmacokinetics. We have already shown, and the Food and Drug Administration has drawn your attention to the fact that, for reasons that extend from the way this drug is assayed, the assay accuracy that is available to us, and the inherent variability amongst humans, pharmacokinetic comparison could not satisfactorily be made.

We predicted that at the outset and we confirmed it. We would need to do thousands, if not tens of thousands, of pharmacokinetic studies to show equivalence. We never proposed that that would be our evidence.

Pharmacoequivalence was demonstrated by

us, we submit, by looking at therapeutic equivalence of the two formulations. This study confirms it. In effect, regardless of the formulation, F2 or F3, we achieved, in this study, 99.7 percent parasite clearance. With the two formulations, they were identical in effect, parasite clearance of the two formulations when compared with patients with moderately severe malaria. That is the very patients who were the target of our study.

Mr. Chairman, and members of the committee, since this is likely to be the last time that I will have the opportunity of addressing you, I want to remind ourselves, the committee, that what we are hoping to achieve is what we have in common agreement with the Food and Drug Administration; that is, firstly, that intervention with this particular rectal artesunate in the dose that we propose substantially, reliably, predictably and virtually invariably reduces the parasite count over 24 hours to a point where it is either not detectable or is detectable by an order of magnitude less.

We have shown the evidence and we have argued the logic behind the idea that such parasite

response and such clinical response that attends it, as we have demonstrated, translates to meaningful clinical advantage. We could do hundreds, tens of hundreds, thousands of additional studies. But I do not believe, and I understand the FDA have not proposed otherwise--I do not believe that that will add to the picture that we have put before you of efficacy for this particular indication and in this particular dose.

With regard to toxicity, we appeal that the committee comes to the agreement, the joint agreement between the Food and Drug Administration and ourselves and even the Swiss authority that, in this dose, there is acceptable safety including neurotoxicity.

Thank you.

DR. RELLER: Dr. Archer?

DR. ARCHER: I am still seriously confused.

PROFESSOR FOLB: Sorry.

DR. ARCHER: If Study 013 shows that there is no difference in mortality between placebo and rectal artesunate, doesn't that defeat the purpose for giving rectal artesunate?

PROFESSOR FOLB: It means that we will not

be able to make the claim that clinical advantage demonstrated translates in the field to reduction in mortality. It, in no sense--

DR. ARCHER: But isn't that the only reason you are doing this is to decrease mortality?

PROFESSOR FOLB: No. Our reason for doing it is to intervene, to enable to the patient to get to hospital. We infer, and we hope--

DR. ARCHER: Without dying.

PROFESSOR FOLB: Without dying.

DR. ARCHER: That's mortality.

PROFESSOR FOLB: That's mortality. We want the patient to get to hospital, in a situation where there is no treatment available at the moment

DR. RELLER: Dr. Glod?

DR. GLODE: Could I ask, in Study 013, if, in a subset of patients, you are planning to look at secondary endpoints of clinical response and reduction of parasitemia because the valuable information, I think, to be gained that is not present now is the 56 percent of patients less than twelve months of age.

So I don't think we currently have the information on reduction of parasitemia and clinical response in that particular young age

group that would be relevant; is that correct?

PROFESSOR FOLB: We agree. We agree that our evidence does not answer your question about children under the age of two. The answer to your question about secondary objectives is that we have, indeed, one secondary objective and that is the safety, in particular the neurotoxicity. So this is a large simple study aimed, as quickly as possible, to come to the additional point that we would hope to prove that implementation in this way translates to reduction in mortality.

If we were not to demonstrate that, it in now way compromises the clinical evidence that we have put before you.

DR. RELLER: Dr. Patterson.

DR. PATTERSON: Could I ask Dr. Binka about Study 013. Do you think that maybe one of the reasons the mortality is lower than expected in the study is because there is a Hawthorne effect from the education of the field workers and the community in general about malaria and the importance of getting to the hospital?

DR. BINKA: Yes; I would agree with that. This is a disease that we all understand kills. The way that we have designed it is not the really

optimal way to design it. We are mindful of the fact that this disease kills. There is a lot of support for both those who are in the placebo group and the treatment group to get to the facility to get treatment.

Obviously, that creates a problem to try and--whatever estimate we are finding now is a clear underestimate of what we really would find if we were to design this in such a way that we maximize the design effect.

DR. RELLER: Dr. Bell and then Dr. Archer again.

DR. BELL: He has a quick follow up.

DR. RELLER: Gordon, go ahead.

DR. ARCHER: I just have a question. If this drug is approved at this time, would it compromise Study Trial 003 at all? That is, would rectal artesunate become so widely available that you couldn't do the study?

PROFESSOR FOLB: Rectal artesunate, if approved, is a product of the World Health Organization. We have made public advertisement and received a number of responses from countries where the implementation and further implementation, contingent on the results of Study

013, will be done in collaboration with governments, regulatory authorities, communities.

So we have planned--and we are not compromising on this--we have planned very strict release.

DR. RELLER: Dr. Bell?

DR. BELL: I want to come back again to the reasons that we would need this drug in the United States. I am a little confused. There are obviously decisions that have been made here about what type of indication to seek, to this agency and so on. But, again, we don't have people dying before they can get to hospital of malaria in the United States.

What we do have is the specter of multidrug-resistant malaria imported from overseas for which this would, at least for some strains such as now found in Southeast Asia, be potentially a lifesaving drugs because these strains are resistant to the other approved drugs that we have in the United States.

I am a little confused why resistance has not figured more prominently in this discussion as a reason for approval of the drug. Even overseas, the logistics of conducting the necessary trials

were more formidable than this one. But could somebody address the use of this drug for treatment of multidrug-resistant malaria that would presumably require multiple doses?

What experience is there in Thailand? Perhaps, Dr. White--we know that multidrug resistance is increasing in Latin America and Africa. My view is that the reason we would like to have this drug in the armamentarium in the United States, whether in this preparation of some other, is because of the specter of cases of imported resistant malaria.

Could somebody talk about the drug resistance issues.

PROFESSOR WHITE: Firstly, there are two parts to your question. One was the question of delay. I don't know whether things have changed but when the mortality of U.S. servicemen in the Viet Nam conflict for malaria was compared to those who were treated in Viet Nam and those who had malaria when they came back, I understand the mortality was significantly higher in the United States. This was attributed to late diagnosis.

So there is a delay, whether that delay is one of referral or diagnosis, and the result is

that a higher proportion of patients present with severe malaria.

In Thailand, as in much of Southeast Asia--as in the adjacent countries, the standard recommended treatment for multidrug-resistant falciparum malaria is a combination of oral artesunate--for uncomplicated disease is oral artesunate given for three days together with a split dose of mefloquine. And you don't have oral artesunate yet.

DR. BELL: We don't have any artesunate. If a person from your area of Thailand were to show up in a hospital in Atlanta, we would have trouble because we don't have any artesunate here. I think that is the issue that needs to be brought up as well.

PROFESSOR WHITE: To be fair, proguanil is effective against those multidrug-resistant parasites. I would like to say it wasn't and, therefore, you would have to use it.

DR. RELLER: There are two times for ample discussion on not only more about resistance but any other relevant issue after Dr. Goldberger's charge to the committee. For proper procedure, we thank Professor White for his comments that were

just made.

Dr. Kemmler spoke on behalf of Swissmedic at the Open Public Hearing. Are there any other members who wish to speak in the forum of the Open Public Hearing, not sponsor, not committee members, but from the public.

If not, the Open Public Hearing is closed. We will move to Dr. Mark Goldberger's charge to the committee and then Dr. Rotstein and others, we will open the discussion for any topic of relevance to the charge given us. Then there will be full and open discussion of all the relevant participants, a break, more discussion and then the vote on the questions posed to us.

Mark?

Charge to the Committee

DR. GOLDBERGER: What I will do is go through the questions, make some comments and try to emphasize some points that we particularly would like you to include as you discuss these questions and issues.

For the first question, the applicant has demonstrated the activity of artesunate by showing a decline in parasitemia over 24 hours--it is just important to emphasize that we have no disagreement

whatsoever to the fact that that has, in fact, been shown--and a 24-hour clinical outcome--we have no disagreement either with that.--similar to that seen with comparator drugs of hospitalized patients with moderately severe malaria.

Are these results sufficient to support the approval of artesunate as initial therapy in patients without other therapeutic alternatives. We have slightly modified the wording of the proposed indication from the WHO to, I think, reflect, at least from our perspective what, in fact, the actual indication would likely be.

In your discussion, please include the usefulness of parasitemia as a measure of efficacy. One thing to keep in mind is we believe that, if this drug were to be approved, it would be approved under the FDA's accelerated approval regulations which allow the use of surrogate endpoint.

Surrogate endpoints in the past have included mycobacteremia, CD4 count, viral load and this would yet be another example. Beyond the issue of accelerated approval requiring you to show a benefit over therapies that currently exist, one would also need to have some evidence, or at least a suggestion, that the surrogate is likely to

correlate with a longer-term, more durable benefit.

So one thing is we would like you to at least make some comment about what you think about parasitemia as a surrogate. We would also like you to talk about the importance of recrudescence rates at Day 28 and issues of understand therapy. I think that one of the things, when we look at a surrogate, we look at issues of what is the longer-term endpoint.

At a minimum, we think the longer-term endpoint, for instance, might be the status at Day 28; that is, whether the person has, in fact, been cured. That also raises the issue of how to integrate artesunate into more definitive therapy.

Some issues have been raised about increased rates of recrudescence. We don't know if those are geographic, if those are specific to certain treatment regimens, et cetera. These issues are potentially important in providing advice in product labeling to physicians who might be using the product as to how treatment should, for instance, be continued.

There is also the issue that has been touched upon several times of whether mortality is the definitive endpoint. That may certainly also

be the case. There have been some issues about whether a mortality difference can be shown. I think that is something you may want to comment on as well as to whether that needs to be required or whether showing ultimately that the Day 28 recrudescence rates can be made similar would be sufficient.

We will come back to the issue of how that might be shown in subsequent studies in a couple of minutes.

Finally, the issue of the differences in the study population and the intended-use population. There has been, obviously, already a lot of discussion about the point. From a purely U.S. perspective, it might appear that use within the United States, how the drug might, in fact, be used, might not, in fact, be that dissimilar to the way the drug was, in fact, studied in hospitalized patients.

People from the United States who go abroad, missionaries, Peace Corps workers, et cetera, obviously we be somewhat different than the way the drug was, in fact, studied to date in the studies that have been submitted to us. Obviously, there has been considerable discussion about the

issue of how the data that has been presented to date, how that population compares to the actual intended-use population that might occur in other countries, for instance.

I think that, at one level, it probably is important for you to think about your level of comfort as to the real intended-use population, in fact as stated by the WHO, and how comfortable you are that that represents a genuine population that has some degree of unmet need. You have heard a lot of discussion about Study 013. Study 013 may be one approach to looking at such a population but, as has been said, even Study 013 may not really duplicate what happens in even more remote settings.

If your answer to the above question is no, then we would like you to indicate what additional information would be required to demonstrate sufficient evidence of efficacy.

For the second question, is the safety information and safety profile of artesunate sufficient to support the approval of artesunate for use as initial therapy in patients without other therapeutic alternatives. In your discussion, please include the differences in the

clinical trial and the intended patient populations, addressing the potential risks and benefits in the empirical use of the product for emergency therapy.

Again, it is important to include, as has already been discussed, that patients without malaria will almost surely receive drug and there is a question as to whether patients who get the drug might be more likely to then not seek additional medical care if they, in fact, have malaria. Whether that you believe is, on balance, a significant issue to overcome potential benefits of the drug in terms of reducing parasitemia.

If the answer to the above question is no, please indicate what additional information would be required. If the answers to Questions 1 and 2 are yes, please indicate if there any caveats or restrictions that should be included in product labeling. These can include the populations who should or should not receive the drug, issues about how many doses should be administered, issues about how definitive therapy might be used, any other considerations you think are relevant.

Again, this information obviously would be important for any U.S. physicians prescribing the

drug. It would also, we think, potentially be quite helpful to foreign regulators, foreign countries, perhaps nongovernmental organizations, et cetera, who may have involvement with present or future development of this product.

Finally, the last question; if this product were approved under our Subpart H regulations--that is, the accelerated approval regulations of which I spoke a few moments ago--what additional studies would be required in the post-approval period?

The accelerated approval regulations give us the authority to require additional studies be completed or performed. Unlike the normal phase IV postmarketing studies which are agreements reached between FDA and a sponsor but which FDA has no means to compel the sponsor to actually do.

Examples of such things could be completing Study 013, providing the results, doing some studies with different types of definitive treatment regimens to understand whether there are interactions, pharmacodynamic or otherwise, between artesunate and other treatment regimens, pharmacologic, toxicologic studies or other things that you think are relevant to better understanding

the product.

We think that a number of issues potentially have already been raised and we think providing that type of advice would be quite helpful if, in fact, you advise that the drug be approved so that we can ensure that, over time, we have satisfactory information about the product.

Thank you.

Discussion

DR. RELLER: The discussion is open and includes questions to anyone with potential answers.

DR. ARCHER: I have a question about the questions, the charge to the committee. Are we just talking about single-dose, 10 milligrams per kilogram, artesunate? It seems to me the discussion has also included the availability of the preparation, itself, in all kinds of doses and dosage forms. Are we to limit ourselves only to--

DR. GOLDBERGER: The WHO is proposing to make two dosage forms available, an adult suppository and a pediatric suppository. Those are, in fact, therefore the subject of the discussion today. The fact is that these products, or at least different forms, have been available

for some time as over-the-counter products, for instance, in both, I believe, Africa and Asia, is obviously an issue but not clearly an issue for discussion except, perhaps, as how this might relate to that in terms of resistance, et cetera.

