

**Open Forum II: Key Issues in TB Drug Development - Day One:  
Approach to Developing a Non-Rifampin-Based Line Regime:  
TB Alliance  
December 12, 2006**

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**DAVID MCNEELEY:** I have to say when I found out what this topic that Anne [misspelled?] had assigned to me, I felt a bit like Carol, like she was out to punish me. But then I thought again, well, it's not so bad because I haven't really developed a Rifampin-free regimen, so I can't really have people ask questions about something I don't know anything about. So it's not so bad. And if they do, I'll ask Anne to answer questions in the Q&A period.

See if I can get out of this and get on to the presentation. What I'm really going to try to do is to focus actually on a continuation of this morning's talk and talk a little bit about TMC207 and how we're approaching the Rifampin issue. As I mentioned this morning after we got our EBA results back on the trial that we did last year, the question was for us, well, what do we do with that? Because we didn't have the early activity that one sees with Isoniazid and other drugs with very rapid bactericidal activity. And the whole team, of which there are several members here, and I want to say the work I'm presenting is thanks to all of them that are here. We scratched our heads and thought about, if you're deciding what to do with your drug, you have to think about the bug itself. And this has been mentioned today in other talks, there's the early bactericidal activity that is acting upon the rapidly replicating organisms according to the model that we

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understand of TB infection. And they are the persisters and the non-replicating organisms. So where does TMC207 or any of the compounds are under study and being talked about today. Where do they fit in that? I think you have to think of the bug and what is your drug do.

We also know from our pre-clinical work that we have activity demonstrated in both susceptible and resisted isolates. And we know that we've used our compound, which we call "J" here, for Johnson and Johnson, that's sort of our cute little device, conceit, that in the mouse model where you'll see the first column on the left is the control group that are infected and they all die off. And the back row will represent sacrifice of mice at four weeks and the front row at eight weeks. And here you'll see controls and next column to the right is our Hz, sort of standard therapy. And then where we've substituted TMC207 in different places in the regimen. We do know then from the studies that we have succeeded in sterilizing the mice lungs at eight weeks, which is very good news. So we know we can offer something to treatment regimen.

So I'll just review here again the trial that we had done earlier which I mention. So I'm going through the process of us putting together all of our thoughts after the previous trial. Most significantly, we know we have a Rifampin interaction and therefore we're going to have to avoid that and an add-on scenario in drug susceptible regimen. One would be

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hard to show because the standard regimen's very good, but so that we can't use our drug in a substitution along with Rifampin or on top of the standard treatment and this just a review again.

So what are the optimistic development scenarios for any drug? Could you reduce active disease from four drugs given for six months to maybe three drugs given for less than three months? Could you shorten treatment of MDR-TB four, five, six, depends, some places use seven drugs down to three, four drugs? And what about latent TB? Could you decrease pill burden from 270 pills maybe down to 12?

We weighed all of this together and decided that given the limited efficacy data that we have for our compound and given the drug interaction with Rifampin that the most favorable scenario for us right now would be to look at an MDR treatment population. And we felt that, given limited safety and efficacy, that that's the favorable benefit risk situation there for MDR-TB, which has very sick patients with not a very great treatment regimen to benefit from with lots of side effects, their drugs.

So these were the questions that we were looking at. How do we look at efficacy beyond seven days? How do we avoid Rifampin resistance? And of course, there's high unmet need for MDR-TB, and so we're planning this next trial which I'll describe in a second, but with the rejoinder that activity in

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MDR-TB and the next trial does not exclude for us or for anybody development in drug susceptible TB, we just think it's the direction for us to go now given the limited information that we have on our compound.

