

**Open Forum II: Key Issues in TB Drug Development- Day Two:  
Developing Combination Regimens Containing Multiple Novel  
Drugs  
TB Alliance, Bill and Melinda Gates Foundation,  
Treatment Action Group, and Stop TB Partnership  
Working Group on New Drugs  
December 13, 2006**

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**RICHARD CHAISSON, M.D.** Okay, the next portion of the program is Challenges in Developing Novel Treatments for Drug Susceptible TB, and the first presentation will be by Zhenkun Ma from the Global Alliance.

**ZHENKUN MA, PhD:** Good morning. My name is Zhenkun Ma from TB Alliance. I am going to discuss today initiative development by TB Alliance for pre-clinical selection of the new drug combinations. Since active TB must be treated by combination therapy, the reason to do that is really to prevent drug resistance and also improve efficacy. So really the basic unit for clinical development of TB drugs in Phase 2 and 3 should be regimen or combination, not a single drug.

Because of this we believe a pre-clinical program should really include two components. The first one includes like a normal therapeutic, other therapeutic area, include evolution of safe and the efficacy of each new chemical entity or NCE. The second component is a little bit unique for TB which includes an identification regimen or combination in which this NCE can be developed.

In the past few years we have seen so many exciting advancements in the TB drug R&D area, and now we have multiple drugs in clinical trials which include two fluoroquinolones. The first one is [inaudible] processing,

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the second one max processing. We also have one ATP synthase inhibitor—KMC 207, two nitric emitters compound—OPC 67683 and the PA is [inaudible]. And the two other compounds, SQ109 and LL3858 also in Phase 1 clinical development.

The current approach for TB drug development is basically replacing one drug on the current regimen at a time. In terms of regimen, for example, characterization we know we know based on the presentation we heard yesterday. In Phase 3 trial we will be replacing [inaudible] in a standard regimen much processing, and replace [inaudible] from our standard regimens, and TMC27 will be added to the baseline regimen for MBI indication. We don't know what regimen is going to be eventually used for OPC and PA but based on animal data we have it appears replacement of [inaudible] gave the best efficacy. And we also heard from [inaudible] they have intention to replace [inaudible] in the current regimen for their clinical trials.

So these are very exciting developments. But I think the question we have to ask, are we going to really [inaudible] regimens, each of them soon to have very similar incremental improvements. I think another question, are we really taking advantage of what the new drugs can potentially offer for us?

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It's probably really helpful to look at the problem from a different perspective from the drug target point of view. If you put all the first-line drugs and the second-line drugs together, it's not a very short list, but if you really group them together based on the mode of action or targets, then actually we really don't have too many choices.

We probably don't want to combine [inaudible] in the same combinations or combine steatomas and kinemes in the same combination because of the cross-resistance. The new drugs really add a lot of targeted diversity to what we have today, and give us a lot more choices in terms of trying to find the synergies between different drugs in the combination. It may give us much better drug combinations.

In terms of really the need for [inaudible], the major issue in current TB chemotherapy probably would be really among duration of treatment, drug resistance, and also TB-HIV co-infection. We believe a drug combination that can address all the three problems at the same time should be the biggest impact for the field. In order to do this we almost need to replace almost every drug currently in the regimen because each of them may have its own problems or issues.

For example, Recentium we know has NDR problems. At the same time it's a [inaudible] inducer, which is the reason for drug interaction with ARAs and also interaction with

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other drugs like TNT47. Isoniazid also has NDR problems which we also don't know how much this drug really contributes to sterilizing the infection. In terms of [inaudible] we really don't know what's the real contribution of this drug for the combination.

So I think that the need for a totally novel combination seems pretty clear. We need to really open up and consider all the drugs possible, available to us, explore all the potential opportunities, and try to pick out the best combination which may contain more than one new drug in the regimens. But to do this we also probably need a new approach, and if we take a conventional approach, which is basically replace one drug at a time from a current regimen, if we really want to develop a combination which contains three new drugs that will take about 18 years. So if we can put all the drugs together and really rationally try to select what's the best possible combination and pool this combination into clinical development, this process could be much, much shorter.

I think what I try to say here is it's probably impractical to study all the potential combinations in human clinical trials. The table really shows you some simple calculations if you want to investigate, for example, eight drugs, and all the potential combinations—two drug

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combinations, three drug combinations, four drug combinations—the number is very significant. It's very, very hard probably to do such large numbers of combinations in humans.

If you simply increase the total drug number from eight to ten, you can see the number increase even much bigger, and also I think it's probably unnecessary to do this just because a lot of people complain that the animal models today are not perfect, but I think it's good enough for us to really narrow down the possibilities.

So I think the TB Alliance recognizes this need. We really need a new approach to identify the best possible combination with old drugs and the new drugs, and so we put together a request for proposal with advice from many members of our scientific advisory committee board members and some consultants, and these are appearing this September, this proposal solicitation and review process, and we plan to start this project some time early next year. So if you have not seen our [inaudible], which is there on our web, you can log in if you are interested.

The objective for this combination study, and it's [inaudible], and we hope to identify a three-drug combination with the better drugs we have today, a three-drug combination properly adequate to address the two main issues. One is

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reduce the chance for developed resistance. Another is really improved efficacy.

We hope we can identify a three-drug combination, which can shorten treatment to two months, and can be used together with ARAs and also effective against NVR and XTR TB.