I think it is a legitimate issue if you wish to think about what the likelihood is of multiple-dose use, how much of a problem that is. That would potentially be germane to the discussion.

But the WHO is coming forth with a proposal for artesunate for the suppository dosing form only in two different strengths. So that should be the substance of your discussion.

DR. RELLER: As important as oral formulations may be, we have heard no data on their efficacy or safety directly.

The discussion is open now. Dr. Rotstein had his hand up even before the discussion opened, so we will fairly turn to him first and then Dr. Cross and the other hands that were up.

At the beginning of the meeting, we had introductions around the table. We did not have an opportunity for you to introduce yourself, so please do so now, your name and affiliation, for

the record.

DR. ROTSTEIN: Coleman Rotstein, MacMaster University, Hamilton, Ontario, Canada.

DR. RELLER: Thanks.

DR. ROTSTEIN: I do have a comment and then I want to try to answer one of the questions. The comment I have is what we are seeing around the table is really tremendous uneasiness with this compound. We see how it is being used elsewhere and then we see how it may be used, whether it be in the United States or whether it be in Switzerland, in two different types of situations.

I think it is being used in young kids overseas and it is being used readily--here in North America, it may be used, or, for that matter in Europe, it may be used totally differently. We are not exactly sure if it is applicable to our situation. There is uneasiness about the table about that, so I think we have to acknowledge that and approach our discussion with that sort of jaundiced view, will it be used appropriately here in North America.

A comment about some of the questions. Usually parasitemia is really relevant in severe malaria and we don't know if this is going to work

in severe malaria where we have more than 5 percent parasitemia. We have comments about moderate to severe and we know that there is a reduction in the parasitemia but will it really work in severe malaria. Some of the people we are going to see here, because of the delay in diagnosis that we have heard about, may actually be severe malaria with more than 5 percent parasitemia and we are unsure if it will work there.

So I am unclear about that at this moment.

DR. RELLER: Thank you.

Dr. Cross?

DR. CROSS: I think part of the issue is how will this supply of this drug be managed if approved. It is my understanding that the World Health Organization will be contracting the production of this drug to subcontractors. However, the control of the marketing, if you will, of this drug will be in the hands of the WHO as opposed to some independent subcontractor being responsible for the marketing and supply of the drug.

I am just wondering whether, in fact, the WHO can confirm how the supply of drug will be made available and under whose aegis is it distributed.

Is it only with the imprimatur of the WHO or will some other organization or manufacturer also make this available perhaps independently of their approval.

DR. RELLER: Dr. Gomes or others, could you address this?

DR. GOMES: I can address the second of the two points but, perhaps, Professor White will refer to the first point. The intention of the WHO is to control the way in which this drug will be made available within the malaria-endemic countries. At present, what we have done is commissioned all of the work--that is the development of the active ingredient, the formulation into the suppository formulation--and we have agreements with what is often referred to as the final tool manufacturer, the group that would be packaging the drug.

If this drug is approved by the FDA, we would want to work with the company with whom we have worked--it is a small, Danish company with whom we have worked for fourteen years in making multidrug therapy for leprosy. We have a long-standing relationship with this company. We would want to continue with this company to be able

to control the manner in which the drug is made available which would be within countries through WHO.

DR. RELLER: I can't remember who was first up here. There were three hands at once. Let's just go down the line. Dr. Parise?

DR. PARISE: I have sort of a related question. It may be to the FDA. The rectal formulation today, how would that affect the ability in the United States, say, for an IV formulation of this later? Would that have to also be covered under the agreement with WHO? Would other companies be able to develop that?

DR. GOLDBERGER: That should have no impact. I don't believe that that would have an impact. Certainly not for treatment of malaria which is a very different indication. I am not even sure that it would have an impact for the identical incidence such as this because--I would have to go back and look at the details of orphan-drug exclusivity but, practically speaking, clearly this is a different indication than treatment of malaria and, in fact, it is a different indication even than prevention of malaria.

So I don't think, actually, it would have a major impact except for another, perhaps, suppository dosing form for a similar situation. That seems, frankly, to be pretty unlikely.

PROFESSOR WHITE: I wanted to talk to Dr. Rotstein's question, if that is possible. Dr. Rotstein was uneasy. I wanted to try and make him easy. You said would it work in severe malaria.

[Slide.]

This is the slide that Professor Folb showed. This is cumulatively by far and away the largest treatment experience in severe malaria. It is the individual patient overview from 1,900 patients, half of whom received artemether.

In the prospectively defined group of adults in Southeast Asia, artemether was associated with a significant reduction in mortality. Although the overview of all patients the p was 0.08, in the prospectively defined subgroup of adults from Southeast Asia, it was significantly better.

[Slide.]

Artemether has a much inferior pharmacokinetic profile to either rectal artesunate or parenteral artesunate. So we would maintain

strongly that this drug would work in severe malaria. If the ingredient gets into the blood, then it would work.

DR. ARCHER: I have two questions that you may be able to answer. In the briefing document, there is some in vitro data about antagonism between these drugs and other antimalarials. I wonder if there is any clinical evidence of that.

And then, secondly--if you can remember the second question--the recrudescence problem; would it be safe to assume that recrudescence is related to the shorter half-life of this drug compared to quinine, for instance?

PROFESSOR WHITE: Yes. There are a lot of papers published in synergy and antagonism of antimalarial drugs. They usually refer to slight bowings of the isobologram. There is no evidence at all from the a clinical impact of these. In fact, the only clinically important synergy that occurs with antimalarial drugs is the synergy between the antifolates and the sulfalomides, which sulfadoxine/pyrimethamine exploits. But there is no evidence for either faster parasite-clearance time when you have a synergistic drug or a slower parasite-clearance time when you have an apparently

antagonistic drug. To be quite frank, the degree of synergy and antagonism is very mild.

Thank you very much for the second one because we have rehearsed, that is the question of recrudescences.

[Slide.]

I would like to congratulate the statistician because I thought it was a very beautiful analysis and it illustrates a very clear scientific point. The short answer is yes, but may I take a few minutes to say why?

Here is the paradigm. What happens is that if you give a single dose of drug, of artemisinin, you will have a very profound effect on the parasitemia. But it is such a short half-life drug that, if you don't give any more, then you don't have any further reduction. You have to keep maintaining that. You have to maintain the presence of the drug until all the parasites have been eliminated from the body.

With a slowly eliminated drug, of course, the plasma concentrations persist and you have antimalarial effect persists. But, for a rapidly eliminated drug, it has to be present until all the parasites have gone which means seven days in an

autoimmune individual.

So this illustrates the point that the longer you give the drug, and this applies to both the artemisian derivatives and quinine, which is still a rapidly eliminated drug but much slower. That is of relevance. That explains beautifully, I think, the Malawi findings.

So, the longer you give the drug, the greater the opportunity you have of suppressing parasitemia to cure and the longer it takes if you don't cure the patient for recrudescence.

[Slide.]

So if we remember these worrying--or at least they worried you--the results from Malawi and we had a much higher recrudescence rate in the children who received this single dose of artesunate, followed, then, by, effectively, an ineffective drug, sulfadoxine/pyrimethamine.

So the treatment response relied very much on the first drug, artesunate versus quinine. Now, the mean dose of quinine is four doses. Quinine has a terminal elimination half-life in malaria of about sixteen hours. So we would estimate that you would have antimalarial activity in the blood for at least 48 hours after the last dose of quinine.

[Slide.]

Now, quinine actually kills more slowly but it is present for an extra cycle. So the net result is better and, in some cases, where you have good background immunity--these were semiimmune children--you will cure. If you do have recrudescence, it will occur later on.

So what we were seeing with the Malawi studies is a better contribution from a less effective drug simply because it is present for longer in the blood. So the true comparator would have been to give artesunate for the same number of cycles. Artesunate only affected one cycle. Quinine affected two or possibly three cycles.

Finally, you showed very beautifully how the difference was most evident at seven and 14 days. By Day 28, in Malawi, which is a high-transmission setting, had a lot of reinfections confounding the issue. So you had a combination by Day 28--of course, there was no genotyping done in that study to distinguish it--of reinfections which would have been equally distributed amongst the two groups, plus recrudescences which were more in the artesunate group because only a single dose was given.

DR. RELLER: Dr. Bell?

DR. BELL: I have two questions, also. One is I would like to be sure I understand clearly what is known about the safety of repeated dosing of artesunate in any form, rectal followed by oral. Is it just that there is limited information to assess that it is safe or not or is it that we actually have reason to believe that it is harmful. That is one question.

I know that is not the indication that is being sought, but Study 005 in Thailand was repeated dose of artesunate although the subsequent doses were oral. Just in general, repeated dosing.

PROFESSOR WHITE: Humans and then animals. In man, we use artesunate. Artesunate is standard treatment now in the multidrug-resistant areas. It is given either--preferably in a combination with another antimalarial drug over three days or, in the case of reduction infections, it is given for seven days. People have multiple courses.

Professor Folb showed you in those studies where patients were selected for having had multiple courses and matched with controls from the same community who had not had artesunate. There was no evidence, either clinically, audiometrically

or, in terms of auditory-evoked potentials, there were no detectable abnormalities.

The animal data that we have presented for artesunate shows that you need absolutely enormous doses to produce anything given by any route

[Slide.]

In fact, I think you brought it out very nicely in your presentations on toxicity that, basically, the problem appears, which was discovered initially by Dr. Berne and his colleagues, is related to artemether or artemether given intramuscularly because these provide a sustained concentration throughout the 24-hour dose interval.

Whereas, give the same drug orally, which has a much more rapid absorption and elimination and is much less neurotoxic, if you want to make the oral drug neurotoxic, you can do so by providing a plasma-concentration profile that approximates the intramuscular injection by giving it constantly with food.

So, if you coat food pellets with artemether, it becomes neurotoxic because the animal is eating it all the time and has a constant exposure. But, for artesunate given in any way,

considerably, about six times, less neurotoxic.

I don't know if that answers what you--

DR. BELL: I guess what I think I am concluding is that, although there is some reason to be concerned about neurotoxicity and we would like to have more evidence to assess how common this is, based on the evidence we have, at least in people, it is not a significant problem.

PROFESSOR WHITE: We just simply haven't been able to find any. We don't know how else to look. We thought that auditory-evoked potentials would be about the best way to bring out any abnormality. There is not a single documented case of plausible neurotoxicity in man.

DR. BELL: I have another question, but if somebody else wants to--

PROFESSOR WHITE: In fact, I will just say that they are just remarkably safe antimalarial drugs when you compare them with all the others.

DR. BELL: I will pose my other question and then the Chair could decide if it should be postponed. I am a little confused when the discussion goes around to how this drug will be used in actual practice overseas. The FDA's responsibility is for how it will be used here. I

am not sure how much it is relevant to FDA approval for use in this country, how it will be used in the field overseas. To me, that is more of a WHO issue and the local governments there.

But I would like to ask WHO, because I am not sure I quite got an answer this morning, how important is FDA's approval for WHO's plans for malaria control overseas for FDA's approval of this indication in the United States. Maybe more specifically, what will be WHO's future course of action in terms of distributing this drug if FDA approves it for use in the U.S. or not?

DR. RELLER: Dr. Folb?

PROFESSOR FOLB: Our original purpose in approaching the Food and Drug Administration was to achieve the highest possible level that we could think of of review of our proposal. The Food and Drug Administration has a record and a commitment to public health that goes beyond the United States of America.

It was to that that we appealed and to which the Food and Drug Administration responded. It was important to us, but I do want to make it clear that we do not have in our minds that this drug, as proposed by ourselves, will be used

differently in the United States or by United States citizens outside the United States to that which we propose in developing countries.

We believe that it needs to be used well and precisely and with the same kind of information support and package. That is inherent in our plans and we are quite committed to it. All the countries we work with know that.

What was the reason for the importance of the Food and Drug Administration approval of this application. Firstly, it is clear that that will unlock, for any number of countries, the regulatory process in their countries. The importance of the Food and Drug Administration is important. This will enable us rapidly and appropriately to move to a public-health need that goes beyond the United States.

Secondly, we have worked and will continue to work very closely in this regard with UNICEF, the United Nations Children's Fund, and with the World Bank and other United Nations organizations. It is remarkably important to them that the Food and Drug Administration should concur with our view that this is effective, safe and of good quality.

That has been our purpose in coming to the

Food and Drug Administration, or rather those have been our purposes.

DR. RELLER: Dr. O'Fallon had a question earlier.

DR. O'FALLON: I thought we were going to do toxicity later, but we keep getting back and forth, so now we are there. What is bothering me a great deal is the lack of information about toxicity profile in children.

We are being told that in Study 013 roughly half, like slightly over half, of the people enrolled in that study are under the age of five and we have, just really basically, a handful of children in these other studies that have any kind of neurotoxicity evaluation according to the information that was put out for us, eight in one study, for example.

I believe that the new regulations for the FDA, when it comes to putting in an indication or labeling indications, there is much more information needed in the very young children. But it isn't just enough to be treating them like this and looking for mortality.

I think we really do need to see some information, some real toxicity data, about these

children and how they are reacting to this drug since they are going to be the prime target, apparently, for this treatment.

DR. RELLER: Dr. Sumaya, Wald and Poretz.

DR. ARCHER: No one answered that question. Are they monitoring neurotoxicity in that study in these young children, in Study 013? Is anybody looking at neurotoxicity?

DR. RELLER: It was on the list but the details of how it is being looked for, we could use further exposition.

DR. SUMAYA: My concern is as those of Dr. O'Fallon. She mentioned more toxicity. I am very unclear in my bias is completely insufficient data on the efficacy of the drug as it is being proposed in young children again. Being a prime target, I would want to know where the WHO stands on do they feel they have sufficient data at this point and, if not, what is going to be done about that, in young children.