So as all of you know, in MDR-TB the treatment's quite long, 18 to 24 months. And we're proposing a randomized placebo controlled double-blind study where our drug is given on top of standard background regimen compared to an arm that has placebo on standard background regimen so everybody's getting standard of care therapy. I had the word dose finding. This is not correct. We actually have selected a dose for this study but we will confirm the dose and dosing regimen in this trial. And by doing an interim analysis after 50 patients out of 200 total have been dosed for two months. And this trial will be monitored by a data safety monitoring board and they will review safety efficacy and PK data obtained during that first stage of the trial. And if that dosing is confirmed or if slight modifications need to be made, that will be done. And then we will go on to a six-month exposure at the end of which, everybody at either stage will continue their regular treatment under the care of their physicians and according to the guidelines acceptable within the country.

This trial has been submitted to protocol as part of our IND application with the FDA and we received a response back less than a week ago with, as usual, some questions to

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answer, but with a go-ahead for the program. The primary efficacy end point in the trial will be the time to conversion, although we have a host of secondary endpoints that will be looked at. The whole host of ones you've heard about today, rate of conversion at different periods of time. We'll be doing serial speedum [misspelled?] counts on these people over the period of study drug administration. And so we will be quantifying the fall in colony forming units as well. That will be in a subset of subjects in centers who are experienced in performing quantitative speedum cultures. And in other centers and in those they will be doing qualitative speedums and other studies.

Now the question is, what do you do after this supposing that we have a good study result, we've been able to demonstrate the intrinsic activity of TMC207 and we have a drug that can be used? Where do you go next with that? Or, suppose you have another compound - I'm not speaking from the point of view of Tibotec, but I work for Company X or something, and you want to go into testing your compound into a drug susceptible population. I don't really have a magic answer to that. I felt like there was kind of an alignment going on today between things that Danny was saying and things that Carol was talking about in that Phase II has to look at regimen combinations and dosing and so on, whereas Phase III needs to look more at shortening therapy.

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What I'll say here is not reflect official Tibotec policy or decisions we've made as a team as to where to go. But this is the outline of standard therapy, which you all know. And I would put some prerequisites, this is the way I feel personally about going now into say a Phase II/III trial directly into susceptible TB with a new compound that you have to have successfully completed all the pre-clinical and non-clinical studies that are required. And there's a lot of talk about how can you shorten development, which I'm totally for. But there's just some basic stuff that has to be done. Now, whether the way we do it now is the only way to do it, I don't know. But there's certainly regulatory agencies prescribe this pathway because it's been shown to be the pathway that gets you to a compound on the market that has safety and efficacy data that can support use. So there's a whole lot of work in this and I'm only outlining broad topics. But when you talk about toxicology studies, pre-clinical microbiology, it is years' worth of work. And as everybody here know too, and especially the people in industry that compounds just fall aside as you go along. Much more fails than ever will get through all of this to humans. You have to do the requisite Phase I studies and I'm kind of intrigued by the proposal that I think will be discussed more tomorrow, the other sessions about trying to shorten this development through the proposal that the Alliance has put out, RFP recently. How the pre-clinical study design

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that was in there is going shorten all of this, especially talking about regimen development.

And as Carol mentioned earlier, all of us who, I think, who are working to try to get a drug out are very interested in the future regimen. But it's unlikely that we will be doing that regimen by ourselves because you're talking about multiple compounds coming together at one point. So it really is our responsibility to get what we have in hand out there that's safe and efficacy demonstrated so people like all of you guys will be coming together to see how you're going to put that in a new paradigm that's going to change treatment globally.

As I said this morning, the EBA trial is important for certain compounds but it's certainly not going to answer the questions for all compounds. And so we really need a lot more information on how to test other drugs that are active in these different lifecycles of TB, basili [misspelled?] and infection was the object of the first slide. I think that if you were just talking about substituting a single compound into standard therapy then in a classic Phase II/b sort of trial it's something like this.