To do this of course, I think that we all recognize the challenges to do this. It's not that straightforward. The technical side and I think the problem is do we trust the animal model. Can we relate this animal model to narrow down the choices and move this small number into a few month clinical studies?

And in terms of regulatory we definitely need clear guidelines from regulators around the globe how to develop such a novel combination, which may contain more than one new drug. And I think another challenge from a sponsor point of view, we really need the cooperation from all sponsors. At the least stage, I think in the research, pre-clinical stage we probably could do the study, but without the cooperation of sponsors that becomes a meaningless exercise, and we eventually need the cooperation from sponsors in order to move forward into clinical development and approval.

This is really a process. We thought how this process could take. We're envisioning a parallel process. Once a drug moves into pre-clinical development, and the

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[inaudible] studies, we're going to take this drug forward into Phase 1 single dose and multiple dose studies, and also [inaudible] studies.

In parallel to this we're going to pursue another arm, which is pre-clinical in vitro synergistic antagonist study followed by PK drug interactions and then a screening type of animal model to really narrow down the potential combinations, and then use a long-term animal study to really pick up which [inaudible] best chance for [inaudible] and duration. And probably we have to make sure this drug doesn't have chemical interactions, make sure it doesn't have PK interactions in other species as well, and we also want to confirm this efficacy, not just in mice, but also in another species, and really use medical archives about the combination for further variation.

Eventually these two lines will merge at the three-drug Phase 1 [inaudible] and I'm going to go through three-drug Phase 2, 3 and eventually move to better treatment. In this RP we request the following five activities to support this study, quicken this study. Activity number one is an in vitro synergistic antagonistic study, and the purpose to do this really to understand any new drugs, whether or not they have mechanized based antagonism, and such drug may not be good combination in a regimen.

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The second activity is to study [inaudible] PK interactions, and the third is to use a screening model to really try to narrow it down quickly since we're dealing with a large number of potential [inaudible], which can really help us to pick out which combination can give the best chance for [inaudible]. And activity five confirms this and selective combination using a secondary model to make sure we didn't miss something.

We hope after going through all this process we can end up with three to five combinations, and then can move on to further pre-clinical and clinical development.

I think the first question to do this is what drug do you want to include into your study. To do this I think that the first step would be, is to really to review the TB drug database, which equals the first line, and the second line drug being used off label for TB, the new compound in clinical and the pre-clinical development, really try to collect all this information including the physical chemical properties and the potency efficacy information, PK-TB interactions information, in a safe way for getting information and then we're going to set a certain criteria. I think that probably clinically we want the drug to be active in order to be studied, and have to meet a certain

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efficacy and safety criteria before we want to include it into this study.

We hope we can eventually end up with about 8 to 10 best agents, and then move forward with all the following activities. Activity one is the in vitro study, and I'm going to go through this quickly. We're also in active discussion with investigators who have got to implement the [inaudible]. Different investigators have the capacity to assign such experiments, and this is just some examples we thought maybe make sense to give people some idea of how we are envisioning this activity can be done.

Activity one is to study potential two drug combinations for potential synergy and antagonism. And we hope we can study this property under both replicating and non-replicating conditions because to come to fruition it may be different under different conditions. And compounded with the same binding size of targets. Probably in all these studies this probably doesn't make much sense. A good example is the cati[misspelled?] process and the maxi[misspelled?] process. They have exactly the same binding size, the same mode of action. It doesn't make too much sense to really study the potential synergy between these two drugs.

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And to give you an example, if we have eight drugs, and the total potential two-drug combinations is 28, then for each of these two-drug combinations we are probably going to go through this checkerboard type study under both conditions – replicating and non-replicating conditions – to understand the potential interactions between the drugs.

And having done this, we plan to move into activity two, the PK interaction study, in which we try to study all the potential three-drug combinations for their PK interactions. And we're dealing with a very large number of combinations. If you look at the bottom, if we have eight drugs, the potential three-drug combination is 56. So we like to use a triage process based on information available to us to really narrow this down to a smaller number so we can really physically do the study. This [inaudible] includes the probability of known antagonism between any two drugs, identical mode of action, and known chemical interaction, and unmatched [inaudible] kinetics, same metabolic pathway, same toxicity and target organ, and we'll remove it from our list. And by doing this we hope to really narrow down to a much, much smaller number. Then physically to do a three-drug PK compare it with a single drug PK to understand the potential interaction between the drugs.

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Activity number three is quickly to screen the remaining three-drug combinations after the PK interaction studies, the short-term screening mass model, those selections we hope for the drug already being used in humans, use a human equivalent dose for drug. Not that you'll see human yet. We can use the mouse [inaudible]. After this exercise we hope to identify smaller, five to ten combinations based on the level and the speed of CIT reductions. The bottom really just shows you one potential example of how this experiment can be designed.

The following activity is really taking this smaller number of three-drug combinations to a more elaborative study to try to understand the duration needed for each combination to favor eradication. And also the bottom shows you examples of the [inaudible] design of such an experiment.

The final activity – we call it the confirmation model – and a lot of people think mass model means all of it is totally predictive of human studies. It makes sense, actually, to take the best compound moving into a different model and use this model really to prioritize the final combination to move forward.

Out of this, and probably we need to do some original studies before moving into a clinical study, chemical stability interaction, more PK interactions [inaudible],

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toxicology in the safety of pharmacology for all the three  
drugs together.

I think that's my presentation. Thank you very much.

[Applause]

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