DR. ARCHER: Just as another comment related to this, in that Study 013, the children are getting 100 milligrams, not a milligrams per kilogram dose as I saw the slide. So, in small kids, that is going to be more than 10 milligrams

per kilogram. So the toxicity might be greater; is that correct?

DR. RELLER: Dr. Gomes and then Professor White will address these questions. We have got several waiting in the wings. Go ahead.

DR. GOMES: To answer the question on the follow up in relation to neurotoxicity, specifically in Study 013 and in general, as Professor Binka would have indicated earlier, this is an ongoing study with an intended recruitment of about 10,000 patients initially on the expectation that there would be about 5 percent mortality.

[Slide.]

The current recruitment is much greater than the safety update we showed you earlier for 3,366 patients. The main endpoints are whether or not there is a survival benefit and whether or not there are serious neurological sequelae.

Every single child is monitored between 7 and 30 days for the second or the first endpoint. So every single child would be seen with a case-record form to see whether there are new behavioral changes with a series of events that are predictable from the preclinical studies.

In one of those study areas that is Ghana

where more than 1,000 patients have already been recruited and where a lot of the patients--in fact, I think it was Dr. Kemmler that indicated that half of the patients are in children under the age of 24 months--there is a very specific study which is full neurological monitoring of those children.

All of the children would be followed up by a clinician and fully examined for potential neurotoxic effects. So we are as serious as one can possibly be in attempting to follow up every human being that has been exposed to this drug in a proper and coherent and systematic way so that we can understand, ourselves, what, if any, are the safety considerations associated with this drug.

This will continue until that trial is terminated.

PROFESSOR WHITE: Regarding children and neurotoxicity, the artesunate in combination with mefloquine has been the standard treatment for falciparum malaria in the community in which we work on the northwestern border of Thailand. It is about 120,000 people. It has been used since 1994. It is used in all ages and in all the studies which we have had before you, there is no relationship at all between age and parasite-clearance measures.

So there is no suggestion that parasite clearance, or parasite reduction, starts to slow down when you get younger. The two studies that Professor Folb presented to you were case-controlled studies where, as I explained, cases who had had multiple exposures were compared with controls.

At the time they were studied, they had had multiple episodes of exposure. Now, both these were conducted in low-transmission areas, one in Viet Nam and one in Thailand. Now, the first exposures were often when they were very young. It would be possible to go back to those data and identify, I think, precisely at what age they were exposed. But, by the time you have had four or five courses, you are often five-years old. That is when the study was done

So you have it logged at five-year olds. But, actually, the exposures were much younger.

DR. RELLER: Dr. Wald.

DR. WALD: It just strikes me as a little bit unusual that the FDA did not either have the opportunity or take the opportunity to review the raw data on any of these studies. Is that unusual and will there be an opportunity to do so and would

that be something that we would want to happen?

DR. GOLDBERGER: The raw data in which of the studies?

DR. WALD: In general, when industry presents data, the FDA reviews the raw data.

DR. GOLDBERGER: We reviewed the raw data from multiple clinical trials that the applicant submitted. I think Dr. Sacks and Dr. Johann-Liang went through a whole bunch of studies, as many as thirteen studies, all of which the raw data was reviewed from.

In addition, the applicant presented, in essence, I believe, a summary of the literature to support additional safety. That is not something that they necessarily would have to produce the raw data. They may not, in fact, have access to it so that I think, as, in particular, Dr. Johann-Liang spoke about that issue, I think she made the point very clearly that we, in fact, did not have the opportunity to review the raw data.

That would be entirely dependent on the applicant being able to submit that information. In general, unless an application is literature-based, which occasionally occurs, and in which sometimes the raw data is made available, the

best that one does with the additional information from the literature is that it represents some level of support to the actual clinical trials that were conducted and whose data was submitted in detail.

So I think that, in this case, there was a large safety review. I think that, realistically, the best that can be done with it is the issue that it may represent some level of support beyond the controlled clinical trials that were reviewed in more detail.

This issue is slightly more confused by the fact that, as was mentioned, with regards, again, to the safety analysis, there is a question about the differential degrees of potency of preparations that were used in these different studies. That, of course, can lead to problems in drawing conclusions even if you had access to a certain amount of the raw data about what one could conclude about safety.

That is the best answer we could give you. The application came with what would be described as probably the lower limit of what one would normally expect in terms of actual safety data from controlled clinical trials that were submitted in

detail; in other words, in terms of the number of patients that one might expect and then supported by this additional information.

But they had somewhere close to 500 patients. That is probably about the lower limit of what we would normally expect to see. Again, it is important to keep in mind that how one looks at all this depends ultimately on the seriousness of the underlying disease, the expected benefit from the product and the availability of alternatives.

That was a point I made during the charge to the committee. At some level, in making your determinations, you have to decide on your level of comfort with the construct that WHO has put before you of a group of patients, a substantial group of patients, out in very remote situations who, at a high risk of acquiring malaria which may manifest itself with fairly significant clinical manifestations, who do not have access to parenteral therapy and who are not able to take oral, and that there is this population who would benefit from a dose of therapy that would allow them to get to a place where they could get more definitive therapy and that the benefits of the therapy would not be outweighed, either by patients

not deciding to continue to some other health center or by the fact that some of these patients won't have malaria.

At some level, you need to be comfortable with that construct, I believe, is sort of part of your deliberations.

DR. RELLER: Dr. Poretz.

DR. PORETZ: Aside from these studies, I know in some countries this drug and similar drugs are commercially available. I have had patients who come to my office with these medications. I have no experience with it myself. Certainly, through the years, as these drugs have been available, there must be Americans and other individuals who have had access to these drugs.

Did they abuse it? Did they take a dose when they were sick, when they were in the Peace Corps somewhere in the bush and felt so well that they didn't seek further medical care? Did they take another dose? Surely, this has to be experience of our own population, of our own people, who have had access to their drugs. Does anyone know?

DR. PARISE: I have talked to some of these people on the phone. They usually have not

take a rectal formulation. My experience in talking to various physicians or patients it the it varies how many doses they take. I have the impression that they usually take as many as they were given, often five-days' worth or so. But that is just a general impression.

DR. RELLER: Dr. Ramirez?

DR. RAMIREZ: I have several issues regarding resistance because, in this committee, we always discuss the antimicrobial but we also discuss how the antimicrobial is going to be used. We mentioned that antimicrobial, for a single patient, may be a lifesaving antimicrobial but, from the public health, may develop a serious problem if this antimicrobial develop a resistance for a particular organism.

I still concerned with the possibility of the misuse of the drug and the development of resistance. It was mentioned during the presentation this morning that, in several African countries, 90 percent of these children die at home with fevers, seizures, and they die at home.

I wonder if having one dose of this medication, we are going to have still 90 percent that are going to die at home with one drug of the

medication. Why is it going to make the mother travel the ten kilometers to see a doctor, having suppository or not having a suppository? This, to me, is a big issue because otherwise you are going to have a mother with a suppository and I can see a mother giving a suppository, the patient was in a coma, today is awake.

Tomorrow, the mother is going to use this suppository for whatever, for headaches, for any form of fever because the suppository works. It was already mentioned here that if we want to develop resistance, overuse of the medication, use of the medication basically without the right indication, use of a low dose of the medication when the patient has the right indication.

Besides this, I would like to ask the FDA if when we discuss here drugs, even when we discussed recently aseptic drugs that was for severe asepsis, we are concerned if physicians were going to use the drug in patients with sepsis that was not severe sepsis. There was this idea that this drug should be only for some specialists to use.

I still have a difficult time to approve a drug that is going to be given by a mother. Or, I

am twenty-years old. I am working in the bush or working and I put my suppository--I don't have any more fever. I feel better. Why I am going to travel 10 kilometers?

It is difficult for me not to separate how the drug is going to be used in real life with the approval of the drug. If we are assuming that this drug is active against even the resistant organisms, then are we setting the standard for developing resistance to this family of drugs because of misuse of the medication?

Should we be concerned with these issues when we are discussing approval? I can say, well, the drug is effective. The drug is not toxic. But I may still not want to approve the drug.

Do I set any standard to myself that tomorrow the company is going to come here, is going to say, "I have these great antibiotics that work for all these respiratory infections and it is going to be given in the pharmacy without prescription." I would have a problem with this.

And I don't say that the drug is good and I don't say that the drug can be used. And I don't say that it is perfect for this situation where the drug has been looked at for these countries in

Africa. I totally agree with this approach, but, do we set a standard of approval with the actual use that is going to be developed? I see development of resistance coming.

DR. GOLDBERGER: It sounds like some other people want to comment on this as well. As a general rule, we certainly think it is appropriate for the committee to comment on how a drug might be used in practice if they believe that that is going to be much different than how the drug was studied because that sometimes raises different risk/benefit issues.

The issue here is, perhaps, a little more subtle and that is as you have talked about it, whether a patient will travel 10 kilometers, the mother giving the dose, et cetera. That, actually, really applies to the use in other countries really apart from how it might be used in the U.S. and probably how it might be used even by and large in U.S. citizens outside the country.

So, on one hand, as someone asked earlier or commented earlier, there is the issue of should you just be limited in terms of thinking how the drug is going to be used for the U.S. indication, et cetera. I think that, strictly speaking, you

could certainly limit your deliberations to that.

However, as was mentioned a few minutes ago by Dr. Folb, there is a belief or an expectation that decision that is made by the FDA will impact upon the availability and use of the product potentially in many other countries. Therefore, although you are certainly not required to do so, I think, if you choose, it is reasonable to take into account some of the concerns that might exist about the use in other countries recognizing that your decision is likely to have an impact on that.

We are not required to do that, but it is certainly something that you could consider and, in the past, advisory committees in various situations have elected to look at issues more broadly than specifically the FDA, itself, might.

DR. RAMIREZ: Then, with this thought process that if you have to take an early disease to prevent mortality, why not approve an oral to give to mothers and they can give an oral medication for these 24 hours, and we can approve the rectal and the oral and whatever. It is going to be one medication after another for the mother to have in the cabinet as soon as they live 10

kilometers from the hospital.

I have a problem to add this as a need because I also agree with Dr. Bell. Are we approving a drug for five patients that we may have in one year? As he mentioned, probably that everybody that goes from the United States to any one of these places taking the prophylaxis is not going to need the rectal suppository at any point.

It is a challenge. It is a different type of meeting than our standard meeting.

DR. RELLER: Thank you.

Dr. Ebert, Patterson, Leggett and Parise.

DR. EBERT: This is actually a very related question for Dr. Goldberger, trying to narrow down, perhaps, or maybe broaden the questions that are posed to us. I noticed in all the phrasing of all the questions the term "initial therapy" is used, or initial therapy when there are not other therapeutic alternatives.

Should we, as a group, conclude from that that you mean as a single dose for initial therapy are is there also the potential that if this is a patient who is at a very remote location that there might be a possibility of two days of therapy, three days of therapy, if that patient doesn't have

access to other care or are we restricted to a single dose.

DR. GOLDBERGER: You should include that issue in your deliberations. You will notice, for instance, Question 3, in fact, deals with the issue, for instance, are there any caveats or restrictions if you believe the drug ought to be approved.

One may be that it needs to be limited to, for instance, a single dose. That is our understanding of how the drug would, in fact, ideally be used. One thing that you may wish to get clarification from the WHO is the approaches, for instance, for the situations where they will be providing drug as to how they will try to ensure that it is used as it is intended to be used.

With regards to U.S. use, I think that the normal approaches are, in fact, to, at a minimum, include information in product labeling about how the drug ought to be used. How effective that sometimes is is limited although, in truth, for internal U.S. use, not for travelers leaving the country, the likelihood of substantial abuse of this drug, given the amount of cases of malaria and the cases that it would used in are probably fairly

sick people, the risks of substantial abuse are fairly low.

Issues about how the drug might be employed for people leaving the country to travel to remote areas, Peace Corps, missionaries, are a little more complex. Obviously, having clear information and labeling about this would, at a minimum, be very important in terms of dealing with that.

DR. PATTERSON: Just with regard to the issue of self-treatment that you were discussing, we already have recommendations for self-treatment for U.S. travelers, Peace Corps workers, for this disease because of the rapidity with which it kills and because of where the disease occurs which is in the field where you don't have access to medical care.

It just seems to me that what we are considering is facilitating this recommendation to the communities in developing countries where the mother would be administering the medicine instead of the self. But I also wondered a question for WHO is that, with regard to issue of the concern for resistance and recrudescence, has there been a consideration for when this drug is distributed as

a single dose, distributing with it a dose pack for continuation of follow-up therapy of whatever the standard of care is in the community? Could it be distributed as a multidose pack?

DR. GOMES: The current sense that you have in relation to the follow-up treatment is one that we share. We, as Professor Binka would have indicated to you, are wanting to have a phase of controlled deployment one of which will be potentially using the drug or making it available with the follow-up treatment.

There is a risk and a benefit associated with that. On the one hand, you want to encourage proper use. You essentially provide an antimalarial that can have a substantial effect and you want to refer people to a point at which you have definitive treatment.

So you don't want to encourage a position in which that referral process does not occur. By making available the follow-up treatment, and we would have found, and you would have seen from that data, a substantial proportion of children return, or patients return, to per os status within 24 hours.

Clearly, the need for going to a hospital

declines the longer it takes. So it is this balance that we have in our minds in attempting to want to ensure that people actually get to a hospital for referral treatment and yet accommodating reality to the extent that we know that many people, if they return to per os status, won't actually go that far.