I don't have control arm up here by the way, but that would be standard of care. Classically you are going to substitute different doses of compound X into a regimen here. I have proposed E is parentheses so you take out Rifampin but you probably could get rid of E if you had the right compound

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and say have a three-drug regimen over a two-month period of time and then continue treatment through standard continuation phase. And if you get into the real regimen then you've got these permutations of compounds W, X, Y that perhaps you could get together and cut out this whole intensive continuation phase of drugs so that you are eliminating the biphasic treatment. I think that would be ideal. Again how you're going to sort out this regimen is the real challenge.

The idea of doing this pre-clinical screening to see what goes together is very attractive. And at the other hand you think two H's and an O don't make two H's and an O, but H<sub>2</sub>O, which is different. So I'll be interested to follow the presentations the next day to see how other people envision that coming together.

I don't have any magic answer for developing a Rifampin free regimen. We are going to look at our compound in a regimen that can't use Rifampin. I think when we started this a couple of years ago, we didn't really consider that. And then we don't feel bad about it because we, I've said my colleagues and I and other that I've talked to at any rate, if TMC207 was licensed tomorrow it's going to be used for MDR treatment. Even if it was licensed for drug susceptible, somebody's going to use it off-label for MDR. It's not going to get incorporated into the Health Department regulation to the 150 countries overnight. And that's true for all other

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compounds. So I think whether or not you go into an MDR route or into a drug-susceptible route in your Phase II/III depends on how comfortable you are with safety and efficacy data, the characteristics of your compound, and whether or not you have a Rifampin interaction, etcetera. But then regimen issue is much more complex. So if there are questions, as I said, Anne has to answer all the questions today.

**MODERATOR:** Okay, thank you very much. There's a question down in the front here. Is there a microphone in the front row?

**MALE SPEAKER:** Thank you, David, for your presentation. Just regarding the question of whether or not to include your drug in a regimen that has Rifampin in it, if you look at the story of Rifabutin, we see that the dose varies from 150 milligrams in the context of a Ritonavir regimen versus 300 milligrams without Ritonavir, versus 600 milligrams with Efaviren [misspelled?]. So there already is precedent for dose based on concurrent medication. So at least that would still be a future consideration.

**DAVID MCNEELEY:** We're aware that we could think about dose adjustments, but right now we just don't feel we have the kind of information we'd like to have in hand to do that.

**MODERATOR:** Down in the front here, Professor Mitchison.

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**DENNIS MITCHISON, M.B.:** David, I'd like to ask you on two issues about Rifampin and J. The first thing is does J regularly reduce the Rifampin level by 50-percent? If it does regularly could you just increase the dose?

**DAVID MCNEELEY:** No, Rifampin -

**DENNIS MITCHISON, M.B.:** I mean, J -

**DAVID MCNEELEY:** Rifampin reduces ours. Rifampin effects our, you switched it around that we reduce Rifampin.

**DENNIS MITCHISON, M.B.:** Well, what's said is there's an interaction between J and Rifampin such that the Rifampin levels are lowered to about 50-percent. Is that right?

**DAVID MCNEELEY:** TMC207.

**DENNIS MITCHISON, M.B.:** It's lowered is it?

**DAVID MCNEELEY:** Yes.

**DENNIS MITCHISON, M.B.:** So you could actually give an increased dose of J.

**DAVID MCNEELEY:** That's, I think, what Chuck was kind of getting at, but we have not done that. And we're aware that that's possible, but -

**DENNIS MITCHISON, M.B.:** Do you have any information on interactions with ARVs?

**DAVID MCNEELEY:** No, but we suspect because of the way it's metabolized we'll have some interaction. But that doesn't mean we will see the magnitude of what we've seen there. But

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we haven't done those studies. And that needs to be done at one point. We're aware of that.

**MODERATOR:** That's enough of the questions. I'd like to thank David and the rest of the speakers for today. And thank everybody very much for your attendance today.

I have one announcement. The meal this evening is going to be in this room, but if you can please remove all personal items at the moment, any notes or anything that you have with you. Take them with you at this time because the room's going to be reorganized, obviously for the meal tonight.

So I'd just like to bring this session to a close and thank you all for your attention.

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