It is this balance that we need to get a better understanding of in the next controlled phase and ensure that we get and optimize the use of the drug as much as possible, firstly restricting its use to the narrow indication and, secondly, providing the follow-up treatment where there really is no alternative to that.

Peter, did you want to make an additional comment?

PROFESSOR FOLB: I think WHO should deal with the question as to whether this is self-prescribed or to be prescribed by mothers. That is, indeed, a decision that would be taken by the regulatory authority of the national government of each country and they will differ between countries.

It would be in the decision of the different countries. Our proposal to the Food and

Drug Administration and for the United States is that this should be a scheduled medicine to be prescribed by a physician.

DR. PARISE: I wanted to make a couple of comments. First, as far as the drug-pressure and drug-resistance issue, it is my impression that, as combination therapy, if sources become available and there is a way to pay for this drug, as that moves out in Africa and other places, my guess is the drug pressure caused by this indication is not going to be that much compared to how much use there may be of other forms like oral artesunate in combination with other drugs.

I thought that the FDA raised quite a few safety concerns that concern me. My feeling is that, if the results of Study 013 were available, I think that would be an important consideration because that would switch the risk/benefit quite a bit, I think.

As far as use in the U.S., I think, if this is approved, there will be--I am almost certain there will be off-label use, there will be multiple dosing. We want to have some good mechanism to be able to get a handle on how safe that is.

DR. RELLER: Dr. Shapiro?

DR. SHAPIRO: I guess I had two points, one with respect to resistance. The lessons from cancer and from HIV and from malaria, itself, have taught that multidrug intervention helps to protect against the emergence of resistance. If this strategy is to go in early, why not go in early with two agents instead of one. I wonder what the thinking is on that from the WHO.

The second question is whether there are any data at all relating to this indication from non-immune patients.

DR. RELLER: Professor White?

PROFESSOR WHITE: We do agree that multidrug treatment is the way forward in malaria. The consolidation treatment, as it is termed here, would not be with an artemisinin derivative alone. It would ideally be with a combination. Of course, it depends on what is approved in the individual countries.

I assume that we are not worried about resistance developing outside the endemic areas. So the idea would be that there would be a consolidation treatment with, ideally, an artemisinin-based combination so the parasites

would not be exposed to artemisinin alone.

DR. SHAPIRO: Why not ensure that by including two drugs in the suppository?

PROFESSOR WHITE: By putting both in the same suppository?

DR. SHAPIRO: Yes.

PROFESSOR WHITE: It is an interesting approach. It is that the rectal route hasn't been particularly easy for the other antimalarial drugs. There is a rectal formulation of chloroquine, but chloroquine is no longer very useful.

There is some evidence, and some studies, with quinine. But quinine is quite irritant. So I think there might be a difficulty choosing which drug. So our approach at the moment is to try very much to ensure that the follow-up treatment is adequate and that treatment will be ideally the combination preparation.

DR. RELLER: Study 013 had what seemed to me to be impressive proportion of patients with confirmed malaria, 76 percent. Given, particularly in younger children, the difficult clinical distinction early on and a nearly impossible dilemma, I would think--this is not chicken pox--but for a parent to recognize malaria versus

some mimicker at eighteen months.

So I have a question about what is the effect of, used ideally, a single stopgap, potentially life-saving, measure of single-dose rectal artesunate on the ability, if is done what all would to see happen--that is, get to healthcare--what does it do to the objective diagnosis which is so much easier for malaria than it is for the mimickers.

I mean, there is more capacity to diagnose malaria in impoverished places than there are the other things that can also be lethal, like the four known patients with bacterial meningitis and who knows in the vast number who die at home before even entering into Study 013 or any other study.

So what is the effect of a single dose of rectal artesunate on the ability to make a diagnosis when somebody reaches healthcare?

PROFESSOR WHITE: That is a good question. I forgot the second part of Dr. Shapiro's question and that is simply answered because the patients in Thailand are relatively nonhuman. They have the EIR. There is now about 0.3 and there is very little background immunity, particularly in the under-10. So I think that population would be

equivalent to an expatriate population.

It is a very good point that you raise. The advantage of these drugs in producing rapid parasite clearance is potentially a disadvantage in that, then, the parasitemia may go below the level of detection by microscopy.

But, fortunately, there may be an answer to that and that is we hope increasingly that malaria diagnosis will also be possible by dip stick which is apparently about 50 cents. So the dip sticks, which are based on HRP2, remain positive for considerably longer than the parasitemia because of the very slow clearance of HRP2.

So, in Viet Nam, where there is a lot of community use of artesunate, we are seeing patients admitted late with negative parasitemias, the dip sticks remain strongly positive. Of course, that depends on dip-stick availability, but there is as general move to try and improve the distribution to rural areas of dipstick diagnosis.

DR. RELLER: Another question that I had, while you are at the podium, is a couple of people have mentioned, from diverse backgrounds, about comments on questioning the appropriateness of

mortality as an endpoint.

In your persuasive presentation, you emphasized the rapid road to death when the parasitemia reached, with the amplification, more than logrithmically. If the principal use of the single rectal dose of artesunate is to keep people alive long enough to get a potentially definitive diagnosis, or at least definitive treatment based on a clinical algorithm of some sort, why is it so difficult, and why is it even inappropriate in the only placebo-controlled trial that we have heard about, Study 013, to demonstrate what, at the outset of the presentation, was principal reason for considering approval of the drug?

PROFESSOR WHITE: Do you mean why has it been so difficult to prove that this drug saves lives?

DR. RELLER: Yes. There is a little bit of sort of an impossible dilemma here. In fact, there are two, to me, major concerns from a big-picture perspective. One is that where this is likely to have the greatest effect in saving human lives is in very young children, under two, the very group for which we have next-to-nil data, eight patients.

Appropriately, there is no intention in the request, in labeling, to use it under age two because the data are not there; correct? But, in fact, knowing what the clinical epidemiologic realities are, this is potentially, whether it is off-label or after Study 013 where it may have the greatest effectiveness, indeed there is some evidence to suggest that that may be the case in that 56 percent of the patients enrolled in Study 013 are under age two years, as I recall, if I have got my numbers straight.

The second sort of global concern was that what is presented, whatever its merits, is quite different from the actual intended use that was emphasized in the presentation by Dr. Kemmler.

Now, given that, Study 013 sort of moved closer to intended use but still was pretty controlled; that is, field workers, village--I mean, some--and, as a consequence, it was stated that the reason that the mortality was not as great as what one would have expected in actual use, is because this was a semi-supervised, if not actual in-hospital treatment, at least supervised therapy.

It wasn't just putting out an educational effort to mothers, many of whom have not had the

advantage of much education. In other words, the mortality is down but the flip side is that the opportunity to assess more rigorously safety is there. So you sort of have a dilemma.

If you put it in the real world where it is going to have the greatest use, we have got the greatest concerns about safety because it is almost like making it an over-the-counter drug except that it is not sold, it is distributed.

So one has this dilemma of greatest effect, greatest evidence for efficacy, would be placebo-controlled with an unequivocal endpoint and what at real purpose is to save children to enable definitive treatment.

So why have people raised the question of--not that you would go on and children would die unnecessarily, but that you would stop as soon as there was a definitive answer that, in fact, it did save lives which is the whole intent of your presentation in the first place.

Is that clear enough?

PROFESSOR WHITE: Yes. We have a response to that and then a plan for the future. So the response to that is that, as you quite rightly say, you inevitably perturb the system by studying it.

We could not ethically start studies in a life-threatening disease in patients who had a high mortality. So that is why the studies are presented in an intermediate risk group rather than in severe malaria.

Study 013 has had 99 deaths. The Data and Safety Monitoring Committee want to go on to their three standard deviations between the two groups. That is what they say and that is what they have done in other--for example, ISIS 2, the pivotal myocardial-infarction intervention--and that to provide absolutely unequivocal evidence.

With 99 deaths, we know there is some way to go. There may be a huge effect. But I think it is probably premature to say that at this stage.

So it may not be too difficult to show this difference. It is in their hands and it is not in ours.

DR. RELLER: Do you think in the context of Study 013 that, from your scientific clinical perspective, that, for the purpose intended in this study that mortality is a legitimate endpoint?.

PROFESSOR WHITE: I think it is legitimate endpoint but this is not a phase IV study. We are testing an approach of which the rectal artesunate

is a component. If we don't show a difference, it may not mean that rectal artesunate isn't a life-saving drug. It may just mean that that approach needs modifying.

So we are testing an approach in a situation where healthcare is imperfect. Of course, if you are present in a place where healthcare is imperfect, it is very difficult not to intervene and make healthcare better. So it has been very difficult to approach this very delicate subject which you phrase quite clearly.

It is a very difficult path. We have progressed towards, to try and to provide you with the data that would be convincing.

DR. RELLER: Just a follow up because it is, I think, an important and crucial--I mean, it is a delicate issue. The approach, perhaps, being flawed if it doesn't show but it doesn't mean that it wouldn't or couldn't show. Do you mean that, then, the challenge would be to try to--if you believe, and I think everyone here does believe, that parasitemia is given--I mean, it is not a single-dose knockout but it is a severe blow to the organism; that is, the malaria parasite to experience the metabolic derivatives of artesunate.

But the challenge would be to move the treatment back even further than the context of Study 013 to get at those 90 percent, 80 percent, 70 percent of children, the under-fives, who are dying at home before they get to a village healthcare worker or anybody else. Is that what you are saying?

PROFESSOR WHITE: Yes. My own opinion, for what it is worth, is that the benefit would be inversely proportionate to the level of healthcare. The worse the situation, the greater the benefit.

DR. RELLER: It is a sort of pushing back where you get that full benefit with the potential, then, for what--but then, the greater the benefit, then the more risk you are willing to, in terms of potential toxicity, to sustain to achieve that difference in mortality is what you are saying.

PROFESSOR WHITE: Yes, although I would say that it is remarkably nontoxic.

DR. RELLER: What I mean is that there is that balance. But it becomes--what is already small may be vanishingly small pretty early in the process of moving back toward the level required for greatest efficacy, or greatest likelihood of being able to definitively show the efficacy as

judged by mortality differences--not that you need it to show efficacy, but to show efficacy with that clinical endpoint.

Yes; Dr. O'Fallon?

DR. O'FALLON: You bring up a question about--I keep having trouble with this. How do you foresee using this drug? You keep talking about pushing it back. Right now, it is going into places where there are trained medical people to help with the distribution and administration, in essence, and education of the mothers that would be giving this drug.

If we were to approve it, recommend approval, how would it be used in these nations? I come from a small-town area, myself. Some places don't have a pharmacy anymore even in the United States. How is it going to be distributed to the people further back than are involved in Study 013.

How are they going to be trained? If a child in some tiny little area, there are just a few people living there, gets sick, how is the mother going to get hold of the drug? How will they go for it? What kind of training? That is the issue that I am concerned about.

DR. GOMES: Just to repeat what Professor

Folb said earlier, at least in the case of the United States, we would be making an application for a prescription-only drug. The scheduling in the different countries would really depend upon what the regulatory authorities for each of those nations decide.

However, there will be certain countries, perhaps Ghana would be one of them, that would want to push it back to the point at which you get the greatest benefit and as early as possible.

I would like to hand over to Professor Binka.

DR. BINKA: Thank you. I think, generally, for the control of malaria, we all agree that there is a need to push back the treatment further to the home. In most of these countries, there is clearly recognition that we need to incorporate what currently called the private sector in all this process.

So there is training going on for most people and we are making sure that, as far as we can, there are people who are trained and supervised to be able to help provide care. In fact, if you read recently in the last Malaria Day on April 25, I think in Uganda--Uganda is about to

put together about 80,000 people who have been trained and located in places to help.

In my own country, in Ghana, currently there is a major move to move community-health nurses into villages where they live, are trained and they provide care. So, gradually, that recognition is there and is a massive effort to try and support this process.

So when I showed the last slide, I was indicating that this is part of several interventions, part of which includes both the preventive measures and also the treatment. I think this will not just be left to the hands of people who are not trained but the level of training will vary from each country--I mean the person that is trained.

We cannot have pharmacists trained all over in Ghana, for example. But we can have another level of health worker that is trained to be able to help the mothers to administer this drug.

DR. RELLER: Dr. Sumaya and then Dr. Wald.

DR. SUMAYA: My question is will the approval or disapproval or recommendation from this committee to the FDA, from the FDA's standpoint,

approval or disapproval of your request affect or influence whatever happens with this drug in other parts of the world, distribution, access, investigations?

PROFESSOR FOLB: I have indicated that if FDA approval will probably profoundly affect the decisions of other authorities. That is always true for FDA decisions regarding medicines that are considered in other countries.

But that question introduces trouble to our proposal because our proposal clearly--our proposal and our request clearly--is that the judgment should be made in terms of the evidence that we have provided for efficacy against safety, the risk/benefit between the two and the quality of the product that we have produced.

So I feel that, as important as that question is, as profound as the influence will be of the FDA, that the decision be made on its merits.

DR. RELLER: Dr. Wald and then Dr. Ramirez.

DR. WALD: I have two questions. How different are the patients that are being entered into Study 013 in overall severity as the patients

in the pivotal studies, 005, 006. The second question is are there not sufficient safety data already generated from Study 013 to reassure us if more than 3,000 patients have been entered, 56 percent were less than one year of age, are there not already a lot of safety data that might be reassuring?

DR. GOMES: My colleague will be putting up a slide that was, I think, part of the original presentation of Professor White in terms of the representativeness of the population that we are likely to see in reality that is Study 013 and the population that we saw, we examined, in the pivotal trial.

[Slide.]

Essentially, all of the studies, apart from one in Thailand where there had been previous data that showed there was high risk of mortality in patients who were hyperparasitemic. All of the patients in the other studies were non per os which is the same inclusion criteria for Study 013, the same degree of consciousness, more or less the same history of seizures.

The difference here is that, in the hospital-based studies, the inclusion criteria for

entry into the trial was positive parasitemia. That inclusion criteria, in reality, is clinical presentation, inability to take drugs by mouth and suspicion--normally it is associated with malaria season in different countries--that the likely reason for this clinical condition would be malaria.

As I said earlier, the likelihood of the clinical condition being malaria, very often you have an overlap in presentation, particularly with acute respiratory infections. So no further or better diagnosis, you will have patients with acute respiratory infections who are essentially parasitemic as well.

So you would not be able, in a certain proportion of cases, be able to separate the two. In a large proportion of the cases, 74 percent, essentially, this would have been the primary cause of the illness.

There was a second question.

DR. WALD: That is why I think it is confusing that we can't show any difference in mortality that, on the one hand, the pivotal studies, we are loathe to use a placebo and we use a comparator drug because we say we can't risk

placebo. In this field, the mortality is decreasing and so we are not going to be able to show a difference in 10,000 cases. We are estimating that we are going to need a sample size that is two or three times greater than that. So it still leaves me a little bit confused if the overall severity of these patients is so similar.

The second question was about are there sufficient safety data at this point from Study 013 to reassure us?

DR. GOMES: This essentially would be safety data from Study 013.

[Slide.]

All patients, 3,366 would have been examined between seven and thirty days for the second major endpoint of that study which is severe neurological sequelae. You have been taken through the presentation of those patients of which two out of the 16 patients could possibly be sequelae that are attributable to artesunate.

Your question, the way you phrased it, also referred to a very young age group. We are not applying for a label that would be under two years. We have very few patients in our pivotal trials, nine in total, that were under two.

We plan, and we have submitted a pediatric plan, to recruit four hospital-based trials, a significant number of patients where we can examine the efficacy, clinical efficacy--and this is not a mortality trial--in this young age group.

[Slide.]

But, in order to study this population well, we would have to include patients only with that age group and we would have had to have produced a dosage form that can be taken by that age group. So this has limited our ability and we essentially plan to start that study as soon as possible.

So this is a dedicated study that would be looking at patients between three months to 24 months in this young age group. We would be looking at moderately severe malaria.

DR. RELLER: Thank you. It is exactly 3:30. We will take a brief break, come back refreshed for follow-up discussion and voting on schedule. We will be back at 3:45, please.

[Break.]

Continued Discussion and Voting

DR. RELLER: I should like to call this afternoon's portion of the meeting to order. I am

certain that our brief break enabled generation of additional questions to continue the discussion before voting on the questions put to the committee by Dr. Goldberger and colleagues.

Any additional clarifications of information presented before the voting, additional questions or comments from the committee members?

Dr. O'Fallon?

DR. O'FALLON: It was pointed out to me during the break, actually there is quite a lot of information available about the neurotoxicity in children that has already come off of that infamous Study 013.

It is in our packet but I didn't recognize it when I read it, myself. Perhaps the WHO guy would like to explain it a little bit better so that we knew a little bit better about what was going on.

DR. GOMES: Study 013, this was slightly repeating the discussion that I would have had earlier with Dr. O'Fallon, recruits patients that would be the intended population, patients who have suspected malaria, who would not be able to take drugs by mouth and who would, essentially, be referred to a hospital or healthcare center for

definitive treatment.

The protocol is essentially to randomized patients to either receiving a placebo or an active that is a suppository with either 100 milligrams or 400 milligrams of artesunate. All patients in this study are automatically followed for two endpoints; one is whether they survive or do not and the second endpoint is whether they have serious neurological sequelae.

There is a case-record form during the follow-up period between seven to thirty days where every single patient, if that is alive, is examined by the health worker who does the follow up and is assessed for different behavioral--have you had new problems in walking and talking, in speech, in playing.

Essentially, it is a form that evaluates each child or each patient that would have been exposed to the drug for potential neurotoxicity. If there is any one of the items that has been marked yes--that is, there is a new difficulty or behavioral problem, each and every one of those patients is then followed up by a clinician and has a full clinical evaluation by a clinician.

In one of the study sites, this goes even

further. There would be a very detailed neurological examination of those patients. The study began in different countries, at different points. It is about eighteen months into recruitment. Our approach was to begin very slowly so that we could do it--it would work perfectly; that is, we wanted to be able to be sure that, in a community-based study, we could effectively monitor every child or every patient between seven to thirty days.

It is a very unusual thing in communities to be able to actually get 100 percent, or as close to 100 percent, follow up in the kinds of conditions that we are talking about. We wanted to have as little lost-to-follow-up so that there was no bias in the results at the end of the day.

So we have moved in a phased direction to include patients in our target population. We now have sufficient confidence about eighteen months into the study that we can, in fact, recruit properly, that there is adequate follow up. We gave a safety update to the Food and Drug Administration. This would have been at the end of March where the DSMC evaluated the data and said there was no reason to terminate the trial, we

should move forward.

Between March and today, we have doubled the recruitment. It is almost a geometric progression because once you get confident in doing this kind of study where, initially, we would have wanted to make sure that every single child was monitored and the hospital had adequate drug in the hospital.

Of course, these things affect the endpoint, mortality. Now, we broaden it into places which are much closer to the bush where we give the drug. This is much further from a hospital. Patients take longer to get into the hospital and likely the effect will be seen as we expand the study.

I gather this was not clear either from the documentation or the description in the briefing document and I just wanted to make sure that you had this information because it was pointed out to me it wasn't there.

DR. RELLER: Despite the Study 013 being closer to the reality of the potential population for treatment, still, it has all ages, differences in background immunity. Quite honestly, is it designed to show the endpoint or, as Professor

White alluded to in the earlier discussion, if it doesn't show differences in mortality or much larger numbers are necessary, that wouldn't negate the possibility of showing that difference with the appropriate population.

So, are we putting too much emphasis, potentially, on Study 013 for showing the very thing that your briefing document emphasized is the goal of the appropriate use of this formulation?

Related to that, and I realize we don't have the code broken yet, but is part of that design to capture in actuality what the time is by patient and age group and outcome of time from receiving rectal artesunate to the time of getting definitive therapy, recognizing that no one has the intention of a single dose of rectal artesunate being sufficient for the appropriate therapy of malaria?

DR. GOMES: You have brought up two issues; one concerns the design of the protocol and the secondary endpoints that allow one to measure whether or not in the subgroup analysis if one doesn't see an overall effect, one would see, let us say, an effect in patients that are further from the hospital than those who might be closer.

That kind of secondary endpoint varies between studies but certainly it is there in the majority of cases; that is, parasitemia would be measured at--there would be different endpoints, one of which would be time to return to per os status and distance, what time it took to reach definitive treatment.

The second point that you brought up, to which Professor White referred to, is the emphasis on Study 013. Our indication, the way that we have phrased it, is for the initial management of acute malaria in patients who are unable to take oral drugs and cannot reach parenteral treatment, we are making a claim that we have shown benefit parasitological that has converted into return to per os status for patients who cannot take drugs by mouth and who normally would be at risk of death, an unknown unquantifiable risk of death, but, if they had progressed further, would have certainly have died in the absence of treatment.

We are making the argument that the way we have phrased that indication is that we have shown a clinical benefit. We have not yet shown a survival benefit and we do not make a claim in the indication that we do so.

So what we are asking for approval is on the benefit that we have shown in the pivotal studies bearing in mind the safety that we have also shown and keeping in mind the fact that, for these patients, there would be no alternative.

We have put in place, corresponding with the regulations of the FDA, what we originally referred to as phase IV trials and now are referring to as Study 013, trials which we believe would convert the clinical benefit that we have shown, returning to per os status, returning to a clinically stable position, so that the patient can take definitive treatment, that we want to confirm whether or not that actually converts into a survival benefit in real-life conditions.

Our argument is that you do not need to wait for the results or the continuation of that study although we would be wanting to present you with those results. In as much as you would want to know whether or not there would be a survival benefit, the WHO would wish to know whether or not there is a survival benefit because it affects policy. We would want to be able to, should we confirm that benefit, to convert to labeling to stating that there would be a potentially

life-saving benefit with this drug.

But we are not claiming that at present and we would only want to do that should Study 013 show that benefit was there. We have tried, in every way we can, to show that the patient population that we have seen in the pivotal trials, although they were done in hospitals, was as close as you can get to the patient population at baseline that we actually see in Study 013 so that they are clinically not substantive different.

We are making an argument, the case, that if we had done more hospital-based studies, it would not change the picture substantially, that what we see with rectal artesunate compared with quinine is what you see in any form of artesunate given compared with quinine and that adding patient numbers to the hospital patient population will not change.

So, in my view, the emphasis on Study 013 would be to establish whether or not it confirms the survival benefit would not change the indication that we are seeking but it might change the indication at a later point. Its value, I think, in this connection would be that it has a substantially much larger number of patients for

which there is secure safety data in relation to this indication.

DR. RELLER: Dr. Shapiro?

DR. SHAPIRO: Can I follow up on that presentation by asking what happens if Studies 013 and 014 don't show a reduction in mortality? We then have an approved intervention that affects the laboratory results and clinical results but not survival.

DR. RELLER: Comment?

DR. GOMES: If it did not show survival benefit, we would not want to persuade you to change the indication; that is to say, we would essentially live with the indication we have at present. We are essentially saying that we would be, then, limiting ourselves to the clinical benefit that we are seeking now and not a survival benefit. I am making the distinction.

We have shown a return of the patient to a clinically stable position on the current evidence.

DR. SHAPIRO: But one interpretation of a lack of impact on mortality is that you have protracted or, perhaps, eliminated the visit for definitive treatment and so, to pursue and continue using a drug for the indications that you seek

currently might be counter productive.

DR. GOMES: I am not quite sure I understand the question. Would you be able to repeat it?

DR. SHAPIRO: Yes. One of my concerns is that intervening--the mother's intervention with rectal artesunate will achieve some clinical response and will either delay or prevent the mother taking the child for definitive treatment. If the intervention in Studies 013 and 014, which are looking at mortality, don't show a difference or, perhaps, even show a difference in the wrong way, one possible reason for that is that you have taken away the incentive for the mother and child to go for definitive treatment.

So, to persist with the use of the drug in this indication in the face of either adverse or nonexisting mortality benefit, I can't quite understand.

DR. GOMES: I would interpret it in a slightly different way although I would like Fred to come up. I may have misunderstood the question, but there are two points I wish to make.

Firstly, this trial is in progress and we are informed by the Data Safety Monitoring

Committee that we should continue, that there is no evidence one way or the other for a termination of the trial from which I understand that there is no evidence one way or another and, therefore, I don't think that anyone can conclude that we have not shown a difference definitively. We are still dealing with a trial in progress.

The second issue, and it might just be an interpretation, if, let us say, that we do not show a difference at the end of the day, it would not necessarily mean that people would not have taken definitive treatment. I am not quite sure I understand the second point but, perhaps, Fred--

DR. BINKA: I think the second point you raised is quite important and that is the reason why this study is in place, because we will be able to answer that question that you have raised, will this drug lead to--if mothers do not go to seek additional treatment from one short treatment from rectal artesunate, what will be the consequences of that.

I think that is what is the strongest drive to have a placebo-controlled trial in this phase of the trial because we really didn't have to a placebo-controlled trial. So that question will

be answered. I think the likelihood is much lower.

DR. SHAPIRO: But the fact that you are seeking approval prior to the availability of those results--Study 013, as I understand it, could show three things; rectal artesunate reduces mortality, rectal artesunate is no different from placebo in affecting mortality, rectal artesunate is worse than placebo in affecting mortality.

Those are three possible outcomes from that study and we don't know which of the three it will be. At the moment, it seems not to be the worst-case scenario. Otherwise we wouldn't be in limbo.

But if approval is rendered at this point while Study 013 is still outstanding, the possibility exists that we will learn something, either that rectal artesunate does not improve mortality or, arguably, that it makes mortality worse. And we will have on the market an approved drug with uncertain data about mortality.

DR. BINKA: That is a good point. I think this is where we need to restate our case. I think the most important thing is that we are not trying to put in the drug one rectal capsule to reduce mortality. I think you should look at the other

benefits that we get from bringing children who are getting seriously ill into a situation where they can't take oral drugs.

If you see the huge advantage they will get in terms of hospital admissions, in terms of being able to treat these people appropriately even in the conditions in which they are, then that makes a lot of difference in the benefit.

Most of these kids that we are directing this drug to are those ones that are getting into the severe case. If you were to succeed in doing that, in preventing of the progression mild disease into severe disease, this would be a real major contribution towards reducing the burden. I think that is the case that we are putting across now, that even if this doesn't show survival benefit, it definitely provides lots of benefit to the control of this disease in terms of making sure that patients don't produce severe disease and that we are able to treat them appropriately.

DR. RELLER: I had asked earlier about the time to definitive therapy because, within the no differences, it may be that there are fewer deaths owing to malaria but more deaths owing to something else depending on what the distribution of the

background illnesses are.

But the other possibility is that, on balance, the delays in getting definitive therapy are sufficiently short that it is not possible to show a difference either in--realizing that study is not complete, do we have some idea of what the ranges are in the population being studied? It may not be a population that is--the populations may not be distant enough to be able to demonstrate a difference because the delays to therapy--because this is something outside the hospital, community-based, but maybe not far enough away to be able to--any comments on that? It is just an additional complication within the basic concern that Dr. Shapiro has raised.

DR. BINKA: I think Dr. Gomes alluded to extension of this project. In the initial phase, when we started recruiting patients, we had to do it in such a way we could learn how to do this properly. Currently, lots of the patients that are being recruited are being recruited from quite a few more places that would allow us to address this question.

I think that the Data Safety Monitoring Committees request that this should not be

unblinded should not necessarily mean that this is not showing any benefit. I think the need for the study to be stopped or to be unblinded, you don't only have to show a benefit but you have to show it within a reasonable doubt.

Maybe that is a part of the confusion. Nobody is saying that this study might not show the difference. But, at the time that the data was reviewed, there was truly no reason to unblind the study. Maybe that should correct it. I think the way it is designed it will answer the question.

DR. RELLER: Dr. Ebert and then Dr. Sacks and Ramirez.

DR. EBERT: This is potentially a two-part question. At what point are the children enrolled in the study? Are they enrolled when they present to the physician for follow-up care or at an earlier time.

DR. BINKA: Currently, once the mothers find that the children cannot take things orally and they are sick, we have field workers that live in communities that are recruiting these patients. So they are not necessarily reporting to the facilities but they are being recruiting in those distant places where there is no care. That is

where the studies have been carried out.

DR. EBERT: So there is not a risk of a mother administering the dose and then not presenting and not being enrolled in the study so that you could have more than 50 percent of the patients who might have received placebo.

DR. BINKA: No. This is a well-controlled study. We have shown the follow up to 99 percent. I think that is what is happening now.

DR. SACKS: I just wanted to perhaps communicate my own discomfort with making too much of a judgment on the results of Study 013 which, a), we don't have and b), we do not really know the details of the protocol.

In the course of the review, we requested copies of the protocol at least to understand what was being done. To me, the study does carry potential difficulties which I think we should be aware of before we can conclude that it either may or may not show a mortality benefit.

In particular, I think, in my mind, it is important to stress the drug effect in order to see the mortality benefit. For example, if patients who are getting the placebo prior to definitive therapy only receive placebo for four hours and end

up getting their definitive therapy at that point, the difference between the two arms will really not be visible in terms of morality benefit.

Second of all, the study population, although it bears some similarity to that shown in clinical trials is different in a substantial way and that is the clinical trials admitted patients with a certain minimum level of parasitemia whereas the study population is likely to dilute that considerably because we don't know what the entry parasitemia is in this patients.

We don't know what the level of immunity is. We don't know what the level is of other illnesses in patients who have immunity with background parasitemias so I think before knowing a little bit more detail about the actual structure of the protocol and before knowing more detail about the nature of the results, it is difficult to conclude whether the results show a mortality benefit, no mortality benefit or are unable to demonstrate a mortality benefit.

DR. RELLER: Dr. Parise?

DR. PARISE: I am sorry to go back to Study 013 but is there an ability in that study to look at the safety of kids who may have gotten

multiple doses and do you have any data on that if there isn't the ability to look at that?

DR. GOMES: Can I clarify that you mean multiple initial doses?

DR. PARISE: No; I mean may have been treated several times.

DR. GOMES: We do have data on all of the people that are recruited into the study. All patients just get one dose, as you know, initially. But, in the study that we have in Tanzania where it would be something like 1,400 patients so far, about ten in total would have had an attack more than once.

DR. RAMIREZ: I just wanted to make a comment that even though, in real life in some of these countries, you may have to go one step farther. For the Americans that are going to be in this countries, the design of this study, the study that we don't have the answers yet, is probably more real life because you are going to have a mother that is going to be very committed, is going to be educated, is going to know that this is one suppository that you want to run to see the physician, either one hour, two hours, or ten hours.

This is a study that, even though they are influencing now the mothers with education, this, to me, is a more real-life study how people are going to be using this drug.

If we don't show that there is benefit in mortality, then, in my mind, when I start looking risk/benefit, I will have to say to this mother, well, you take this pill and what happens; you decrease the number of parasites? I would like to see something else because we still don't have enough on the safety in these children.

Even if it is two cases of neurological deficit, we still don't know how many are there. Then it is going to be a balance as you have this risk for neurological deficit and what is the benefit. The benefit is that you are going to be sick two extra days or three extra--I would rather take being sick for a couple more days.

I am looking at the second question here. I still don't have probably enough information to answer the second question.

DR. RELLER: Dr. Parise?

DR. PARISE: I still think one of my concerns is that, in African children, they will get multiple treatments. You know, we don't know a

lot about that. Granted, there are about 320 patients in Southeast Asia but not African kids. Is there any data on that? I am assuming no because we haven't heard about it and is there any plan to get any of that? It may even be in postmarketing. I don't know what the plan is but I think that is a concern.

DR. GOMES: Can I try and understand your question? Is it related to this repeated treatment?

DR. PARISE: Yes. Kids of Africa, as you know, get malaria many times. Many times, they will be able to take an oral medication but sometimes they won't. So they will get multiple doses of this potentially.

DR. GOMES: Every single patient that is recruited, we essentially monitor. That is why we would know that about ten of the total would have had a repeated attack. Perhaps I should also say, while you were talking about postmarketing surveillance, we are in the process, in Study 013 of, of course, understanding what goes on in communities in relation to a presentation of disease that we have never done community-based studies about before.

So this kind of work is done for the first time. But in our plans, and the plans are already in effect, we plan to not just make the drug available in any quantity to anyone but to be able to record in the same way that we have recorded in the current study, every single patient who does get exposed to the drug. So we would have not only repeated the understanding of safety and efficacy for repeated exposures in special populations, young children, pregnant women. Essentially, this forms part of a broader postmarketing survival that we consider or take very seriously and are committed to.

DR. RELLER: Dr. Bell.

DR. BELL: I also have questions about the safety of multiple dosing. Let me just ask, in Africa, say, if a child is unable to take oral medications and isn't near a place where they have intravenous medications, what happens to them? Do they die? Do they progress to cerebral malaria and by the time they get IV medications, they have had possible neurologic damage due to that?

Is the question about safety of multiple dosing the difference between a theoretical unknown versus a highly likely adverse outcome?

DR. RELLER: Dr. Binka?

DR. BINKA: If children developing severe malaria cannot take things orally and cannot get injectables, yes, they go on to develop severe malaria and they die. They do die. Lots of them die for not getting treatment. I think that is the real emergency that we have now that there is a need to find something that can have that emergency situation.

DR. RELLER: The time is soon approaching. Any other questions or comments from the committee members or any additional comments the sponsor wishes to make before we address the questions?

Dr. Wald?

DR. WALD: Just under ordinary circumstances, when a child is not that advanced and they can take oral medicine, who does dispense it? I am revealing my ignorance. I have no idea about the healthcare system? So you have a remote village and a child who probably has malaria but he is not the sick yet. Who dispenses the medication?

DR. RELLER: They have to get to someone who has the medication. That may be a health center dispensary.

DR. GOMES: I'm afraid I didn't hear the

question very well.

DR. WALD: Under ordinary circumstances, when a child develops early malaria and seeks medication, where is it dispensed? Where do they go?

DR. BINKA: Currently, the majority of oral medication is dispensed by healthcare workers. A large population of private-sector workers who provide services to most of the population. That is what I said earlier on, that there is a major move to make sure that these people are part of the formal health system and training has been provided to make sure that the services that are provided are better. But, generally, healthcare workers provide the drugs.

DR. RELLER: Dr. Folb.

PROFESSOR FOLB: Mr. Chairman, you have invited a concluding comment from the sponsor.

DR. RELLER: Please.

PROFESSOR FOLB: Dr. Shapiro raises a possibility that in more realistic practice than we have shown, the benefit that we claim may not, indeed, be seen. On the contrary, mothers may decide not the to follow through with what is advocated for this treatment.

Our concluding comment must be that this efficacy must be seen in terms of this indication and the claim for efficacy must be seen in terms of what we advocate. We advocate that the mother takes her child to a clinic for substantive curative follow-up treatment as is the policy, as may be the policy, in the health center in the country concerned.

Our indication is critically dependent on that happening. Now, it may be in your minds that this won't happen in many developing countries. If it is in your minds that that is the case, I hope that my colleagues have said sufficient to contest that.

We have shown in work done so far, and it is our determination to work with governments to achieve this, that this medicine, as currently advocated, will be taken together with the advice that we propose. The medicine, plus the advice, which is the obvious and only advice that we can give to it, will achieve what we have shown repeatedly and consistently.

Thank you.

DR. RELLER: Dr. Goldberger?

DR. GOLDBERGER: This applies to a couple

of different comments that people have made. As we mentioned earlier, should this product be approved, it will be approved under accelerated approval using the parasitemia as a surrogate marker. Although there hasn't been a huge amount of discussion about it, my sense is that people feel that the parasitemia is of some value in looking at least at activity of the drug.

The accelerated approval regulations do require that some ultimately clinical endpoint, a more definitive endpoint, be demonstrated to validate the benefit of the surrogate. That might turn out to be what happens by Day 28 although the regimen, as proposed by the applicant--at least a single dose to tide people over--is not necessarily going to translate to any advantage at Day 28.

That may raise a little bit of question, therefore, as to what the parasitemia means. Should Study 013 not, for instance, show a mortality benefit, then that also raises a question about what the value is of the parasite.

However, as has been pointed out, including by Dr. Sacks, we are not completely sure about the details of Study 013 to conclude that it is the best vehicle to do that. But the point I

want to make is that we would have an expectation that if parasitemia is used as an endpoint that some other clinical benefit beyond simply reducing parasitemia would accrue to patients who receive the drug, whether it is a mortality benefit, whether it is less sequelae or some other things, that there would be a benefit to patients beyond simply reducing the parasitemia.

That would be an expectation that we would have to work with WHO to ensure that there were studies available that could show that. I mean, I have to say that we are reasonably comfortable although if anybody else has any comments about parasitemia, this would be a good time to bring them up.

That would be a useful surrogate but we would expect something beyond that and I have given a couple of examples. Should you recommend approval, for instance, for this product, Question No. 4 deals in a little more detail with making recommendations about the kinds of studies you would like to see to further understand this drug.

DR. RELLER: If I might summarize succinctly, the decrease in parasitemia is a necessary but not sufficient criterion for a good

clinical outcome in patients with severe malaria as reviewed earlier by Professor White. The key is getting, in the most severe patients, the--well, in all patients--the elimination of parasites altogether at the earliest opportunity and, in some patients, the additional supportive therapy, be it glucose, fluids, that are necessary for clinical success.

So let's get to the questions.

DR. BELL: I just have a question for Dr. Goldberger. If I am reading this right, the comparators, at least in Studies 006 and 007, are quinine given parenterally. Is there some reason that this cannot be viewed as a noninferiority trial of a rectal preparation versus a parenteral preparation bearing in mind that the indication is for situations where parenteral therapy is not available? Does that take care of the clinical outcome at 24 hours?

DR. GOLDBERGER: I think the problem is in the treatment of malaria is a clinical outcome at 24 hours a sufficient clinical endpoint to be satisfied versus actual cure of patient which will occur with the subsequent therapy that is given to them.

I think that there is some concern that the 24-hour status, although an extremely useful measure of drug activity, doesn't represent a definitive clinical endpoint.

DR. BELL: But the indication is for one dose given once and nobody anticipates that that effect lasts for weeks?

DR. GOLDBERGER: But we are using--in other words, the approach we would be using to approve this would require that early benefit mean something else to the patients because I am not sure that, otherwise, that early benefit represents an established endpoint that people would feel comfortable would normally be the way you would evaluate a drug for malaria.

I think because of the nature of the indication they are seeking, how they are approaching it, the expectation is that this early effect translates into something more. Otherwise, what does this early effect mean?

DR. BELL: I am still confused because it is the consolidation treatment that takes over that is what you judge the final--how can you ask this drug to do better than--how can you really evaluate this drug beyond 24 hours when, after that, it is a

consolidation treatment that takes over?

DR. GOLDBERGER: Because the argument that has been, I think, raised at different points during the day is that the real purpose of the drug, of course, is not to use it in a hospital setting and then to see what happens at Day 24. But the patients who get it who have no other alternative will accrue some overall longer-term benefit. One argument has been mortality, whether there are benefits in sequelae, et cetera. That hasn't really been talked about although that is possible.

Unless people are willing to say that a 24-hour endpoint in malaria is sufficient, then it is not clear what the drug necessarily is adding versus no therapy. That is, I guess, what we are saying, what would it then be adding versus not giving any therapy.

DR. BELL: But the trial is against quinine. The trial is not against placebo; right?

DR. GOLDBERGER: In other words, I don't think we would evaluate quinine as a treatment on malaria based on where a patient was at 24 hours, at least not in terms of giving it an indication. That would require making a decision that that was

a useful indication of its own.

In other words, what has been requested here ultimately is the initial use of this in patients who don't have another alternative with the statement either implied or expressly stated in the protocol and during the meeting that benefit would accrue to patients.

Otherwise, the indication would stand on its own, simply that, at 24 hours, the patient had lower parasite counts without any regard to what happened to them. I don't know that that clinically makes sense.

DR. BELL: Let me just ask one more question because I actually think this is pretty important. The sponsors are not applying for approval for a new malaria treatment. If I understand right, they are applying for approval of a drug to let a critically ill patient survive the first 24 hours until they can get parenteral therapy.

They have demonstrated--is this correct--that a), there is parasitemia decrease and also there is noninferiority compared with parenteral therapy at least in terms of clinical response at the end of the first 24 hours which is

all they are seeking approval for.

DR. GOLDBERGER: The more strongly you believe that that, in fact, will translate into a benefit for the patient--i.e., as you said, I think to prevent mortality until they can get definitive therapy. That implies that what you are trying to do ultimately is influence mortality.

The more you believe that this model, that there are these patients who do not have alternatives, that the rapid reduction in parasitemia will translate into a benefit, perhaps the less you need to worry about how much evidence down the road there is of an actual clinical benefit.

That is something that there hasn't been a whole lot of discussion at the meeting although I must say, from listening to many of the committee members, it seems as though most committee members had an interest in seeing something along the lines of some benefit in mortality or other benefit to the patient beyond what was shown in the in-hospital studies. I don't know whether it is worth asking people for that opinion.

DR. BELL: I just think that there are lots of intervening issues that come between

24-hour clinical status and eventual outcome as has been alluded to, study-design issues. I just am less certain what that means. Perhaps, that is noninferiority also.

I don't know. But I guess I am just wondering how fair it is to ask for the sponsors to demonstrate essentially improvement in ultimate mortality when maybe they don't have the right study to do that and if it is really the first 24 hours that we should be looking at.

DR. GOLDBERGER: For instance, if it is not the right study, then that can be addressed by considering is there a study that could be done that would be better able to show it. It is more of a problem if you truly believe it would be impossible to show such a difference. Then you would have to think, well, why, exactly, would you being doing this? Why, exactly, would you be giving the drug when down the road a few days, a few weeks, it will make absolutely no difference to patients.

Part of this from an analytic point of view is the difference often between an intent-to-treat analysis and an evaluable-patient analysis in terms of who you are looking at to see

an effect. I mean, that is kind of tied up a little bit when we actually look at Study 013.

I don't know if that helped, really, that exchange helped any members of the committee. It is not clear to me whether it did or not.

DR. RELLER: We will see from the voting.

Just to review the guidelines. All of the current members of the committee are authorized to vote on the questions posed. In addition, Dr. Parise and Dr. Shapiro are voting members of the committee today.

Question 1; are these results, namely, decline in parasitemia at 24 hours and 24-hour clinical outcome in moderately severe malaria as presented--are these results sufficient to support approval of rectal artesunate for use as initial therapy in patients without other therapeutic alternatives?

Dr. Parise? We will start at the right and move around. Yes or no?

DR. PARISE: Yes.

DR. RELLER: Dr. Archer?

DR. ARCHER: Do you want us to address the other things at this point or just to answer yes or no?

DR. RELLER: Yes or no. The caveats--clearly, it is under Subpart H. There are conditions and what those conditions are--if this should have no level of approval, you vote no. There is a place for it. I think the way these questions are phrased, you would vote yes. And then what else you would want before the labeling and all the other issues.

DR. ARCHER: I would say yes but I am not yet convinced that parasitemia is an appropriate surrogate for whatever endpoint is being looked at. I don't think there is enough data.

For instance, if we were looking at a bacterial infection, the rate at which a bacterium is cleared from the CSF or the blood doesn't necessarily correlate with outcome. So the rate of parasitemia drop is not necessarily a measure of outcome. We just don't have enough data.

Mortality was the only other one that was given. If we had neurologic sequelae or return to active whatever function, or any other kind of surrogate that went along with that, I think that might be helpful. So that is my only caveat.

DR. RELLER: So it is fair enough that you can--the major limitations, if it is a qualified

yes. Dr. Goldberger, is that okay? We want the true sense of how things are.

DR. GOLDBERGER: If people wish to amplify their comments like that, that is certainly helpful. Questions 3 and 4, should Questions 1 and 2 be yes, offer the opportunity to provide advice about any statements in the labeling and, equally importantly, the kind of additional data and studies that members would like to see.

DR. RELLER: In a way, it is is it effective for doing something and then what else do you need and is it for that purpose as intended, the labeling requested. Is it safe enough to get that labeling? What other studies were required, mandatory for use beyond the restrictions of the label?

Is that a fair summary?

Dr. Leggett?

DR. LEGGETT: If I understand it correctly, we are not being asked, at this time, as we usually are, to expound ad nauseam about why we are saying yes or no. You just want a yes or no, in which case, I will just say yes.

DR. RELLER: Dr. Glod?

DR. GLODE: I will also say yes.

DR. RELLER: Dr. Bell?
DR. BELL: Yes.
DR. RELLER: Yes, with limitations that we will get into later.
DR. PATTERSON: Yes.
DR. SUMAYA: Yes.
DR. WALD: I would say yes also but I want to just ask a question. Suppose we impose these restrictions and, ultimately, we don't find that there is any other benefit besides a reduction in parasitemia? How will that ultimately affect the labeling of the drug? Really, what I am asking is is this really tantamount to approval no matter what else happens and, therefore, imposing these restrictions is not really meaningful?
DR. RELLER: That would not be my intent, but this we will get to in 3 and 4.
DR. GOLDBERGER: To answer a little bit of your question, the accelerated approval regulations, in addition to utilization of a surrogate marker, also allow, in truth, for accelerated withdrawal of a product if the confirmatory trials don't show any other benefit.
One thing that, of course, would be helpful as you talk in, for instance, Question 4,

would be to talk about the kinds of things that would make you feel comfortable that the drug was demonstrating a benefit more durable than parasitemia unless you feel, as Dr. Bell very articulately argued, that the benefit that they have shown to date may in and of itself be sufficient.

If people feel that, you don't have to say that now. You can reserve that for a discussion in Question 4.

DR. RELLER: Dr. Ebert?

DR. EBERT: Yes, subject to caveats and restrictions to be discussed later.

DR. RELLER: Dr. Shapiro?

DR. SHAPIRO: A reserved yes.

DR. RELLER: Dr. Ramirez?

DR. RAMIREZ: I would like to make a comment. This committee, we have just recently discussed the idea of looking at surrogate markers mostly in patients with multiresistant organisms. How are we going to be able to test new antibiotics in clinical trials of patients, when don't have enough patients, are very difficult to evaluate.

I think that even though there is some reluctance, we will have to, sooner or later,

figure out that the prospective double-blind study looking at clinical outcome at 30 days is not possible in every setting.

The same that we do for antibiotics. What can we ask for an antibiotic? Just to kill the bacteria. There is nothing else that an antibiotic can be doing. I think that what can we ask for an antiparasitic, for an antimalarial drug? Just to kill the parasite.

I will say that this surrogate marker is appropriate. Now, the problem here is that we ask--we want to see what happens at 24 hours. It is not that the drug doesn't work. It is that we didn't give time for the drug to work because we showed, or we were told, that you give time, you give one week, you kill all the parasites.

Then I agree with Dr. Bell. At 24 hours, no drug is going to be able to kill all the parasites. That, to me, is an adequate surrogate marker to say that if you are using an antimalarial drug and you start killing the parasite, and you see a two-log decrease in 24 hours, it has very good antiparasitic activity. Then my answer is yes.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: My answer is yes. I keep remembering that this is a new formulation. There is no such formulation in any of the other antimalarial drugs as I remember. So this was developed to meet a need of a population that right now doesn't have a therapy of a known effectiveness.

So I think that that is an issue that needs to be kept in mind as well. I am, of course, worried about the age problems. But in terms of I think that they have shown that it at least knocks the parasites, or to a great extent.

DR. RELLER: Dr. Cross?

DR. CROSS: My answer is yes.

DR. RELLER: Question 2; is the safety information and safety profile of rectal artesunate sufficient to support approval for use as initial therapy in patients without other therapeutic alternatives. In your discussion, please include the differences in clinical trial, intended patient populations, risk/benefits, empirical use for emergency therapy.

We are to give a yes or no on this. Again, in 3 and 4 in the discussion, it will be important to articulate those things that we would

feel would be important to be done including the restrictiveness of the labeling. Dr. Goldberger has opened the emphasis for if we think other things we be required for maintaining availability to articulate those.

Let's go the reverse direction this time. Dr. Cross, is this drug, as requested in its indication, sufficiently safe to be used that way?

DR. CROSS: My answer is yes. I say it because they asked only for a single dose which is shown to be, in a fair number of patients, nontoxic. It was also pointed out to us that there is a difference between the demonstrated class neurotoxicity and the data specifically related to this preparation.

So, so far, we haven't seen any data to say that this specific preparation is any more toxic. So I would say, based on that, I think the answer would be yes.

DR. RELLER: The request is rectal route, over 24 months of age, single use.

DR. CROSS: Yes.

DR. RELLER: Correct? Dr. O'Fallon?

DR. O'FALLON: Yes. I think that the toxicity data, at least as we have seen it, are

okay. Again, but not in children.

DR. RELLER: Dr. Ramirez?

DR. RAMIREZ: Did I miss the two years because the proposed indication here says initial treatment when no alternative is available. But we don't discuss the age of the patient and we don't discuss--I don't see the 24 months.

DR. O'FALLON: It was in what we saw originally but I don't see it either.

DR. RELLER: I am operating on the assumption that what we are talking about is also what the sponsor requested which is the usual--I mean, if we do not think the safety support that was requested, that is one issue. If we want to go beyond what was requested, I guess we could do that, but there was--

DR. RAMIREZ: I read in the proposed indication in the document. It said initial management of acute malaria in patients who cannot take medication by mouth and parenteral treatment is not available.

If I look at this indication, it is different from what you just mentioned because you removed all the patients that I would say no.

DR. RELLER: Dr. Goldberger, help me. I

realize that all of the details are not in this question, but the sponsor clearly requested what they had data for and there were only eight patients in the pivotal studies that were under eight years of age.

DR. GOLDBERGER: The indication that you have seen is what the sponsor proposed. In their proposed package insert, they provide information on dose and administration for adults and for children basically from the age of two up or from a weight of 9 kilograms up. They indicate that there is not adequate information on children less than two years of age.

So that is what basically the proposed package insert would say, at least at this time.

DR. RAMIREZ: But if I read this proposed indication and the question is safety demonstrated for this proposed indication, my answer is no because this drug is going to be mostly used according with the clinical data in patients that are less than 24 months, less than 24 months of age, and this proposal is for all patients initial treatment.

DR. RELLER: Dr. Shapiro?

DR. SHAPIRO: There seems to be a

discrepancy between the proposed labeling and what we are seeing in the ongoing Study 013 which is to say that more than half the patients are in this group that we are saying is not on the labeling. So I am a bit confused about what exactly is being sought here.

If it is true that most of the deaths in malaria occur in the very young children, this is the population we most want to treat. Conversely, it is the population in whom we have the least, if any, safety data.

DR. GOLDBERGER: Unfortunately, you saw the information that we presented in terms of safety data from a bunch of studies which included 166 children. However, only eight of those children were less than two years of age.

As you noted, there is a much better enrollment of younger children in the ongoing Study 013. However, as a practical matter, essentially no information has been submitted to us about Study 013 other than about two or three pages of summary data. So we are not, certainly, in a position to, in any way, utilize Study 013 other than as a little bit of supportive data much as literature articles might be to just strengthen a little bit

of the overall safety impression but certainly not to make a major change in our understanding of what we know about the safety of children, for instance, under the age of two.

DR. SHAPIRO: I understand Study 013 is not even designed to acquire that except in the sense of neurotoxicity. So we won't learn anything about hepatotoxicity or any other form of toxicity that might occur.

I think the thing that I am wrestling with is that whereas it seems the request is for two and up, indeed, the ongoing use is substantially for less than two. So I am not clear about this request. If the request really is for use in less than two, then I don't think we have the data for it.

DR. GOLDBERGER: I think what is requested is clear. The request, in fact, basically the WHO at present does not provide information about how to use the drug in less than age two and basically states there is insufficient data.

You, yourselves, have seen the amount of data that exists for children under the age of two at this time and it is certainly a limited amount of data. It then depends, in part, how comfortable

you might be about a), an extrapolation of what we know in older children in terms of safety, b), the potential benefit from the dose of drug in these young children.

I think that those two issues are obviously important in terms of your thinking about that. Finally, whether or not absent being able to use the drug under the age of two or feeling that off-label use under the age of two might not be appropriate, how much of a concern that would be given the lack of alternatives for this patient population.

DR. RELLER: I phrased the question as I did so that we wouldn't be in an ambiguous situation. Maybe we would do a quick re-run and cut to the point. Alan, is it a yes above two or all comers?

DR. CROSS: Are we clear that we are following what is in our document or what was requested in terms of the label showing recommendations for greater than 24 months?

DR. RELLER: I phrased it one way, but if you answer it as I just mentioned, then we have got it taken care of. So you could say safety has been demonstrated without regard to age, or safety has

been demonstrated to your satisfaction on the 10th of July, 02, of over two. Or neither.

DR. CROSS: Clearly safety hasn't been demonstrated with regard to any age group since, as was pointed out, we have very little data on the less than 24 months. But I have seen sufficient data on those who were greater than 24 months that I would feel comfortable.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: I agree.

DR. RELLER: Dr. Ramirez?

DR. RAMIREZ: I agree. Less than two years, we need data. More than two years, it is probably enough.

DR. RELLER: Dr. Shapiro?

DR. SHAPIRO: I am not sure I am remembering the numbers. I thought it was just a handful that were children that were studied here, regardless of whether it was--wasn't it just a dozen or so of any kind?

DR. GOLDBERGER: 166 children, only eight of whom were under the age of two.

DR. BELL: How many were under the age of five?

DR. JOHANN-LIANG: About 80.

DR. RELLER: Dr. Shapiro?
DR. SHAPIRO: If the cutoff at two is an explicit component, yes.
DR. RELLER: Dr. Ebert?
DR. EBERT: Rectal administration, single dose, greater than two years old, yes.
DR. RELLER: Dr. Wald?
DR. WALD: Yes.
DR. SUMAYA: Yes; over two.
DR. PATTERSON: Yes; greater than two.
DR. RELLER: Yes, as requested; over two.
DR. BELL: Yes; over two and I am placing a strong weight on the phrase here "without other therapeutic alternatives," because I am actually not all that comfortable with just 80 under five either. But if there really are no other therapeutic alternatives, then I would say yes.
DR. RELLER: Dr. Glod?
DR. GLODE: I am going to say a very reluctant yes for part of the same reasons Dr. Bell mentioned. If this was a new vaccine before this committee or a new antibiotic and there were 80 children studies with essentially very few of those having any biochemical studies for hepatotoxicity, neutropenia, et cetera, I don't even think we would

be discussing it.

It is not. It is a rectal formulation of another drug for which there is at least historical safety information and there are no other alternatives. But it is a very reluctant yes with n equals 80 children under five and essentially almost no biochemical studies.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: Yes; as in the product recommendation.

DR. ARCHER: Yes; as amended.

DR. RELLER: Dr. Parise?

DR. PARISE: Yes, but because I have to leave in five minutes for a plane, let me say what I think should be added for No. 4.

DR. RELLER: Please.

DR. PARISE: Which is a review by FDA at some point of the safety data collected in Study 013, some kind of more information on repeat dosing; that is, people who get dosed for multiple episodes of clinical malaria, and probably also for a bigger database to look at the biochemical issue, the lab tests.

DR. RELLER: So those are the votes. To set the stage for the discussion of 3, and, in

part, 4, with the reserved yeses, I voted as I did because I think that there are patients for whom parenteral therapy is not available in remote areas who may be given the gift of time to get definitive therapy is this is used appropriately, and that is a big public-health challenge.

At the same time, for its continued availability or approval in the first place under the regulatory process for accelerated approval, I think its persistent requires evidence, clinical evidence, including mortality or other substantive documented objective neurologic preservation or something along those lines, something beyond a laboratory assessment, however necessary it is, that it is not sufficient.

So let's go around the table and say what would you like to see, Dr. Archer, in terms of additional studies, additional data, caveats or restrictions in labeling, et cetera? I think that it is logical to do 3 and 4 together. What else do you want to see that is required of the sponsor either in labeling or studies or follow up, et cetera?

DR. ARCHER: Let's see. I think as far as labeling goes, the obvious things that have been

mentioned. I think the labeling needs to define what was actually studied, namely no severe malaria, no kids under the age of two, are two that I can remember, and all of those things that were studied needs to be restricted to use in those folks in the labeling because nothing else was yet studied. I guess the labeling can change when Study 013 is finished if there is more data.

As far as other things to do, obviously, toxicity in children under the age of two is a no-brainer. I think better studies to correlate parasitemia with outcome. Other outcome measures besides mortality should be looked at, whatever they may be, just to strengthen the validity of using parasitemia as a surrogate. I think that would be important.

That is really all I have.

DR. RELLER: Dr. Leggett?

DR. LEGGETT: One thing I would like to point out is part of the problem appears to me is the lack of data as brought out by the multiple questions all day long. I would just urge the sponsors, when they come with the follow-up studies of which I am sure there are going to need to be some, that they provide us with more specific data

to make us more comfortable with the choices we are making.

One of the things that I would say is that, in terms of the labeling, as Gordon said, it should be sort of limited to a single dose in combination with appropriate consolidative therapy, da-da-da-da-da, something like that.

In terms of other things, obviously more data, either a complete Study 013 or a subset of those folks who are at higher risk of death, whether that is coma, whatever that is identified, so that we can maybe get by with a smaller n but a higher degree of severity so that we can get the data that we really want to know, and in use in hospital with kids less than 24 months, if that needs to be the way it is done, so that we can get the other biochemical and all the other data that we need to get.

So, other than that, it would just be a repeat of everything else everybody said.

DR. RELLER: Dr. Glod?

DR. GLODE: I would just encourage, since it sounds like this drug needs to be used in children less than two, that, in addition to the neurotoxicity by an exam and a questionnaire, that

at least in a subset of those children, some biochemical studies, basic screening biochemical studies, be done to increase the safety profile for a later indication to expand to younger children.

DR. BELL: I think we need more safety information particularly in children under two and particularly those given repeated courses. It has been said before. I also think it would be helpful to have more clinical efficacy information but I would offer the thought that this might be considered a noninferiority study compared with parenteral treatment and that clinical outcomes--there is equivalent clinical outcome at 24 hours.

Perhaps that is too soon to really make a definitive assessment of noninferiority but, perhaps, a few weeks down the line--I guess what I am saying is we don't necessarily have to show improvement in mortality over placebo. We could show noninferiority compared with parenteral treatment which, presumably, historically has been demonstrated superior to placebo and maybe that might suffice.

DR. RELLER: I voted yes because I think that, used appropriately, both on the efficacy and

safety, that it was important at this juncture in the drug's development and deployment to have a--the alternative of "no" is implying that the drug is neither effective nor safe which I think is the wrong message. To the extent that we say "yes" with a very restricted labeling exactly as was requested, no more but not less than that the data currently allow, would help accelerate the gathering of the definitive information that would be required to properly position and deploy the drug.

That was the basis for my qualified yes on both counts. I think that, unless, the additional numbers of children and safety is demonstrated and that there is clinical benefit that is objective, that can be documented with additional studies, that the opportunity to study, so to speak, should be as rapidly withdrawn as it might be approved.

Dr. Patterson?

DR. PATTERSON: With regard to No. 3, I would like to see something similar to what is on Page 2 of the FDA briefing document for the Warning and Precautions and perhaps to even emphasize under the Precautions not only referral and evaluation for full curative course but also that repeated

initial dosing is not recommended.

Also, something with regard to the dosage, the optimal dosage in liver disease has not been well studied particularly in patients with severe liver disease. Two, with regard to No. 4, the things that have already been referred to with regard to hepatotoxicity--I know that is not planned in Study 013. Perhaps there could be a subset, 13A or something, or to look at it in Study 015 to at least look at a subset of patients with the effect of LFT as placebo versus artesunate.

Also recrudescence. Finally, as a part of the follow-up, to hear what the implementation plan is for the education and distribution, both the field workers and the community, regarding referral and consolidation therapy.

DR. SUMAYA: I am agreeing with practically everything my colleagues have stated. I would mainly reinforce the need to indicate clearly that this is initial therapy and it must be followed with more consolidated definitive therapy as part of a bigger package.

Secondly, again taking comments just made, I think it would be very useful, particularly for the WHO, to look, carefully evaluate critically

with scientific scrutiny how effective the use is of the community health workers in both access to the patient and their families of this drug and appropriate utilization.

It may be useful, although maybe there are some data that wasn't presented, on what is the frequency of other illnesses that may be considered malaria and so therapy is initiated, but it is not acute malaria and is some other illness, and trying to get a better feel for the background noise, not only just to get an incidence or a prevalence of that but is it leading to other types of sequelae or problems in those individuals.

DR. WALD: I think to endorse the use of this single-dose rectal therapy we should be able to demonstrate in the placebo study or at least some subset of patients that those who receive the rectal dose get better sooner and more often of both, that there is a difference in mortality or, again, some very objective outcome and that more safety data be generated both in those above and below age two.

DR. EBERT: I agree with the comments from the previous committee members. I feel that if it is not already available that we need to come up

with a consensus for an objective scoring, if you will, for mild, moderate versus severe cases of malaria so that we can try to determine outcome in those various groups.

Pursuant to the accelerated approval, I think we need to have some additional data that shows that there is a clinical benefit, whether that could be done by completing Study 013 and stratifying by severity or other measures, or by doing an additional study, potentially either, again, a placebo-controlled study, if necessary, or I am not sure whether the FDA is able to accept historical control data but potentially something that would show a benefit of this early administration.

DR. SHAPIRO: I haven't very much innovative to say. I think the issue of safety clearly needs to be addressed, particularly in those less than two. I would very much prefer to see carefully collected data on a rather small number of young children rather than incomplete data on a large number of children.

I think the issue of the two-year break point has been rather pivotal in our thinking here. I think that should be reflected and up front and,

for example, on the front cover of this book and not within the contents of the book.

I wonder aloud what this decision with the two-year and older indication means for Study 013, half of whose enrollees are less than two.

The other thing that I agree with is that we should have a mortality study. This is really the bottom line. We are trying to save lives here. The beauty of the mortality endpoint is that it collects not only efficacy but also safety data. It is possible that mortality is affected by both factors. I think a very carefully controlled mortality study is in order.

DR. RAMIREZ: I think that the types of studies that we all want to see in the future is not going to be given by the data from Study 013 because the sponsor was having different objectives. I was sitting here in the last minute and thinking that if I were to--what I would like to see in a study, in a clinical study.

Probably, we need to--as was mentioned here, time to healthcare facility is going to be an important--first of all, it has got to be placebo-controlled and double-blind. We need to control for time to healthcare facility and,

ideally, we need to have from the same area 50 percent because in one area, people are living at twelve hours of the hospital. If 50 percent of these are going to get placebo, 50 percent are going to get the drug, and then, at the end of the study we are going to know that once you have 50 percent, when we do the median time to hospital care, it is going to be the same time.

Also the problem is that we need to have baseline data time zero and then we need to have time 24 hours, some data, because if we wait until the patient arrives to the hospital and we look at parasitemia there, still we don't know what happened, what was the drop between placebo and the drug.

If we wait until the patient arrives to the hospital to see what is the severity of disease, we still don't know if we include severity or not. This has to be done by the healthcare person that goes to the area where the family is. Somehow, we need to have a simplified Apache score for malaria, five points, seven points, something like that. It has to be very simple that a nurse who is going to give the rectal suppository at twelve hours, we have to figure out some score

because, otherwise, how are we going to know if, when the patient arrived to the hospital, that really the drug is decreasing severity. We will not be able to know.

And, at 24 hours, we need to see parasitemia. We need to see severity of disease with some formal objective score, and we need to see mortality at this 24 hours comparing with time to healthcare facility and looking at mortality and severity, adjusted for severity of disease. Then we see placebo versus the drug.

Then we need to see at 28 days what happened with the patient because there is where we have the neurological sequelae that may be a benefit of the drug for early treatment because, again, if you unplug the capillaries of the brain eight hours earlier, you may have less neurological sequelae than we see with some studies, the early oxygenation.

We need to see the 28 days because this may be beneficial. But all this will require to me a well-planned prospective study. It is not going to be able to have a large study and it is not going to be the Study 013.

DR. RELLER: Thank you.

Dr. O'Fallon?

DR. O'FALLON: Let me just say with some amusement that we could probably do survival-curve analyses on those different treatment groups rather than try to do it at such and such a time, just find out how long they lived and do survival analysis comparison.

I agree with most of what everybody else has said, so I am not going to argue there. But I think my concern, if we are giving advice to somebody and I don't know who this is, I think we really do need to see the data analyzed by age groups.

We haven't. The data have all just been blopped in together. I think it would help us a lot even now to see the data analyzed by age groups.

Another issue that really concerns me is the--I think some of the people were trying to get at it was some people are repeat--this isn't their first bout of malaria. Perhaps, in order to understand what we are seeing in any of these studies, we need to know how often they have had malaria. So there is an immunity issue. I have been nervous or uneasy about the data from the

adults because it seems to me that those adults are the survivors.

They are the ones who have survived previous bouts of malaria. So they are, in some senses, more immune. They have some sort of immunity. So I don't know how much they tell us about what is likely to happen in the more naive patients who are presumably the younger ones.

So I just think that there are some issues here in order to interpret even what we see that might be very useful. I understand they are telling me that Peto is, if not the chair of the DMC, he is the statistician on the DMC for this study. This is like bringing coals to Newcastle.

But I think that the rest of the world would really like to see this data analyzed by some of these issues to see how this proposed therapy works for the ones who are the most vulnerable.

DR. RELLER: Thank you.

Dr. Cross?

DR. CROSS: The information today was presented to us as part of an approach; that is to say, the single dose of the study drug is not being viewed alone but it is being presented as part of a total approach. Therefore, I think that we also

have to have some studies further addressing the recrudescence rate.

For example, if you look at the pivotal studies 005, 006 and 007, it turns out that the recrudescence rate with the artesunate is actually fairly low in Thailand and South Africa but it is very high in Malawi. Some of the initial presentations in our documentation, it was not clear whether the 28-day recrudescence was the sum total of the artesunate plus the consolidation therapy and, if so, are there differences in those combinations that we really have to pay attention to, or is the explanation for what is happening in Malawi what Dr. Binka said, and that is there is a very high rate of infectivity of the mosquitoes and what we may be seeing, therefore, are new cases of malaria occurring in a very short time.

I think at least one way to address this is to have a better characterization of the malarial parasites that are obtained at recrudescence; that is, are these the same or different parasites. We have to have some common definition of how we go about this.

Are we looking at this through PCR only, or PCR and smear, both? I think that has to be

defined. So, in short, I think that the 28-day recrudescence rate really is an opportunity for us to get further information that really hasn't been addressed. As I said, we need more data on the actual parasites themselves, how common is the recrudescence in Southeast Asia, for example, versus Africa.

Then, finally, I think the World Health Organization has to have some plan implemented, perhaps not in the short term, but how will they monitor drug resistance. All of us this morning expressed some concern about that. I think that, as this is put in the field, we have to have some way of capturing that information early.

DR. RELLER: Thank you.

Before concluding, two comments. First, I apologize to Dr. Sumaya who is like in the rear-view mirror in my blind spot here, so I don't think I specifically asked him when the votes took place. I will try to do better tomorrow.

As regards tomorrow, we have a very full agenda. We have guests, consultants from overseas who have to return there. So we must stay on schedule. Consequently, I would like to ask all of the committee members who will be participating

tomorrow to please arrive by 8:20. We will start sharply at 8:30 and I shall seek to be ruthless in adherence to the time table so that we can complete all of the discussions that will be required for reasonable decisions.

Thank you, sponsor, FDA, committee members, for the rigorous discussions. The meeting is adjourned.

[Whereupon, at 5:20 p.m., the meeting was recessed, to be resumed at 8:30 a.m., Thursday, July 11, 2002.]

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